Tetrahedron Letters No. 9, pp. 299-304, 1961. Pergamon Press Ltd. Printed in Great Britain.

THE STRUCTURE OF QUEBRACHAMINE

K. Biemann and G. Spiteller

Department of Chemistry, Massachusetts Institute of Technology,

Cambridge, Mass.

(Received 5 May 1961)

QUEBRACHAMINE is one of the alkaloids of Aspidosperma quebracho blanco Schlecht., from which also aspidospermine and yohimbine ("quebrachine") have been isolated.[1] While the structures of the two latter ones are well known, quebrachamine has received little attention and only rather recently has it been investigated chemically.[2] Quebrachamine was shown to contain an indole system from its ultraviolet spectrum,[2] and the NMR spectrum indicated alkyl substituents in the α- and β-positions but an unsubstituted indole nitrogen.[3] The lack of functional groups other than a tertiary nitrogen atom makes a specific chemical degradation difficult, and it is for this reason that only zinc dust distillation and palladium dehydrogenation have led to products for which structures have been suggested. It is reported[2] that in the former reaction 3,5-diethylpyridine, 3-methyl-5-ethylpyridine, β-methyl- and β-ethylindole, carbazole and a methylcarbazole were formed. The pyridines and the indoles were isolated in the form of their picrates but apparently no pure compounds could be

---

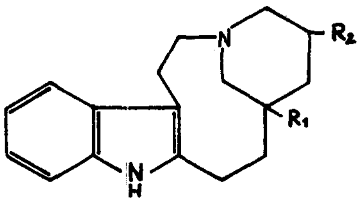
[1] O. Hesse, Liebigs Ann. 211, 249 (1882).

[2] B. Witkop, J.Amer.Chem.Soc. 79, 3193 (1957).

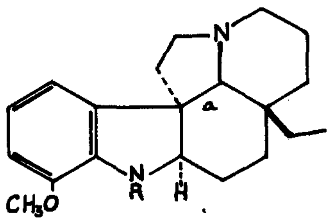
[3] L. A. Cohen, J. W. Daly, H. Kny and B. Witkop, J.Amer.Chem.Soc. 82, 2184 (1960).

obtained and the identity of these degradation products was based on melting points of mixtures and their elemental analyses.

A reinvestigation of the zinc dust distillation of quebrachamine was undertaken employing mass spectrometry for the identification of the products. Preliminary experiments on 3 mg of the alkaloid showed the formation of C_2-, C_3- and C_4-pyridines, C_1- to C_4-indoles and of a compound of molecular weight 280. Repetition of the experiment using 13 mg of quebrachamine, separation of the pyridine fraction by gas chromatography, followed by mass spectrometric determination of the structure of the products and comparison with the spectra of authentic samples showed the pyridine fraction to consist to 75% of 3-ethylpyridine; 12% of 3-methyl-5-ethylpyridine; 5% of 3-ethyl-4-methyl-pyridine; 5% of 3,5-diethylpyridine; and traces of other C_3- and C_4-pyridines. A second experiment led to the identification of 3-methylindole,[4] 2-ethylindole, 2,3-dimethylindole,[4] a methyl-ethylindole, and 2,3-diethylindole. The The formation of the 3-ethyl derivative as the major pyridine, a fact which is in contrast to earlier reports,[2] and the identification of 2,3-diethylindole made structure Ia an attractive working hypothesis; these two



Ia $R_1 = C_2H_5$, $R_2 = H$
Ib $R_1 = H$, $R_2 = C_2H_5$



IIa $R = CH_3CO$
IIb $R = H$

---

[4] Compared with the published spectra of J. H. Beynon and A. E. Williams, Appl.Spectrosc. 13, 101 (1959).

products contain all the atoms present in quebrachamine itself if we assume that all three ethyl groups represent different parts of the original molecule. This structure, containing the carbon skeleton of aspidospermine (IIa),[5] is also a very attractive one on the basis of biogenetic considerations. For the same reason and based only on the previously reported finding that both these alkaloids give the same mixture of 3,5-diethylpyridine and 3-methyl-5-ethylpyridine on zinc dust distillation,[2] structure Ia has in the meantime been suggested by Kny and Witkop[6] and by Smith and Wrobel[7] as a possibility for quebrachamine. The formation in small quantities of 3,5-substituted pyridines requires consideration of the alternative structure Ib which would be related to ibogamine[*] rather than to aspidospermine. The formation of 3-ethylpyridine in such high proportions makes this structure less probable; the iboga-alkaloids yield 3-methyl-5-ethylpyridine as the major degradation product, while from aspidospermine mainly 3-ethylpyridine is obtained.[**]

The lack of appreciable quantities of quebrachamine prohibited a corroboration of structure Ia or Ib by specific chemical degradation, and we therefore turned our attention to a chemical correlation of quebrachamine with aspidospermine (IIa). Since we had shown previously[9] that the identity of the aliphatic carbon skeleton in differently substituted alkaloids can

---

[*] Quebrachamine was found[8] in Stammadenia donell-smithii Woods., a plant also producing voacangin (a carbomethoxyibogaine).

[**] Experiments from this laboratory, to be published in the full paper.

[5] J. F. D. Mills and S. C. Nyburg, Tetrahedron Letters No. 11, 1 (1959); H. Conroy, P. R. Brook and Y. Amiel, Ibid. No. 11, 4 (1959).

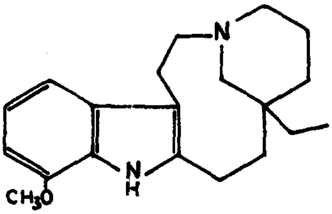
[6] H. Kny and B. Witkop, J.Org.Chem. **25**, 635 (1960).

[7] G. F. Smith and J. T. Wrobel, J.Chem.Soc. 1463 (1960).

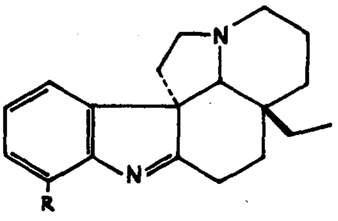
[8] F. Walls, O. Collera and A. Sandoval, Tetrahedron **2**, 173 (1958).

[9] K. Biemann, Tetrahedron Letters No. 15, 9 (1960).

be determined by mass spectrometry, it was not necessary to remove the methoxy group in aspidospermine. It was consequently attempted to prepare III requiring cleavage of bond a in IIa accompanied by aromatization of ring B. Desacetylaspidospermine (IIb) was converted to dehydrodesacetylaspidospermine (IVa) by oxidation under carefully controlled conditions



III



IVa R = CH_3O
IVb R = H

(I_2 and NaOH in methanol, 3 min, room temp.). A mixture of IIb and IVa was obtained on extraction of the reaction mixture, which had been poured into water. The presence of IVa, which could not be separated from IIb, except by gas chromatography, is indicated by the ultraviolet spectrum (λ_{max} = 228, 236(sh), 255, 307 mμ; ε = 16,500, 13,700, 4900, 4500), a molecular weight of 310, and the fact that reduction with $LiAlD_4$ gives a mixture of nondeuterated and monodeuterated IIb (IVa $\rightarrow$ IIb), as shown by the mass spectrum of the product.

This mixture of IIb and IVa was reduced as such with sodium borohydride, a reaction previously used to achieve a similar conversion of a degradation product of akkuamicine into an indole derivative.[10] The product, a mixture consisting mainly of IIa and III, was separated by chromatography on alumina; the fractions containing III were combined (24% yield based on aspidospermine

---

[10] G. F. Smith and J. T. Wrobel, J.Chem.Soc. 792 (1960).

used) and converted to the picrate which after recrystallization from methanol had a melting point 204 to 206°, ($C_{20}H_{28}N_2O\cdot C_6H_3N_3O_7$, Found: C, 57.81; H, 5.71; N, 13.08). The free base (III) regenerated from the analytical sample of the picrate and distilled at 0.05 mm (180° air bath) was a colorless glass which could not be induced to crystallize (U.V. λ_{max} = 228, 278, 291(sh); ε = 43,600, 8020, 5680). Its mass spectrum is shown in Fig. 1 along with the spectrum of quebrachamine. A careful comparison of the two spectra reveals two groups of peaks, one being of the same mass numbers in both spectra and of comparable intensities, while the other group is shifted for 30 mass numbers in the spectrum of compound III vs. the spectrum of quebrachamine. The first group consists of fragments of mass 110, 124, 125, 126, and 138 whereas the second group is at mass 143, 144, 156, 157, 196, 199, 210, 253, 267, and 282 in quebrachamine, while they are found at mass 173, 174, 186, 187, 226, 229, 240, 283, 297, and 312 in III. On the basis of these mass spectra, quebrachamine is assigned structure Ia. A methoxy derivative of Ib would be expected to exhibit a mass spectrum differing considerably from Ia, particularly in the

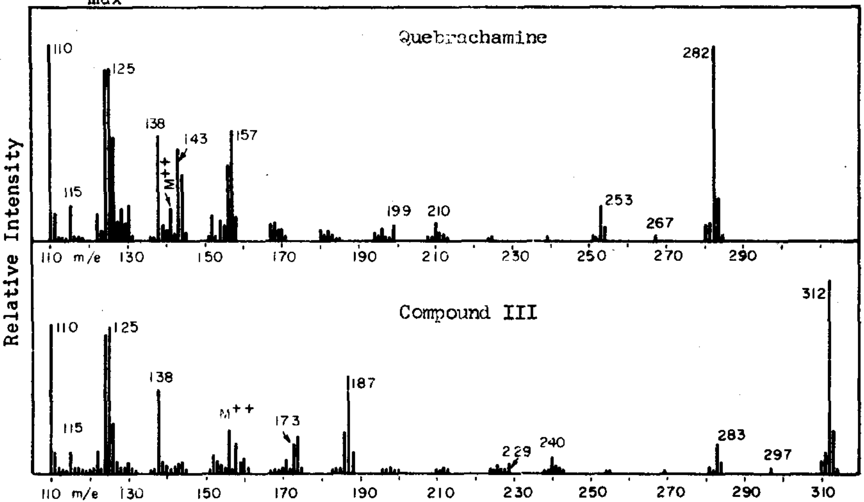


FIG. 1.

peaks corresponding to fragments having specifically lost the ethyl group (mass 283) or retained it (mass 110, believed to represent the piperidine ring plus ethyl). This conclusion is also corroborated by the already discussed formation of 3-ethylpyridine in the zinc dust distillation and by the fact that the mass spectrum of compound IVa is very similar to the spectrum of the zinc dust distillation product of molecular weight 280 mentioned above, with the exception of a shift for 30 mass numbers. This compound is, therefore, assigned structure IVb which implies ring closure of the quebrachamine skeleton to the one of aspidospermine, a conclusion supported by the identification of other products found in this reaction which will be discussed in the full paper.

It is of interest to note that the rotation of III ($[\alpha]_D^{25} = -103^\circ$ in dioxane) and its plain optical rotatory dispersion curve are very similar in magnitude and sign to the one of (-) quebrachamine[8] ($[\alpha]_D = -111^\circ$ in dioxane), indicating the same absolute configuration for both compounds. As methoxyquebrachamine (III) was prepared from aspidospermine, it follows that the (-) quebrachamine of Aspidosperma quebracho blanco belongs to the same configurational series at the quaternary carbon as aspidospermine while (+) quebrachamine,[8] isolated from Stammadenia-donell-smithii Woodson, is thus related to pyrifolidine,[11] the absolute configuration of which is opposite to the one of aspidospermine.

Acknowledgements - We are indebted to Dr. W.I. Taylor and Dr. B. Gilbert for samples of quebrachamine, to Dr. F.G. Smith for 2,3- and 3,5-diethylpyridine in the form of their picrates, to Dr. N. Neuss for aspidospermine, to Prof. E. Leete for 2-ethylindole, to Prof. C. Djerassi and his associates for their determination of the ORD-curve of compound III, and to the National Science Foundation for financial support (Grant G-5051).

---

[11] C. Djerassi, B. Gilbert, J. N. Shoolery, L. F. Johnson and K. Biemann, Experienta 17, in press (1961).