

THE SYNTHESIS OF BERBERASTINE

S.F. Dyke and E.P. Tiley,
School of Chemistry and Chemical Engineering,
University of Bath,
Claverton Down,
Bath BA2 7AY.

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Berberastine (1a)¹ and Thalidastine (1b)² are two examples of alkaloids possessing the 5-hydroxyberbine skeleton. We now wish to report the first synthesis of berberastine, along the lines developed earlier³.

The deoxybenzoin (2)⁴ was converted by standard procedures into the secondary amine (3), which was treated with aqueous methanolic formaldehyde solution⁵. The resultant mixture of 1,2,3,4-tetrahydroisoquinoline derivatives (4; 27%) and (5; 38%) was separated by preparative scale thin layer chromatography, and each isomer was O-methylated with diazomethane and then cyclised³ with 6N HCl solution. The 5-hydroxyberbine (9) was shown to be identical with an authentic specimen³. The isomeric compound (8), hydrochloride⁶ m.p. 202-203° was dehydrogenated to the quaternary iodide (1a), m.p. >340°. The IR spectrum (KBr disc) was found⁷ to be identical with the published spectrum¹ of berberastine iodide. The NMR spectrum of (1a), which is fully consistent with this structure exhibited the following resonances⁸: 4.08 s [3] (C₁₀-OCH₃); 4.12 s [3] (C₉-OCH₃); 4.7-5.3 m [3] (-CH₂-CH-O-); 6.0 m [1] (OH-removed by deuteration); 6.20 s [2] (CH₂O₂); 7.16 s [1] and 7.83 s [1] (C₁-H and C₄-H); 8.23 d (J=6Hz) [1] and 8.04 d (J=6Hz) [1] (C₁₁-H and C₁₂-H); 9.01 s [1] (C₁₃-H); 9.9 s [1] (C₈-H).

REFERENCES

1. M.M. Nijland, Pharm. Weekblad., **96**, 640 (1961); **98**, 301 (1963).
2. M. Shamma and B.S. Dudock, Tetrahedron Letters, 3825 (1965).
3. S.F. Dyke, D.W. Brown, M. Sainsbury and G. Hardy, Tetrahedron, **27**, 3495 (1971).
4. S.F. Dyke, E.P. Tiley and A.C. White, forthcoming paper.
5. We thank Professor A.R. Battersby for details of a similar experiment conducted in his laboratory.
6. Satisfactory elemental analyses were secured for all compounds synthesised.

7. Unfortunately a sample of the natural product is not available to us for direct comparison.

8. Chemical shifts are expressed in p.p.m. downfield from internal TMS.

