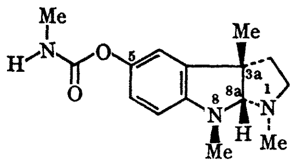
The Absolute Configuration of Physostigmine (Eserine). Application of the Nuclear Overhauser Effect

By GEORGE R. NEWKOME* and N. S. BHACCA

(*Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana* 70803)

PHYSOSTIGMINE, the major alkaloid of the Calabar bean (*Physostigma venenosum*), has been recently shown[1] to have the (3a*S*,8a*R*) configuration by unambiguous chemical correlation to (*R*)-(−)-3-ethyl-1,3-dimethyloxindole, which was synthesized independently from (*R*)-2-methyl-2-phenylbutyric acid.[2] The ring junction of the two five-membered rings was assigned to the thermodynamically more stable *cis*-ring fusion;[3] since, (a) only the natural isomer was obtained during the synthetic ring construction[4] and (b) a Hofmann elimination product isolated during the original degradation studies regenerated the original ring system when treated with acid.[5] We report internal nuclear Overhauser effect (NOE)[6] studies which represent a more direct approach to the assignment of the ring fusion between the fused pyrrole rings and thus a definition of the absolute configuration of the second (8a) asymmetric centre, as well as configurational assignment of the *N*-methyl groups.



The absolute configuration of physostigmine.

From earlier 60 MHz n.m.r. studies,[7] all of the important proton signals have been assigned: 3a-Me (1·42, s)[†], 1-*N*-Me (1·95, s), 8-*N*-Me (2·92, s), and 8a-H (4·12, s). The NOE experiments[†] were performed on a freshly prepared 10% $DCCl_3$ solution of pure physostigmine.[‡] The *cis*- or *trans*-ring fusion was elucidated by the low-intensity irradiation at the frequency corresponding to the 3a-methyl group resulting in a 15% enhancement in the integrated intensity of 8a-H. Irradiation of the low-field *N*-methyl signal also resulted in a 15% enhancement of the 8a-H integrated intensity, whereas similar irradiation of the high-field *N*-methyl did not result in any significant increase in the integration of 8a-H.

These data unequivocally prove that the earlier hypothesis, that the fused five-membered rings in physostigmine are *cis*, is correct. These NOE experiments further indicate that the 8-*N*-Me is *cis* to the 8a-H and is not undergoing rapid nitrogen inversion. However, the failure to observe any Overhauser effect indicates the 1-*N*-Me stereochemical relationship to 8a-H is either completely *trans* or is rapidly inverting under the experimental conditions.

(*Received, March 3rd,* 1969; *Com.* 295.)

[†] The NOE data were obtained on a Varian HA-100 n.m.r. spectrometer operating in frequency sweep mode, with Me_4Si as an internal field-frequency lock. The chemical shifts are reported in p.p.m. relative to Me_4Si.

[‡] Physostigmine, $[\alpha]_D$ −75·6° (1·3, $CHCl_3$), m.p. 105°, was supplied by Mann Research Laboratories.

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[2] D. J. Cram and J. D. Knight, *J. Amer. Chem. Soc.*, 1952, **74**, 5835.

[3] B. Witkop and R. K. Hill, *J. Amer. Chem. Soc.*, 1955, **77**, 6592.

[4] Several recent reviews summarize the chemistry: E. Coxworth, in "The Alkaloids", ed. R. H. F. Manske, vol. VIII, Academic Press, New York, 1965, ch. 2; L. Marion, *ibid.*, vol. II, 1952, ch. 13; W. I. Taylor, "Indole Alkaloids", Pergamon Press, Oxford, 1966, p. 33; B. Robinson, *Chem. and Ind.*, 1963, 218.

[5] G. Barger and E. Stedman, *J. Chem. Soc.*, 1923, **123**, 758.

[6] F. A. L. Anet and A. J. R. Bourn, *J. Amer. Chem. Soc.*, 1965, **87**, 5250; See P. A. Hart and J. P. Davis, *ibid.*, 1969, **91**, 512 for previous examples of NOE, which are cited in references (7—18).

[7] Varian Associates, High Resolution N.M.R. Catalog, 1962, Spectrum 319.