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THE CONFIGURATION OF CARPAINE

M. Tichý and J. Sicher

Institute of Organic Chemistry and Biochemistry

Czechoslovak Academy of Science, Prague

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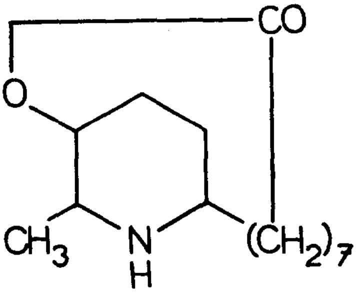
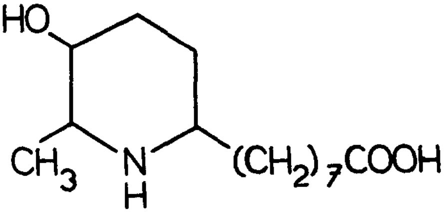
THE alkaloid carpaine (I) has been studied by Barger and by Robinson and their co-workers[1] and its structure was established in 1953 by Rapoport *et al.*[2] and later confirmed by Govindachari and Narasimhan.[3]



I



II

Carpaine, as well as its derivatives with the lactone ring opened, such as carpamic acid (II), can possess one of the four configurations A-D. (Only one formula is shown for each racemate.)

Govindachari and Narasimhan[4] brought forward evidence that the sub-

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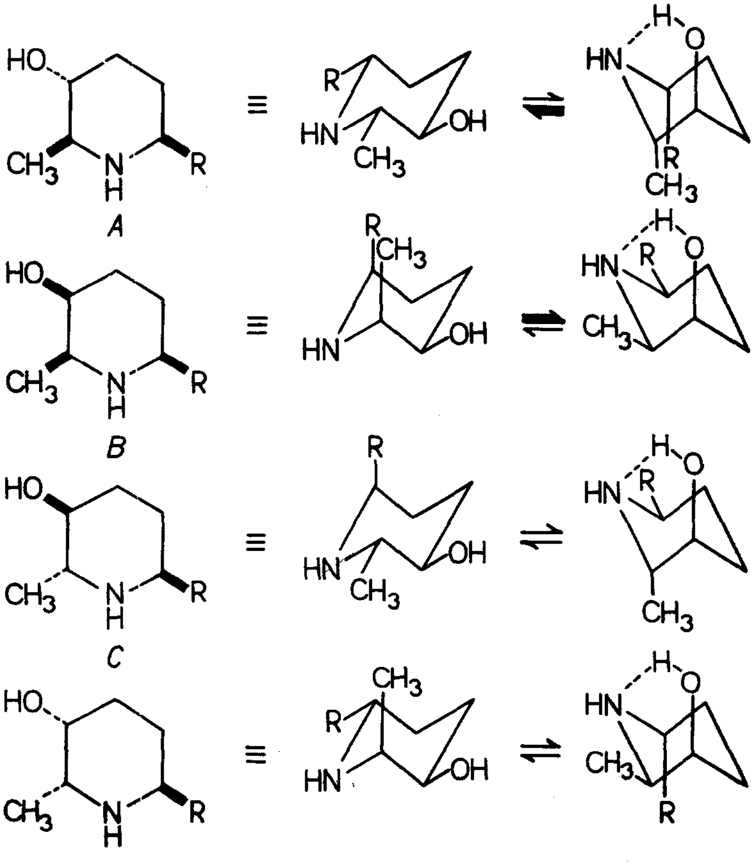
[1] G. Barger, J. Chem. Soc. 97, 466 (1910); G. Barger, A. Girardet and R. Robinson, Helv. Chim. Acta 16, 90 (1933); G. Barger, R. Robinson and T.S. Work, J. Chem. Soc. 711 (1937).

[2] H. Rapoport and H.D. Baldridge, J. Amer. Chem. Soc. 74, 5365 (1952); H. Rapoport, H.D. Baldridge and E.J. Volcheck, Ibid. 75, 5290 (1953).

[3] T.R. Govindachari, N.S. Narsimhan and S. Rajadurai, J. Chem. Soc. 558 (1957).

[4] T.R. Govindachari and N.S. Narasimhan, J. Chem. Soc. 1563 (1955).

stituents in the positions 2 and 6 on the piperidine ring of carpamic acid (II) are *cis* and hence diequatorial. On the basis of negative evidence they also provisionally assigned to the hydroxyl group the equatorial conformation (CH_3/OH *trans*), giving the stereoformula A for carpamic acid. We have now found that this assignment is incorrect and present unequivocal proof for the configuration of carpaine, based on spectroscopic intramolecular hydrogen bond determination in methyl carpamate (III), and the following conformational reasoning.



III, R = $-(CH_2)_7COOCH_3$

Should methyl carpamate (III) possess the configuration A, as provisionally suggested by the Indian authors,[4] it would exist exclusively in the triequatorial conformation and spectra measured in dilute solution would exhibit no bonded OH band, i.e. be similar to the spectrum of trans-2-methyl-3-hydroxypiperidine.[5] If III possessed the configuration B, the hydroxyl would be exclusively axial and hence predominantly bonded. Its spectrum hence should exhibit a large bonded OH band and only a very small free OH band, as do the spectra of cis-2-methyl-3-hydroxypiperidine ($\Delta\upsilon = 106\ cm^{-1}$, $\varepsilon_b/\varepsilon_f = 2.9$)[5] or cis,cis-2,6-dimethyl-3-hydroxypiperidine ($\Delta\upsilon = 104\ cm^{-1}$, $\varepsilon_b/\varepsilon_f = 3.1$). In the isomers C and D the conformation determining effects of the trans-placed groups CH_3 and R are likely to cancel out and the conformational equilibrium between the "OH-axial" and "OH-equatorial" conformers should be similar to that in 3-hydroxypiperidine. The spectra of C and D would therefore exhibit free and bonded OH bands of approximately equal height, as does that of 3-hydroxypiperidine ($\Delta\upsilon = 89\ cm^{-1}$, $\varepsilon_b/\varepsilon_f = 0.8$).[6] Intramolecular hydrogen bond determination should therefore be capable of distinguishing between the configurations A and B and C,D but not between the last two.

The spectrum of methyl carpamate (III) has now been found[7] to possess $\Delta\upsilon = 106\ cm^{-1}$, $\varepsilon_b/\varepsilon_f = 3.6$ and to be very similar to that of cis-2-methyl-3-hydroxypiperidine and of cis,cis-2,6-dimethyl-3-hydroxypiperidine but completely different from that of trans-2-methyl-3-hydroxypiperidine or of 3-hydroxypiperidine. This definitely establishes the configuration B for methyl carpamate (III). Since carpamic acid (II) can be reconverted to

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[5] J. Sicher and M. Tichý, Tetrahedron Letters No. 12, 6 (1959).

[6] J. Sicher and M. Tichý, Coll. Czech. Chem. Comm. 23, 2081 (1958).

[7] The spectra were measured by Dr. M. Horák of this Institute. For the technique used see J. Sicher, M. Horák and M. Svoboda, Coll. Czech. Chem. Comm. 24, 950 (1959).

carpaine (I)[8] these results also establish the configuration of the alkaloid as the "all-*cis*" isomer.

We wish to express our gratitude to Mr. Levan Can (Gialam, Hanoi) for a generous supply of leaves of Carica papaya.

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[8] N.S. Narasimhan, *Chem. & Ind.* 1526 (1956).