Tetrahedron Letters No. 18, pp 1683 - 1686, 1974. Pergamon Press. Printed in Great Britain.

THE STRUCTURE AND ABSOLUTE CONFIGURATION OF (-)-TEMPLETINE

J. R. Cannon, J. R. Williams*
Department of Organic Chemistry, University of Western Australia, Nedlands, W.A. 6009, Australia
*Present Address: Dept. of Chemistry, Temple University, Philadelphia, Penna. 19122, U.S.A.

and

J. F. Blount, A. Brossi
Hoffman-La Roche Inc., Nutley, New Jersey 07110, U.S.A.

(Received in USA 12 February 1974; received in UK for publication 25 March 1974)

Re-examination of the basic material obtained by extracting the leaves of Templetonia retusa (Vent.) R. Br.[1] led to the isolation of (-)-cytisine, (-)-anagyrine, (+)-lupanine, a trace of (±)-piptanthine, and 0.02% of a new alkaloid, (-)-templetine, which crystallized from acetone as prisms, m.p. 120.5-122.0°, $[\alpha]_D -52^\circ$ (c. 1.0 in ethanol).

(-)-Templetine analyzed for $C_{20}H_{35}N_3$[2] and its reactions with methyl iodide, with formaldehyde and with carbon disulphide, revealed that it contained one tertiary and two secondary nitrogen atoms. As (-)-templetine failed to undergo catalytic hydrogenation, it seemed likely that it belonged to the group of C_{20} Ormosia alkaloids. This was confirmed when it was found that vigorous dehydrogenation of (-)-templetine with 10% Pd/C afforded (-)-dehydropiptanthine $C_{20}H_{23}N_3$. This product was identified by comparison of its perchlorate, m.p. 261-263° $[\alpha]_D -126^\circ$ (c. 1.2 in water) with the perchlorate of its enantiomer (+)-dehydropiptanthine, m.p. 260-262° $[\alpha]_D +123^\circ$ (c. 0.8 in water) (by thin layer chromatography, ir, uv, nmr and mass spectroscopy). The latter compound was obtained by dehydrogenation of (-)-ormosanine [(-)-piptamine, OPII][3] prepared by reduction of (-)-panamine (OPIII) with sodium borohydride.[3]

Templetine shows Bohlmann bands at 2800, 2770, 2730, and 2655 cm^{-1} in the infrared spectrum (CCl_4) suggesting the presence of a trans-quinolizidine moiety in the alkaloid. In agreement with this hypothesis, mild dehydrogenation of (-)-templetine with mercuric acetate at room temperature gave an oily monodehydro derivative which was characterized as the sulphate, m.p. 221-222°. Catalytic reduction of the monodehydro derivative then gave only (-)-templetine.

As it seemed that further attempts to define the stereochemistry of the remaining asymmetric centres by chemical and spectroscopic methods would not be rewarding, it was decided to undertake an x-ray crystallographic analysis of (-)-templetine trihydrochloride dihydrate, m.p. 295-300°.

Crystals of the salt are orthorhombic, the space group being $P2_12_12_1$ with cell constants a = 8.83(4), b = 14.201(6), and c = 19.122(12)Å. There are four $C_{20}H_{35}N_3 \cdot 3HCl \cdot 2H_2O$ formula units in the unit cell (d_{calc} = 1.282 g cm^{-3}). The intensity data were collected out to $2\theta_{max}$ = 132° and were corrected for absorption [$\mu(CuK\alpha)$ = 36.2 cm^{-1}]. The size of the crystal used was approximately 0.15 x 0.3 x 0.3 mm. The structure was solved by the multiple solution procedure of Germain, Main, and Woolfson[4] as implemented in their programme MULTAN. Anomalous dispersion effects were ignored during the initial refinement of the structure. Structure factors (including dispersion) were then calculated for both enantiomers and the absolute configuration was taken as that corresponding to the lower R factor (R = 0.101 and 0.106). All hydrogen atoms, except those of water molecules, were found on a difference Fourier calculated near the end of the refinement. The final refinement was carried out by a full matrix least squares in which all atoms were assigned anisotropic thermal parameters except for the hydrogen atoms which had isotropic temperature factors. The final R factor is R = 0.045.[5]

This led to the conformation and absolute configuration of the ion as shown in Figure 1. The absolute structure of (-)-templetine is represented conventionally in **1**.

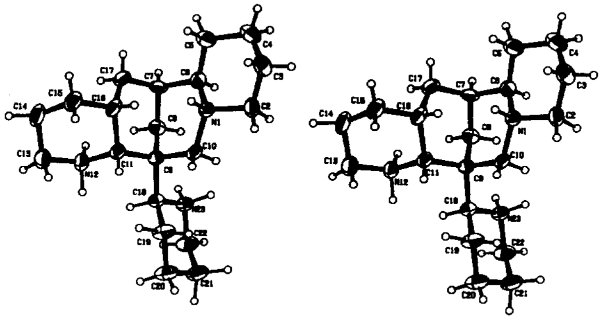
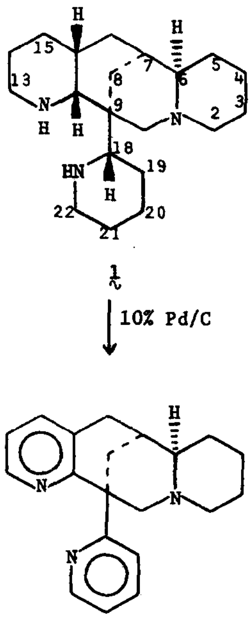
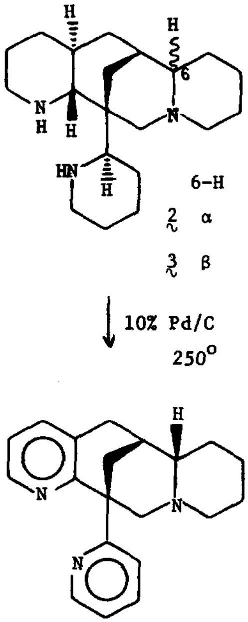


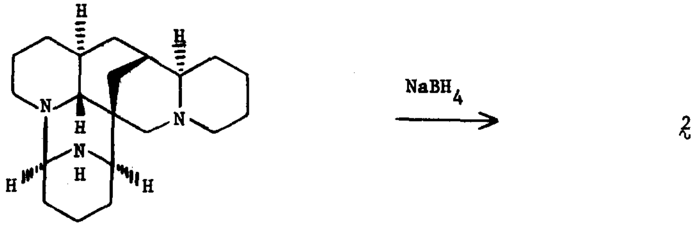
Figure 1. Stereodrawings illustrating the absolute configurations of **1** as determined from the X-ray analysis of **1** 3HCl·2H$_2$O. The ellipsoids represent the thermal motions of each atom at the 50% probability level. The hydrogen atoms are shown as spheres of arbitrary size.



4



5



6

The present degradative work, which has related (-)-templetine to (-)-ormosanine and to (-)-panamine, via the enantiomeric dehydropiptanthines 4 and 5, enables the absolute structures 2 and 6 to be assigned to (-)-ormasanine and (-)-panamine, respectively.[6] Furthermore, epimerization of 2 at C$_6$ yields the more stable isomer 3, which is enantiomeric with (-)-piptanthine isolated from *Piptanthus nanus*.[7] Hence (+)-piptantahine has the absolute configuration **3**.

(+)-Dasycarpine and (-)-ormojanine have been related to one another, and to ormosanine.[7,8] However, the rotation of the optically-active dehydropiptanthine obtained by dehydrogenation of dihydroormojanine was not recorded,[8] and at present it is not possible to assign absolute structures to these alkaloids. Recent work[9] has shown that (-)-ormocastrine is identical to podopetaline mono-hydrochloride the absolute configuration of which has recently been determined by x-ray analysis.[10]

In conclusion it is appropriate that templetine should be associated with Temple University.

Acknowledgments:

We thank Dr. J.A. Lamberton for identifying (±)-piptanthine isolated from *T. retusa*, and for helpful discussions. We are also grateful to Dr. H. A. Lloyd for a generous gift of (-)-panamine diperchlorate, and for her helpful suggestions.

References

1. E. P. White, *New Zealand J. Sci. Technol.*, **33B**, 54 (1951).
2. Satisfactory elemental and spectral analyses were obtained on all new compounds reported.
3. P. Naegeli, W. C. Wildman, and H. A. Lloyd, *Tetrahedron Letters*, 2069 (1963);
   P. Naegeli, R. Naegeli, W. C. Wildman, and R. J. Highet, *Tetrahedron Letters*, 2075 (1963).
4. G. Germain, P. Main, and M. M. Woolfson, *Acta Cryst.*, **B26**, 274 (1970).
5. Tables of the atomic coordinates, thermal parameters and structure factors will appear in the full paper.
6. I. L. Karle, *Tetrahedron Letters*, 1659 (1966).
7. P. Deslongchamps, J. S. Wilson, and Z. Valenta, *Tetrahedron Letters*, 3893 (1964);
   P. Deslongchamps, Z. Valenta, and J. S. Wilson, *Canad. J. Chem.*, **44**, 2539 (1966).
8. Z. Valenta, P. Deslongchamps, M. H. Rashid, R. H. Wightman, and J. S. Wilson, *Canad. J. Chem.*, **44**, 2525 (1966).
9. S. McLean, *Canad. J. Chem.* (in press).
10. N. K. Hart, S. R. Johns, J. A. Lamberton, M. F. McKay, A. McL. Mathieson and L. Satzke, *Tetrahedron Letters*, 5333 (1972).