STRUCTURE AND ABSOLUTE CONFIGURATION OF THE OCHROSIA ALKALOID OCHROMIANINE: SYNTHESES OF (±)- AND (-)-OCHROMIANINE

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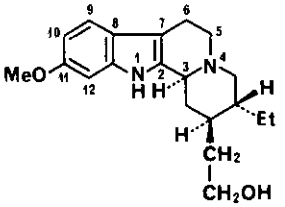
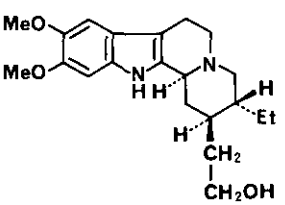
Abstract —— The structure of the Ochrosia alkaloid ochromianine has been established as 11-methoxydihydrocorynantheol [(-)-I] as a result of the racemic and chiral syntheses of the candidate structure I. These syntheses started from the lactim ethers (±)-III and (+)-III, respectively, and proceeded through the intermediates (±)-IV, (±)-VI, and (±)-VIII and through (+)-IV, (+)-VI, and (-)-VIII, respectively.

In 1974, Preaux et al.[1] reported the isolation of ochromianine, a new Corynanthe-type indoloquinolizidine alkaloid, from the bark of Ochrosia miana H. Bn. ex Guill. (family Apocynaceae).[2] They have deduced the structure and absolute stereochemistry of this alkaloid to be (-)-I (absolute configuration shown[3]) from mass, uv, ir, ^{1}H nmr, and cd spectral evidence as well as the negative sign of specific rotation and biogenetic considerations.[1] With a view to confirming the correctness of this con-



(±)-I
(-)-I



II

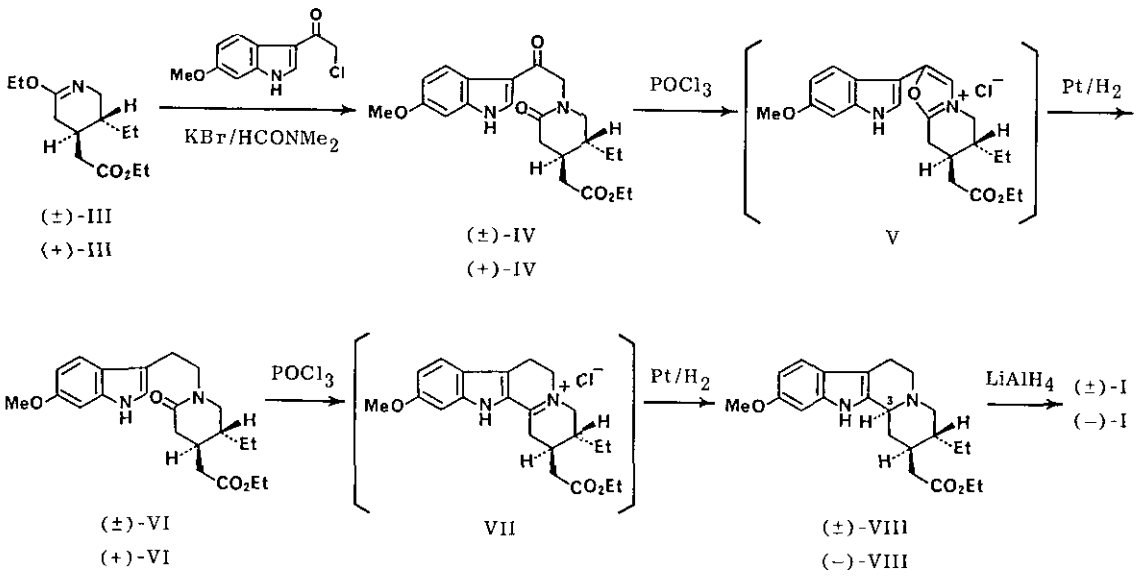


Chart 1

clusion, we carried out both the racemic and chiral syntheses of the candidate structure I in the present study.

The synthesis of I in the racemic and chiral forms was patterned after that of ochropposinine (II), which was recently made feasible by us[4] through the "lactim ether route".[5] Thus, the synthesis of the racemic target (±)-I (Chart 1) started with an initial coupling of the lactim ether (±)-III[6] with 3-chloroacetyl-6-methoxyindole [mp 250–252°C (dec.)],[7] obtainable in 50% yield from 6-methoxyindole[8] by acylation with chloroacetyl chloride and pyridine in toluene (55–60°C, 2 h)[9] according to the general directions of Bergman et al.[10] Treatment of (±)-III with this chloroacetylindole derivative in $HCONMe_2$ at 58°C in the presence of KBr for 48 h gave the lactam ketone (±)-IV (mp 147.5–149°C) in 61% yield. Conversion of (±)-IV into the oxazolium salt (±)-V was effected with $POCl_3$ in boiling toluene for 2 h, and the crude product was reduced by catalytic hydrogenation (Pt/H_2, EtOH, 1 atm, room temp., 2 h) to afford the lactam (±)-VI (mp 98–98.5°C) in 55% overall yield [from (±)-IV]. This two-step reduction of the carbonyl group to a methylene group through the oxazole derivative followed precedents in the literature.[4,11] Bischler–Napieralski cyclization of (±)-VI ($POCl_3$, boiling toluene, 2 h) and catalytic hydrogenation of the resulting quaternary salt (±)-VII (Pt/H_2, EtOH, 1 atm, room

temp., 4 h) produced the tetracyclic ester (±)-VIII [mp 120–124°C; ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3490 (free NH), 3390 (associated NH), 2840, 2810, 2760 (trans-quinolizidine),[12] and 1725 (ester CO)] in 87% overall yield [from (±)-VI]. The hydrogen at C(3) was assigned the α configuration on the analogy of catalytic hydrogenation of similar systems.[13] On reduction with $LiAlH_4$ (tetrahydrofuran, room temp., 1 h), (±)-VIII furnished the desired alcohol (±)-I [mp 174–176°C (dec.)] in 90% yield. Although no sample of natural (–)-ochromianine was available for a direct comparison, the uv (EtOH), ir ($CHCl_3$), ^1H nmr ($CDCl_3$), and mass spectra of (±)-I were found to be virtually identical with those obtained previously[14] with a natural sample, supporting the correctness of the structure and relative stereochemistry proposed for this alkaloid.

A parallel sequence of conversions starting from (+)-III[5c,15] and 3-chloroacetyl-6-methoxyindole (Chart 1) provided (+)-IV [75% yield;[16] mp 98.5–100.5°C; $[\alpha]_D^{21}$ +34.5° (c 0.50, EtOH)], (+)-VI [67% from (+)-IV; mp 81.5–82.5°C; $[\alpha]_D^{19}$ +77.6° (c 0.50, EtOH)], (–)-VIII [91% from (+)-VI;[17] mp 106.5–108.5°C; $[\alpha]_D^{22}$ –22.1° (c 0.50, EtOH)], and (–)-I [87%; mp 162–169°C (dec.); $[\alpha]_D^{25}$ –28.0° (c 1.00, EtOH); $[\alpha]_{577}^{25}$ –29.8° (c 1.00, EtOH); cd (c 1.22×10^{-4} M, EtOH) $[\theta]^{23}$ (nm): +2620 (304) (pos. max.), +660 (285) (neg. max.), +3770 (273) (pos. max.), +1640 (254) (neg. max.), +16500 (238) (pos. max.)]. The chiral identity of the synthetic (–)-I with natural ochromianine [$[\alpha]_{578}^{20}$ –15° (c 1, EtOH)][1] was shown by the same sign of their specific rotations and by their virtually identical cd spectra.[18]

In summary, the structure of the Ochrosia alkaloid ochromianine has now been established as 11-methoxydihydrocorynantheol [(–)-I] as a result of the above racemic and chiral syntheses of I. These syntheses represent additional examples of the extension of the "lactim ether route", originally designed for unified racemic and chiral syntheses of the benzo[a]quinolizidine-type Alangium alkaloids,[5e] to those in the indolo[2,3-a]quinolizidine series.[4,5d]

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REFERENCES

1. (a) N. Preaux, M. Koch, and M. Plat, Phytochemistry, 1974, 13, 2607; (b) N. Preaux, Ph. D.

Thesis, Université Pierre et Marie Curie-Paris VI, June 1976.

2. The name of this species has been revised to Neisosperma miana (Baillon ex-White) Boiteau since 1977: F. R. Forsberg, P. Boiteau, and M.-H. Sachet, Adansonia Ser. 2, 1977, 17, 23.

3. Unless otherwise noted, the structural formulas of optically active compounds in this paper represent their absolute configurations.

4. T. Fujii, M. Ohba, T. Tachinami, H. Miyajima, M. Koch, and E. Seguin, Heterocycles, 1986, 24, 1215.

5. (a) T. Fujii, S. Yoshifuji, and K. Yamada, Chem. Pharm. Bull., 1978, 26, 2071; (b) T. Fujii, M. Ohba, K. Yoneyama, H. Kizu, and S. Yoshifuji, ibid., 1986, 34, 669, and references cited therein; (c) T. Fujii, M. Ohba, K. Shimohata, and S. Yoshifuji, Heterocycles, 1987, 26, 2949; (d) T. Fujii, S. Yoshifuji, and H. Ito, Chem. Pharm. Bull., 1988, 36, 3348; (e) For a recent review, see T. Fujii, M. Ohba, and S. Yoshifuji, Heterocycles, 1988, 27, 1009.

6. (a) T. Fujii and S. Yoshifuji, Chem. Pharm. Bull., 1979, 27, 1486; (b) J. Gutzwiller, G. Pizzolato, and M. R. Uskoković, Helv. Chim. Acta, 1981, 64, 1663.

7. The assigned structures of all new compounds were supported by elemental analyses and/or satisfactory spectral data.

8. (a) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, Tetrahedron, 1958, 2, 1; (b) S. Raucher and G. A. Koolpe, J. Org. Chem., 1983, 48, 2066; (c) P. L. Feldman and H. Rapoport, Synthesis, 1986, 735.

9. A by-product isolated from this reaction mixture was 1-chloroacetyl-6-methoxyindole (2% yield; mp 111–111.5°C).

10. J. Bergman, J.-E. Bäckvall, and J.-O. Lindström, Tetrahedron, 1973, 29, 971.

11. (a) P. C. Young and R. Robinson, J. Chem. Soc., 1933, 275; (b) A. P. Kozikowski and A. Ames, J. Org. Chem., 1980, 45, 2548.

12. (a) E. Wenkert and D. K. Roychaudhuri, J. Am. Chem. Soc., 1956, 78, 6417; (b) F. Bohlmann, Chem. Ber., 1958, 91, 2157.

13. E. E. van Tamelen and J. B. Hester, Jr., J. Am. Chem. Soc., 1969, 91, 7342.

14. The log ε value (2.65) at λ_{max} 268 nm reported in ref. 1a for the uv spectrum of natural ochromianine in EtOH is apparently too small. For a correct value, see Fig. 28 in ref. 1b, p. 93.

15. T. Fujii, M. Ohba, K. Yoneyama, and H. Kizu, Chem. Pharm. Bull., 1985, 33, 358.

16. The reaction was carried out at 60°C for 72 h.

17. The period of each of the cyclization and the reduction was 1 h.

18. The values previously published[1] for Δε in the cd spectrum of natural ochromianine are apparently about 5 times as large as those of the synthetic (−)-I. This initial mistake is most likely due to a transcription or calculation error.

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