Tetrahedron Letters No. 26, pp. 1-4, 1960. Pergamon Press Ltd. Printed in Great Britain

THE STRUCTURE OF DIHYDROTOXIFERINE

V. Boekelheide, O. Ceder, T. Crabb, Y. Kawazoe and R. N. Knowles

Department of Chemistry, University of Rochester

Rochester, New York

(Received 9 November 1960)

THE dimerization of Wieland-Gumlich aldehyde or its methochloride represents an extremely simple synthesis for nor-C-toxiferine-I or C-toxiferine-I, respectively,[1-5] and provided a brilliant break-through in the structural investigation of the principal alkaloids of calabash-curare.[6] Although this discovery combined with the conversion of Wieland-Gumlich aldehyde to C-dihydrotoxiferine[1,2] clearly establishes the carbon skeletons of C-dihydrotoxiferine and C-toxiferine-I, two possibilities still remain for the arrangement of the double bonds in the central portion of the molecule.

---

[1] K. Bernauer, F. Berlage, W. von Philipsborn, H. Schmid and P. Karrer, Helv. Chim. Acta 41, 2293 (1958).

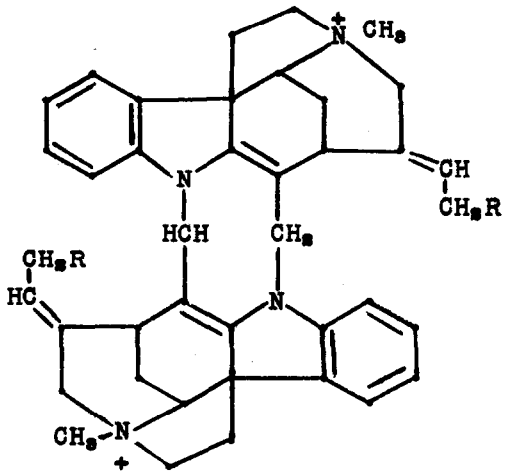
[2] K. Bernauer, F. Berlage, W. von Philipsborn, H. Schmid and P. Karrer, Helv. Chim. Acta 42, 201 (1959).

[3] F. Berlage, K. Bernauer, W. von Philipsborn, P. Waser, H. Schmid and P. Karrer, Helv. Chim. Acta 42, 394 (1959).

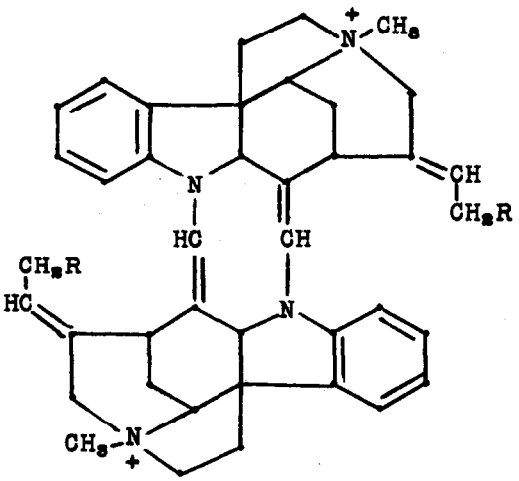
[4] A. R. Battersby and H. F. Hodson, Proc. Chem. Soc. (London) 287 (1958).

[5] A. R. Battersby and H. F. Hodson, J. Chem. Soc. 736 (1960).

[6] For recent summaries, see K. Bernauer, Fortschr. Chem. org. Naturstoffe 17, 184 (1959); and A. R. Battersby and H. F. Hodson, Quart. Rev. 14, 77 (1960).



I, R = -H
II, R = -OH

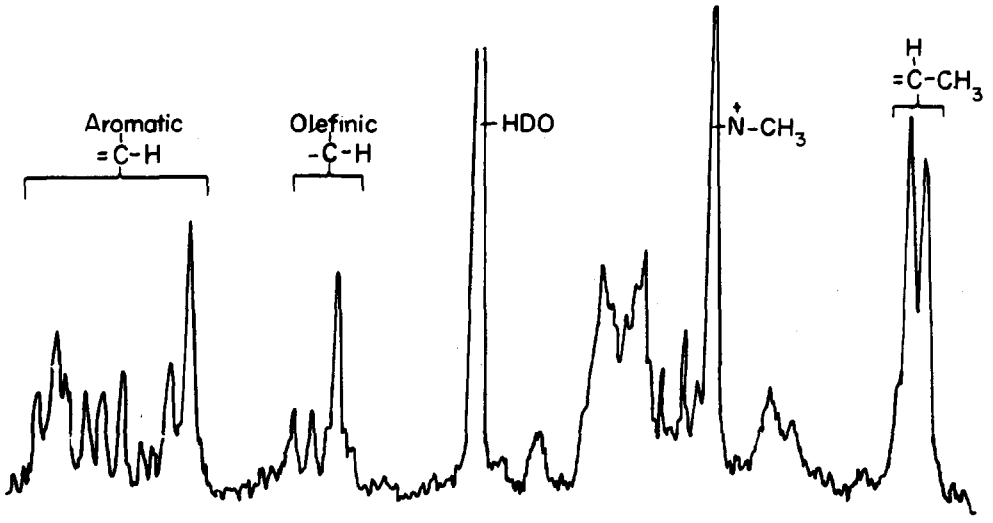


III, R = -H
IV, R = -OH

Because of the similarity of the ultraviolet absorption spectra of C-dihydrotoxiferine and C-toxiferine-I to that of known compounds containing the methyleneindoline chromophore, the Zurich and Bristol laboratories have favored structures I and II, respectively, for these alkaloids. However, since III and IV might be expected to exhibit rather similar absorption in the ultraviolet to I and II, this is not a satisfactory basis for deciding between these possibilities. Since nuclear magnetic resonance seemed particularly appropriate for deciding between I and III as possible structures for C-dihydrotoxiferine, we have synthesized a sample of this alkaloid and examined its nuclear magnetic resonance spectrum. Our preparation followed that reported by Schmid and Karrer and their collaborators and closely duplicated their results.[1,2] Also, the properties of

our material were in accord with those of a sample of dihydrotoxiferine isolated from calabash-curare of the Piaroa Indians.[7]

Dihydrotoxiferine



N.M.R. Spectrum of C-Dihydrotoxiferine

For structure I, it would be expected that the signal in the olefinic region would be a quartet and correspond in area to one-fourth that of the aromatic protons; whereas, structure III

---

[7] A. Zurcher, O. Ceder and V. Boekelheide, J. Am. Chem. Soc. 80, 1500 (1958).

should show signals from two types of olefinic protons, one of which should be a quartet and the other a single sharp peak, with the total area of the olefinic protons being equal to one-half that of the signal for the aromatic protons. Examination of the NMR spectrum of C-dihydrotoxiferine chloride in the olefinic region shows an apparent quartet over which is superimposed a strong signal at -54 cps (relative to HDO). Furthermore, by electronic integration the area represented by the aromatic protons is twice that of the olefinic protons. Thus, the NMR spectrum of C-dihydrotoxiferine is in good accord with structure III but not for structure I.

Likewise, as we have suggested previously,[8] the NMR spectrum of C-toxiferine-I is in agreement with structure IV but not with structure II. Thus, the NMR spectrum of C-toxiferine chloride shows both a triplet and a singlet, each of equal area, in the olefinic region.

We are grateful to Professor David Wilson of the University of Rochester and Dr. L. F. Johnson of Varian Associates for the determination of spectra and for helpful discussions. The spectra were determined using deuterium oxide as solvent and a Varian V-4300C 60 Mc spectrometer. The details of these as well as other NMR studies of the calabash-curare alkaloids will be published shortly. We thank the National Institute of Neurological Diseases and Blindness of the National Institutes of Health (research grant B-671) and the Army Chemical Center for financial support.

---

[8] Lecture, University of Zurich, February, 1960.