AN APPROACH TO INDOLOQUINOLIZIDINE ALKALOIDS VIA FOLATE MODELS°

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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 alkaloids[2]. 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 tc the acyclic tautomer 3b[3]. The salt 2, a model of 5,10-methenyltetrahydrofolate, is available as a crystalline shelf reagent in our laboratory[4]. 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[5]. The structure of 4 incorporates all the carbon and nitrogen atoms required for the synthesis of nor-deplancheine 9[6]. The synthetic sequence starts out with a reductive ring-closure of 4 to piperidone 5[7], followed by a Bischler-Napieralski cyclization to 6[8], in good overall yield. $NaBH_4$ 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 8[10] 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 DIBAH 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 → 13[13] is relatively straightforward, although the selective reduc-

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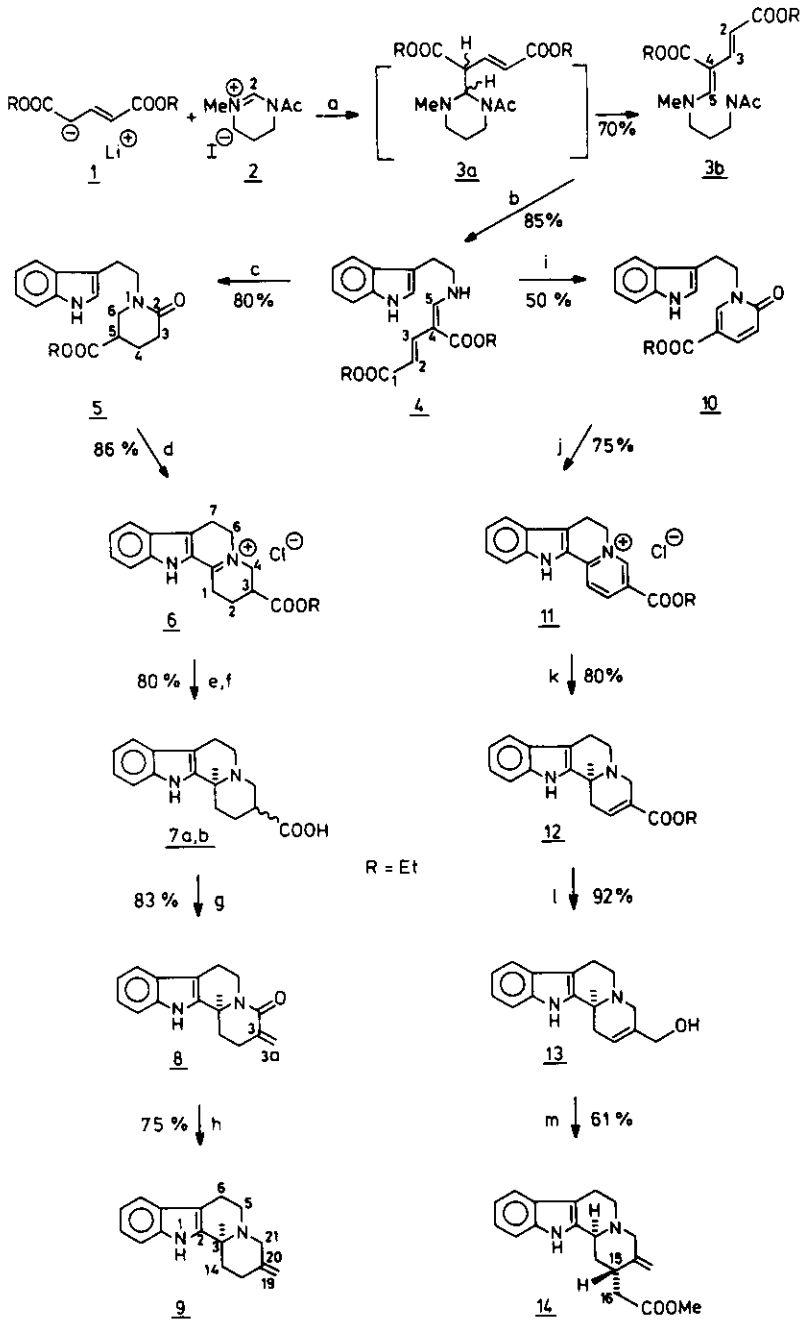
° Dedicated to Professor G. Stork on the occasion of his 65th birthday.



a. THF, -78°C ; b. tryptamine , AcOH / MeCN , Δ ; c. $NaCNBH_4$ / AcOH / MeCN ; d. $POCl_3$, PhH ; e. $NaBH_4$ / EtOH ; f. (i) OH^-, (ii) H^+ H_2O ; g. Ac_2O ; h. DIBAH / THF, CH_2Cl_2 ; i. NaH / THF ; j. $POCl_3$ / PhH ; k. $NaBH_4$ / MeOH ; l. DIBAH / THF ; m. $MeC(OMe)_3$, CH_3CH_2COOH , xylene , 138°C .

tion of 11 → 12 requires carefully controlled conditions[14]. The overall transformation of 13 → 14 via a thermal [3,3]-sigmatropic rearrangement is well precedented[15a]. The generation of the "epi"-diastereomer 14[16], as the major product, is, however, unexpected in view of the reported rearrangement of a geisoschizoate precursor to a mixture of both the axial and the equatorial C(15)-isomers[15a,b]. It should be noted that small amounts (∿ 5%) of the COOMe (eq.)-isomer was recognized in the NMR spectrum of the mixture, but could not be isolated in a pure state. Details of the syntheses of 9 and 14 will be presented elsewhere.

ACKNOWLEDGEMENT

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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 ($CHCl_3$): 1690 (s), 1662 (s), 1600 (s), 1590 (s), 1580 (s). ^1H NMR (250 MHz, C_6D_6): 7.91 (1H, d, J = 15.2, C_3H), 7.47 (1H, s, C_5H), 4.16 (2H, q, J = 7.1, $COOCH_2CH_3$), 4.08 (2H, q, J = 7.1, $COOCH_2CH_3$), 2.09 (3H, s, NCH_3). MS Found: 326.1818. Calcd for $C_{16}H_{26}N_2O_5$ 326.1841.
4. 2: mp 118-120°C (EtOH). IR (KBr): 1730 (s), 1655 (s). ^1H NMR (250 MHz, DMSO-d_6): 9.13 (1H, s, C_2H), 3.48 (3H. s. NCH_3), 2.48 (3H, s, $NCOCH_3$). MS Found: 141.1028. Calcd for $C_7H_{13}N_2O_1$ 141.1028.
5. 4: mp 100-101°C (Et_2O). IR ($CHCl_3$): 3480 (m), 1690 (m), 1662 (s), 1595 (vs). ^1H NMR (250 MHz, C_6D_6): 7.76 (1H, d, J = 15.6, C_3H), 6.51 (1H, d, J = 15.6, C_2H), 6.35 (1H, d, J = 13.6, C_5H), 4.24 (2H, q, J = 7.1, $COOCH_2CH_3$), 4.03 (2H, q, J = 7.1, $COOCH_2CH_3$). MS Found: 356.1720. Calcd for $C_{20}H_{24}N_2O_4$ 356.1736.
6. M. Hämeilä and M. Lounasmaa, Heterocycles, 1982, 19, 1517.
7. 5: mp 109-111°C (EtOAc). IR ($CHCl_3$): 3480 (m), 1730 (s), 1630 (s). ^1H NMR (250 MHz, $CDCl_3$): 8.18 (1H, bs, NH), 4.12 (2H, q, J = 7.1, $COOCH_2CH_3$), 3.69-3.63 (2H, m, CH_2CH_2N), 3.47 (1H, dd, J = 12.2, J = 8.8, C_6H), 3.34 (1H, ddd, J = 12.2. J = 5.2, J = 1.0, C_6H), 2.73-2.61 (1H. m, $CHCOOCH_2CH_3$). MS Found: 314.1594. Calcd for $C_{18}H_{22}N_2O_3$ 314.1630.
8. 6: mp 148-150°C (dec). (EtOAc/CH_2Cl_2). IR ($CHCl_3$): 3300-2700 (m), 1729 (s), 1628 (s), 1550 (s). ^1H NMR (250 MHz, $CDCl_3$): 12.79 (1H, bs, NH), 4.19-3.90 (6H, m, C_4H, C_6H, q, J = 7.1, $COOCH_2CH_3$), 3.38-3.08 (5H, m, C_7H, C_1H, C_3H), 2.25-2.14 (1H, m, C_2H), 2.04-1.95 (1H, m, C_2H),

9. (a) 7a: mp 169°C (MeOH). IR ($CHCl_3$): 3478 (s), 2820 (m), 2770 (m), 2740 (w), 1725 (s). ^1H NMR ($CDCl_3$, 250 MHz): 7.74 (1H, bs, NH), 4.15 (2H, q, J = 7.1, $COOCH_2CH_3$), 3.27 (1H, ddd, J = 11.3, J = 3.9, J = 1.6, C_4H_{eq}), 3.22 (1H, bd, J = 10.4, $C_{12b}H$), 2.49 (1H, t, J = 11.3, C_4H_{ax}). ^{13}C NMR ($CDCl_3$): 41.81 (C_3), 57.03 (C_4), 21.67 (C_7). FD (m/z) = 298.

7b: mp 158-159°C (MeOH). IR ($CHCl_3$): 3478 (s), 2810 (m), 2765 (m), 2730 (w), 1728 (s). ^1H NMR (250 MHz, $CDCl_3$): 7.72 (1H, bs, NH), 4.18-4.06 (2H, m, ABX_3, $COOCH_2CH_3$), 3.51-3.45 (1H, bm, $C_{12b}H$), 3.30 (1H, ddd, J = 12.3, J = 5.3, J = 0.9, C_4H_{eq}), 2.68-2.58 (3H, m, C_4H_{ax}, C_7H_{ax}, C_3H_{eq}). ^{13}C NMR ($CDCl_3$): 40.36 (C_3), 54.73 (C_4), 20.60 (C_7). FD (m/z) = 298.

(b) M. Lounasmaa and M. Hämeilä, Tetrahedron, 1978, 34, 437.

10. 8: mp 218-219°C (EtOAc). IR ($CHCl_3$): 3475 (m), 1655 (s), 1612 (s), 1548 (s), 945 (m). ^1H NMR 250 MHz, $CDCl_3$): 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, C_6H_{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 C_1H_{ax}). MS Found: 252.1270. Calcd for $C_{16}H_{16}N_2O_1$ = 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 (Et_2O) (lit. 106-110°C [6]). IR ($CHCl_3$): 3475 (s), 3078 (w), 3058 (w), 2810 (m), 2780 (m), 2765 (m), 2740 (m), 1656 (m), 905 (s). ^1H NMR (250 MHz, $CDCl_3$): 7.70 (1H, bs, NH), 4.86 (1H, d, J = 1.5, $C_{19}H$), 4.81 (1H, bs, $C_{19}H$), 3.44 (1H, bd, J = 11.6, $C_{21}H_{eq}$), 3.39 (1H, bdd, J = 11.0, J = 2.1, C_3H), ^{13}C NMR ($CDCl_3$): 110.00 (C_{19}), 143.22 (C_{20}), 61.53 (C_{21}), 21.47 (C_6). MS Found: 238.1456. Calcd for $C_{16}H_{18}N_2$ 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 ($CHCl_3$): 3470 (m), 3080 and 3060 (w), 2810 (m), 2780 (w), 1728 (s), 1655 (m), 910 (m). ^1H NMR (250 MHz, $CDCl_3$): 7.85 (1H, bs, NH), 4.91 (1H, s, $C_{19}H$), 4.84 (1H, s, $C_{19}H$), 3.78 (1H, dd, J = 9.0, J = 2.6, C_3H), 3.71 (3H, s, $COOCH_3$), 3.20 (1H, d, J = 12.2, $C_{21}H_{eq}$), 3.07-2.92 (2H, m, $C_{15}H_{eq}$, C_6H), 2.66-2.54 (2H, m, $C_{16}H$). Irradiation of $C_{19}H$ at δ 4.84 results in a positive NOE for $C_{15}H_{eq}$. ^{13}C NMR ($CDCl_3$: 20.52 (C_6), 34.44 (C_{14}), 36.56 (C_{15}), 37.25 (C_{16}), 54.15 (C_3), 56.93 (C_{21}). MS Found: 310.1678. Calcd for $C_{19}H_{22}N_2O_2$ 310.1681.

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

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