AN APPROACH TO INDOLOQUINOLIZIDINE ALKALOIDS VIA FOLATE MODELS*

Axel R. Stoit and Upendra K. Pandit
Organic Chemistry Laboratory, University of Amsterdam, Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

Abstract — Carbon fragment transfer via a 5,10-methylenetetrahydrofolate model has been utilized in the crucial step in the synthesis of heterocyclic systems related to indoloquinolizidine alkaloids.

As a part of our continued interest in the synthetic applications of carbon fragment-transfer methodology, via methylenetetrahydrofolate models, we have recently reported the syntheses of several heterocyclic compounds related to alkaloids. In this communication we report a convenient approach to indoloquinolizidine alkaloids.

The required substituted 5,10-methylenetetrahydrofolate model 3a, which was prepared by reaction of anion of 1 with tetrahydroprimidinium salt 2, underwent ring opening during work up to the acyclic tautomer 3b. The salt 2, a model of 5,10-methenyltetrahydrofolate, is available as a crystalline shelf reagent in our laboratory. Transfer of the C(2) carbon fragment of 3 to tryptamine leads to the central intermediate 4 (85%), whose structure is attested by its spectral data. The structure of 4 incorporates all the carbon and nitrogen atoms required for the synthesis of nor-deplancheine 9. The synthetic sequence starts out with a reductive ring-closure of 4 to piperidone 5, followed by a Bischler-Napieralski cyclization to 6, in good overall yield. NaBH₄ reduction of 6 results in a mixture of diastereomeric esters corresponding to 7a,b (NMR: cis, COOEt 56%; trans, COOEt 24%). Basic hydrolysis of the esters and acidification provides 2,3 in quantitative yields. Conversion of indoloquinolizidine acids 7a,b to the precursor of nor-deplancheine 8 was achieved via known methodology involving acetic anhydride mediated ring opening-ring closure sequence. During this reaction the diastereomeric distinction between 7a and 7b is lost. The amide carbonyl in 8 is selectively reduced by DIBAH to give nor-deplancheine (9). The tryptamine derivative 4 can also be converted to a precursor of nor-epiisogesiasschizocate (12). The sequence 4 — 10 — 11 — 12 — 13 is relatively straightforward, although the selective reduc-

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REFERENCES

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Details of the syntheses of 2 and 4 will be presented elsewhere.

Received in the NMR spectra of the mixture, but could not be located in a pure state.

Co3+ replaces Cu2+ in this reaction to a mixture of both the reactants and the products.

The formation of the overall transformation of 14 to 13.
9. (a) T: mp 169°C (MeOH). IR (CHCl₃): 3470 (s), 2820 (m), 2770 (m), 2740 (w), 1725 (s). H NMR (CDCl₃, 250 MHz): 7.74 (1H, bs, NH), 4.15 (2H, q, J = 7.1, COOCH₂CH₃), 3.27 (1H, ddd, J = 11.3, J = 3.9, J = 1.6, C₆H₃eq), 3.22 (1H, bd, J = 10.4, C₁₂bH), 2.49 (1H, t, J = 11.3, C₆H₄ax). C NMR (CDCl₃): 81.81 (C₃), 57.03 (C₉), 21.67 (C₇). PD (m/z) = 298.

(b) mp 158-159°C (MeOH). IR (CHCl₃): 3478 (s), 2810 (m), 2765 (m), 2730 (w), 1728 (s). H NMR (250 MHz, CDCl₃): 7.72 (1H, bs, NH), 4.18-4.06 (2H, m, ABX₃, COOCH₂CH₃), 3.51-3.45 (1H, bm, C₁₂oH), 3.30 (1H, ddd, J = 12.3, J = 5.3, J = 0.9, C₆H₃eq), 2.68-2.58 (3H, m, C₆H₆ax, C₆H₄ax, C₆H₃eq). C NMR (CDCl₃): 40.36 (C₃), 54.73 (C₉), 20.60 (C₇). PD (m/z) = 298.


10. mp 218-219°C (EtOAc). IR (CHCl₃): 3875 (m), 1655 (s), 1612 (a), 1548 (a), 945 (m). H NMR 250 MHz, CDCl₃: 8.07 (1H, bs, NH), 6.27 (1H, t, J = 1.9, C₃aH), 5.34 (1H, bs, C₃aH), 5.26-5.15 (1H, m, C₆H₃eq), 4.90-4.84 (1H, m, J = 11.1, C₁₂bH), 1.84 (1H, ddt, J = 13.0, J = 11.1, J = 4.1 C₆H₃ax). MS Found: 252.1270. Caled for C₁₆H₁₈N₂O: 252.1262.


12. mp 156-167°C (Et₂O) (lit. 106-110°C). IR (CHCl₃): 3475 (s), 3078 (w), 3058 (w), 2810 (m), 2760 (m), 2755 (m), 2740 (m), 1556 (m), 905 (s). H NMR (250 MHz, CDCl₃): 7.70 (1H, bs, NH), 4.86 (1H, d, J = 1.5, C₁₉H), 4.81 (1H, bs, C₁₉H), 3.84 (1H, m, J = 11.6, C₂₁H₃eq), 3.39 (1H, bdd, J = 11.0, J = 2.1, C₁₉H), 13 C NMR (CDCl₃): 110.00 (C₁₉), 143.22 (C₂₀), 61.53 (C₂₁), 21.47 (C₂₂). MS Found: 238.1456. Caled for C₁₆H₁₆N₂O: 238.1470.


14. Reduction of 11 to 12 proceeds only optimally in methanol at -20°C.


16. amorphous. IR (CHCl₃): 3470 (m), 3080 and 3060 (w), 2810 (m), 2780 (w), 1728 (s), 1655 (m), 910 (m). H NMR (250 MHz, CDCl₃): 7.85 (1H, bs, NH), 4.91 (1H, s, C₁₉H), 4.84 (1H, s, C₁₉H), 3.78 (1H, dd, J = 9.0, J = 2.6, C₃H₇), 3.71 (3H, s, COOCH₃), 3.20 (1H, d, J = 12.2, C₂₁H₆eq), 3.07-2.92 (2H, m, C₁₅H₆eq, C₆H₃), 2.99-2.54 (2H, m, C₁₅H₆eq). Irradiation of C₁₉H at 6.4 Hz results in a positive NMR for C₁₅H₆eq. C NMR (CDCl₃): 20.52 (C₂), 34.44 (C₁₄), 36.56 (C₁₃), 37.25 (C₁₆), 54.15 (C₃), 56.93 (C₂₁). MS Found: 310.1678. Caled for CₙH₂₂N₂O₂ 310.1681.