

AN APPROACH TO INDOLOQUINOLIZIDINE ALKALOIDS VIA FOLATE MODELS^oAxel R. Stoit¹ and Upendra K. Pandit*Organic Chemistry Laboratory, University of Amsterdam, Nieuwe Achtergracht
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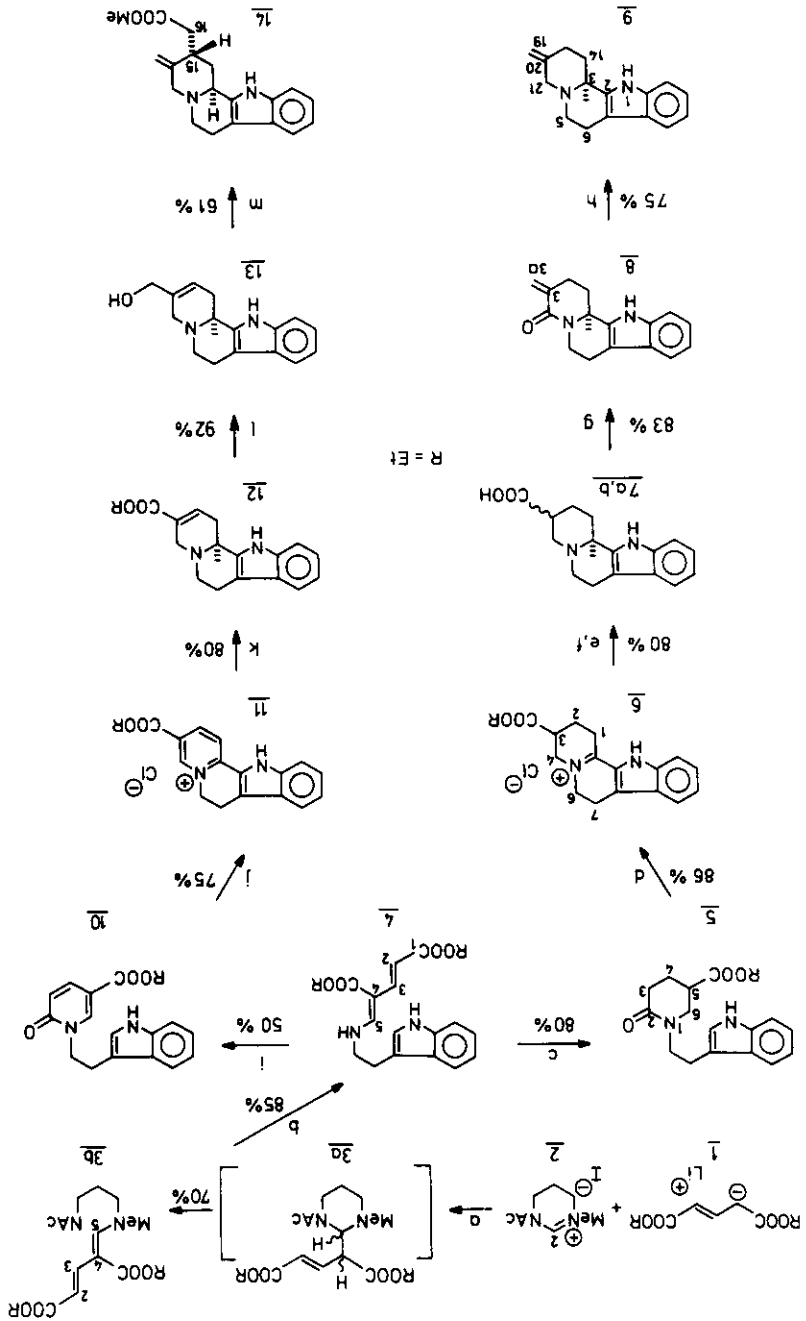
Abstract — Carbon fragment transfer via a 5,10-methylenetetrahydrofolate model has been utilized in the crucial step in the synthesis of heterocyclic systems related to indoloquinolizidine alkaloids.

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 alkaloids². 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 tetrahydropyrimidinium salt 2, underwent ring opening during work up to the acyclic tautomer 3b³. The salt 2, a model of 5,10-methenyltetrahydrofolate, is available as a crystalline shelf reagent in our laboratory⁴. 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 data⁵. The structure of 4 incorporates all the carbon and nitrogen atoms required for the synthesis of nor-deplancheine 9⁶. The synthetic sequence starts out with a reductive ring-closure of 4 to piperidone 5⁷, followed by a Bischler-Napieralski cyclization to 6⁸, 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%)⁹. Basic hydrolysis of the esters and acidification provides 7a,b in quantitative yields. Conversion of indoloquinolizidine acids 7a,b to the precursor of nor-deplancheine 8¹⁰ was achieved via known methodology^{11a-c} 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 DIBALH to give nor-deplancheine (9)^{6,12}. The tryptamine derivative 4 can also be converted to a precursor of nor-epiisogeissoschizoate (14). The sequence 4 → 10 → 11 → 12 → 13¹³ is relatively straightforward, although the selective reduc-

^o Dedicated to Professor G. Stork on the occasion of his 65th birthday.

a. THF, -78°C; b. tryptamine, AcOH / MeCN; Δ : c. NaCNBH₄ / AcOH / MeCN;
 d. POCl₃, PhH; e. NaBH₄ / EtOH; f. (i) OH⁻, (ii) H⁺, H₂O; g. Ac₂O; h. DIBAL / THF;
 i. NaH / THF; j. POCl₃ / PhH; k. NaBH₄ / MeOH; l. DIBAL / THF;
 m. MeC(OMe)₂, CH₂CH₂COOH, xylene, 138°C.



1. Taken in part from the forthcoming doctorate thesis of A. R. Stoit.
2. A. R. Stoit and U. K. Pandit, *Tetrahedron*, 1985, 41, 3355 and references cited therein.
3. 3b: mp 82-84°C. IR (CHCl₃): 1690 (s), 1662 (s), 1600 (s), 1590 (s), 1580 (s). ¹H NMR (250 MHz, CDCl₃): 7.91 (1H, d, J = 15.2, C³H), 7.47 (1H, s, C⁵H), 4.16 (2H, q, J = 7.1, COOCH₂CH₃), 4.08 (2H, q, J = 7.1, COOCH₂CH₃), 2.09 (3H, s, NCH₃). MS Found: 326.1818. Calcd for C₁₆H₂₆N₂O₅ 326.1841.
4. 2: mp 118-120°C (EtOH). IR (KBr): 1730 (s), 1655 (s). ¹H NMR (250 MHz, DMSO-d₆): 9.13 (1H, s, C²H), 3.48 (3H, s, NCH₃), 2.48 (3H, s, NCOCH₃). MS Found: 141.1028. Calcd for C₇H₁₃N₂O₁ 141.1028.
5. 4: mp 100-101°C (Et₂O). IR (CHCl₃): 3480 (m), 1690 (m), 1662 (s), 1595 (vs). ¹H NMR (250 MHz, CDCl₃): 7.76 (1H, d, J = 15.6, C³H), 6.51 (1H, d, J = 15.6, C²H), 6.35 (1H, d, J = 13.6, C⁵H), 4.24 (2H, q, J = 7.1, COOCH₂CH₃), 4.03 (2H, q, J = 7.1, COOCH₂CH₃). MS Found: 356.1720. Calcd for C₂₀H₂₄N₂O₄ 356.1736.
6. M. Hämeilä and M. Louasmaa, *Heterocycles*, 1982, 19, 1517.
7. 5: mp 109-111°C (EtOAc). IR (CHCl₃): 3480 (m), 1730 (s), 1630 (s). ¹H NMR (250 MHz, CDCl₃): 8.18 (1H, bs, NH), 4.12 (2H, q, J = 7.1, COOCH₂CH₃), 3.69-3.63 (2H, m, CH₂CH₂N), 3.47 (1H, dd, J = 12.2, J = 8.8, C⁶H), 3.34 (1H, ddd, J = 12.2, J = 5.2, J = 1.0, C⁶H), 2.73-2.61 (1H, m, CHCOOCH₂CH₃). MS Found: 314.1594. Calcd for C₁₈H₂₂N₂O₃ 314.1630.
8. 6: mp 148-150°C (dec). IR (EtOAc/CH₂Cl₂). IR (CHCl₃): 3300-2700 (m), 1729 (s), 1628 (s), 1550 (s). ¹H NMR (250 MHz, CDCl₃): 12.79 (1H, bs, NH), 4.19-3.90 (6H, m, C⁷H, C⁶H, C⁹H, C¹⁰H), 2.25-2.14 (1H, m, C²H), 2.04-1.95 (1H, m, C²H), 3.38-3.08 (5H, m, C⁷H, C¹¹H, C¹²H), 2.25-2.14 (1H, m, C²H), 2.04-1.95 (1H, m, C²H).

REFERENCES

1. Taken in part from the forthcoming doctorate thesis of A. R. Stoit.

2. A. R. Stoit and U. K. Pandit, *Tetrahedron*, 1985, 41, 3355 and references cited therein.

3. 3b: mp 82-84°C. IR (CHCl₃): 1690 (s), 1662 (s), 1600 (s), 1590 (s), 1580 (s). ¹H NMR (250 MHz, CDCl₃): 7.91 (1H, d, J = 15.2, C³H), 7.47 (1H, s, C⁵H), 4.16 (2H, q, J = 7.1, COOCH₂CH₃), 4.08 (2H, q, J = 7.1, COOCH₂CH₃), 2.09 (3H, s, NCH₃). MS Found: 326.1818. Calcd for C₁₆H₂₆N₂O₅ 326.1841.

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6. M. Hämeilä and M. Louasmaa, *Heterocycles*, 1982, 19, 1517.

7. 5: mp 109-111°C (EtOAc). IR (CHCl₃): 3480 (m), 1730 (s), 1630 (s). ¹H NMR (250 MHz, CDCl₃): 8.18 (1H, bs, NH), 4.12 (2H, q, J = 7.1, COOCH₂CH₃), 3.69-3.63 (2H, m, CH₂CH₂N), 3.47 (1H, dd, J = 12.2, J = 8.8, C⁶H), 3.34 (1H, ddd, J = 12.2, J = 5.2, J = 1.0, C⁶H), 2.73-2.61 (1H, m, CHCOOCH₂CH₃). MS Found: 314.1594. Calcd for C₁₈H₂₂N₂O₃ 314.1630.

8. 6: mp 148-150°C (dec). IR (EtOAc/CH₂Cl₂). IR (CHCl₃): 3300-2700 (m), 1729 (s), 1628 (s), 1550 (s). ¹H NMR (250 MHz, CDCl₃): 12.79 (1H, bs, NH), 4.19-3.90 (6H, m, C⁷H, C⁶H, C⁹H, C¹⁰H), 2.25-2.14 (1H, m, C²H), 2.04-1.95 (1H, m, C²H), 3.38-3.08 (5H, m, C⁷H, C¹¹H, C¹²H), 2.25-2.14 (1H, m, C²H), 2.04-1.95 (1H, m, C²H).

ACKNOWLEDGEMENT

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Details of the syntheses of **9** and **14** will be presented elsewhere.

recognized in the NMR spectrum of the mixture, but could not be isolated in a pure state.

(15)-isomers **15a,b**. It should be noted that small amounts (~5%) of the COOMe (eq.)-isomer was rearrangement of a gelatoschizate precursor to a mixture of both the axial and the equatorial "epi"-diastereomer **14**, as the major product, is, however, unexpected in view of the reported via a thermal [3,3]-sigmatropic rearrangement is well precedented **15a**. The generation of the tion of **11** - **12** requires carefully controlled conditions **14**. The overall transformation of **13** - **14**

9. (a) 7a: mp 169°C (MeOH). IR (CHCl₃): 3478 (s), 2820 (m), 2770 (m), 2740 (w), 1725 (s). ¹H 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, C₄H_{eq}), 3.22 (1H, bd, J = 10.4, C_{12b}H), 2.49 (1H, t, J = 11.3, C₄H_{ax}). ¹³C NMR (CDCl₃): 41.81 (C₃), 57.03 (C₄), 21.67 (C₇). FD (m/z) = 298.
- 7b: mp 158–159°C (MeOH). IR (CHCl₃): 3478 (s), 2810 (m), 2765 (m), 2730 (w), 1728 (s). ¹H NMR (250 MHz, CDCl₃): 7.72 (1H, bs, NH), 4.18–4.06 (2H, m, ABX₃, COOCH₂CH₃), 3.51–3.45 (1H, bm, C_{12b}H), 3.30 (1H, ddd, J = 12.3, J = 5.3, J = 0.9, C₄H_{eq}), 2.68–2.58 (3H, m, C₄H_{ax}, C₇H_{ax}, C₃H_{eq}). ¹³C NMR (CDCl₃): 40.36 (C₃), 54.73 (C₄), 20.60 (C₇). FD (m/z) = 298.
- (b) M. Lounasmaa and M. Hämeilä, Tetrahedron, 1978, 34, 437.
10. 8: mp 218–219°C (EtOAc). IR (CHCl₃): 3475 (m), 1655 (s), 1612 (s), 1548 (s), 945 (m). ¹H NMR (250 MHz, CDCl₃): 8.07 (1H, bs, NH), 6.27 (1H, t, J = 1.9, C_{3a}H), 5.34 (1H, bs, C_{3a}H), 5.26–5.15 (1H, m, C₆H_{eq}), 4.90–4.84 (1H, m, J = 11.1, C_{12b}H), 1.84 (1H, ddt, J = 13.0, J = 11.1, J = 4.1 C₁H_{ax}). MS Found: 252.1270. Calcd for C₁₆H₁₆N₂O₁ = 252.1262.
11. (a) D. L. Lee, C. J. Morrow and H. Rapoport, J. Org. Chem., 1974, 39, 893. (b) D. Thielke, J. Wegener and E. Winterfeldt, Chem. Ber., 1975, 108, 1791. (c) B. Hachmeister, D. Thielke and E. Winterfeldt, Chem. Ber., 1976, 109, 3825.
12. 9*: mp 166–167°C (Et₂O) (lit. 106–110°C⁶). IR (CHCl₃): 3475 (s), 3078 (w), 3058 (w), 2810 (m), 2780 (m), 2765 (m), 2740 (m), 1556 (m), 905 (s). ¹H NMR (250 MHz, CDCl₃): 7.70 (1H, bs, NH), 4.86 (1H, d, J = 1.5, C₁₉H), 4.81 (1H, bs, C₁₉H), 3.44 (1H, bd, J = 11.6, C₂₁H_{eq}), 3.39 (1H, bdd, J = 11.0, J = 2.1, C₃H), ¹³C NMR (CDCl₃): 110.00 (C₁₉), 143.22 (C₂₀), 61.53 (C₂₁), 21.47 (C₆). MS Found: 238.1456. Calcd for C₁₆H₁₈N₂ 238.1470.
13. P. Rosemund and M. Casult, Tetrahedron Letters, 1983, 24, 1771 and references cited therein.
14. Reduction of 11 to 12 proceeds only optimally in methanol at –20°C.
15. (a) G. Rackur, M. Stahl, M. Walowiak and E. Winterfeldt, Chem. Ber., 1976, 109, 3817.
(b) G. Rackur and E. Winterfeldt, Chem. Ber., 1976, 109, 3837.
16. 14*: amorphous. IR (CHCl₃): 3470 (m), 3080 and 3060 (w), 2810 (m), 2780 (w), 1728 (s), 1655 (m), 910 (m). ¹H 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, C₃H), 3.71 (3H, s, COOCH₃), 3.20 (1H, d, J = 12.2, C₂₁H_{eq}), 3.07–2.92 (2H, m, C₁₅H_{eq}, C₆H), 2.66–2.54 (2H, m, C₁₆H). Irradiation of C₁₉H at δ 4.84 results in a positive NOE for C₁₅H_{eq}. ¹³C NMR (CDCl₃): 20.52 (C₆), 34.44 (C₁₄), 36.56 (C₁₅), 37.25 (C₁₆), 54.15 (C₃), 56.93 (C₂₁). MS Found: 310.1678. Calcd for C₁₉H₂₂N₂O₂ 310.1681.

* Biogenetic numbering system. See W. I. Taylor and J. Le Men, Experientia, 1965, 21, 508.