A SHORT SYNTHESIS OF 2,2-DISUBSTITUTED BENZO[a]QUINOLINE AND INDOLO[2,3-a]QUINOLIZINE DERIVATIVES VIA CARBON-FRAGMENT TRANSFER FROM A FOLIC ACID MODEL[1]

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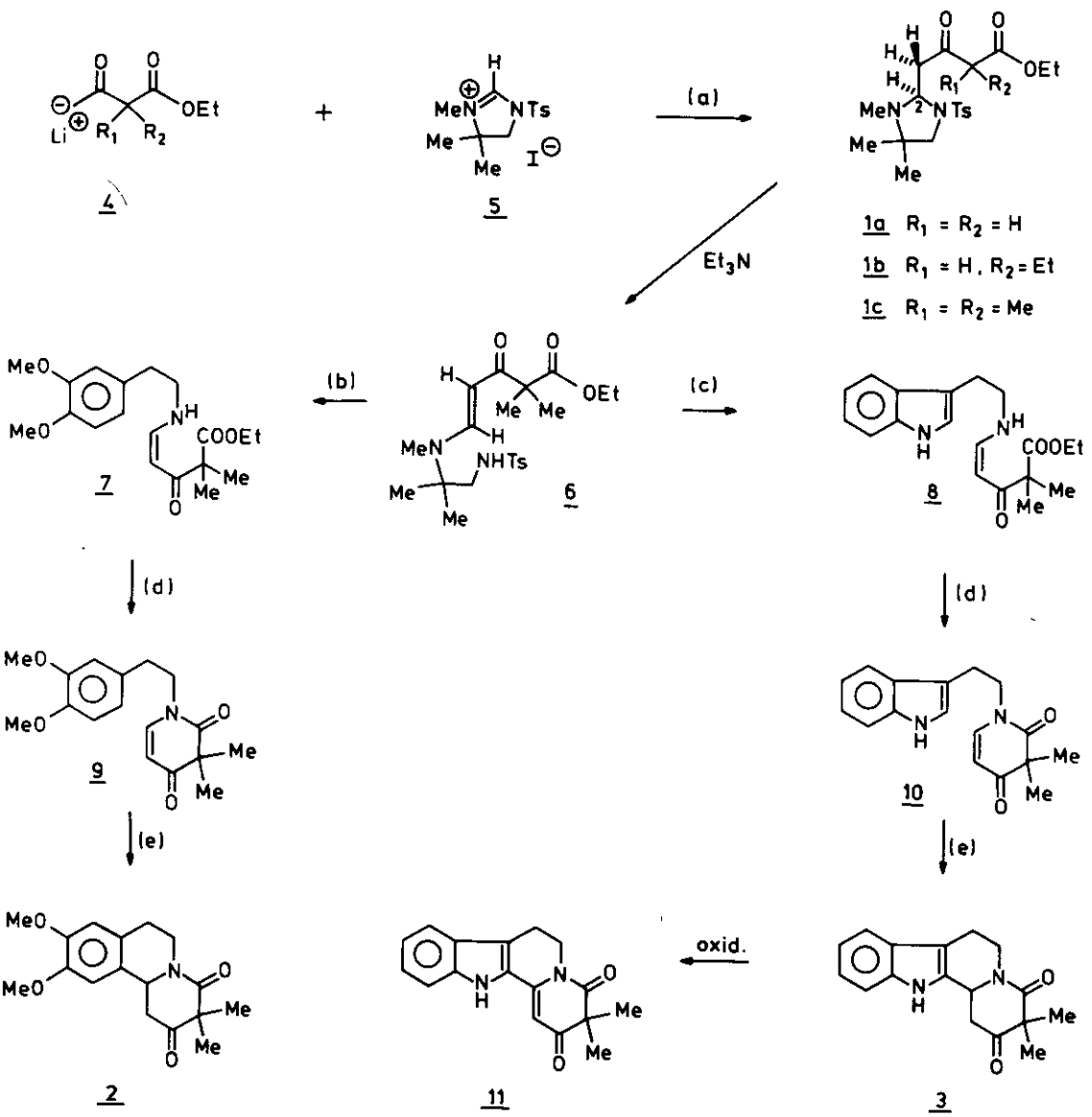
Abstract — 1-Tosyl-2-(3'-ethoxycarbonyl-3'-methyl-2'-oxo)butyl-3,4,4-trimethyl-2,3-imidazolidine - a substituted methylenetetrahydrofolate model - serves as a reagent for the transfer of the 2,2-dimethyl-3-oxo-4-methenylbutanoate moiety to 2-arylethylamine and tryptamine to give products which can be converted to benzo[a]quinolizine and indolo[2,3-a]quinolizine derivatives, respectively, in two simple steps.

As a part of our continued interest in the development of synthetic methodology based upon carbon-transfer reactions of models of folate coenzymes, we recently reported[3] the synthesis and applications of substituted N^5,N^{10}-methylenetetrahydrofolate models 1a,b. The latter models could not, however, be employed for a convenient synthesis of benzo- and indolo-quinolizine ring systems corresponding to the skeletons of compounds 2 and 3, respectively. Although the transfer of C(2) - and the associated substituent of 1a,b - to 2-arylethylamine and tryptamine was achieved, in the first case the intermediate could not be cyclized, while in the second, the β-carboline derivative formed upon initial ring closure was resistant to the second cyclization, except under reducing conditions. These results suggested that enolizable proton(s) in intermediates derived from models 1a,b were interfering with the base catalyzed cyclization, presumably via suppression of the amide anionic species, required for the ring closure step. To test this hypothesis and to develop a facile approach to benzo[a]quinolizine and indolo[2,3-a]quinolizine derivatives we have synthesized the model 1c and examined the reactions leading to its conversion to 2 and 3. The results of the study are presented in this communication.



(a) THF, −40° ; (b) 3,4$(MeO)_2C_6H_3CH_2CH_2NH_2$, MeCN, AcOH, Δ 2h ; (c) tryptamine, MeCN, AcOH, Δ 2h ; (d) NaH / THF, 0° ; (e) HCl / C_6H_6

The imidazolidine derivative 1c was prepared by the addition of anion 4 ($CH_3COC(CH_3)_2COOEt$, LDA/THF, -40°C) to salt 5[4]. The product (1c) was contaminated with varying amounts of 6, depending upon the manner in which the reaction mixture was worked up. It could, however, be readily converted into crystalline 6[5] (mp 130-132°C) by treatment with triethylamine (50°C, 2h). When 6 was allowed to react with 2-(3',4'-dimethoxyphenyl)ethyl amine or tryptamine (AcOH/MeCN, Δ, 3h) the β-keto-δ-amino-γ,δ-unsaturated esters 7[6] and 8[7], respectively, were obtained in good yields.

Orientation experiments aimed at the cyclization reaction sequences of 7 and 8, to the tricyclic and tetracyclic systems 2 and 3, respectively, pointed to the practical advantage of initially accomplishing the ring closure involving the amine and the ester functions. This reaction proceeded in high yields when 7 or 8 was treated with sodium hydride in tetrahydrofuran. The resulting pyridones 9[8] and 10[9] underwent a smooth acid catalyzed (HCl/C_6H_6) cyclization to the polycyclic compounds 2[10] and 3[11], respectively. The indoloquinolizine 3 is prone to air oxidation to the dehydroproduct 11[12]. Thus, in the crystalline state, 3 is a stable compound, when kept under nitrogen at 0°C; while 3 in solution is oxidized either upon standing for long periods or upon handling during attempted purification.

The approach described in this communication can, by employing removable groups (R_1 or R_2) in 1, be utilized in the synthesis of isoquinoline and indole alkaloids. Work in this direction is currently in progress.

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REFERENCES

1. This may be regarded as Part X of the series Models of Folate Coenzymes. Part IX, Tetrahedron, in Press.
2. Taken in part from the forthcoming doctorate thesis of A.R. Stoit, University of Amsterdam.
3. H.C. Hiemstra, H. Bieräugel and U.K. Pandit, Tetrahedron Letters, 1982, 3301.
4. H. Bieräugel, R. Plemp, H.C. Hiemstra and U.K. Pandit, Tetrahedron, in Press.
5. **6**: mp 130-132°C (60%); MS (FD), $M^+ = 424$; IR ($CHCl_3$): 3250, 1715, 1646, 1545;

PMR ($CDCl_3$)*: δ 1.32 (s, 6H, 2 × CH_3), 1.38 (s, 6H, 2 × CH_3), 2.45 (s, 3H, Ar-CH_3), 2.72 (s, 3H, NCH_3), 5.10 (d, 1H, J = 13, =CHCO), 7.92 (d, 1H, J = 13, N-CH=).

6. **7**: oil (80%); MS: Found 349.1906, Calc. for $C_{19}H_{27}NO_5$ 349.1889; IR ($CHCl_3$): 1720, 1635, 1560; PMR ($CDCl_3$)*: δ 1.38 (s, 6H, 2 × CH_3), 2.79 (t, 2H, J = 7, Ar-CH_2), 3.30-3.50 (m, 2H, -CH_2NH), 4.95 (d, 1H, J = 7.5, =CHCO).

7. **8**: oil (80%); MS: Found 328.1794, Calc. for $C_{19}H_{24}N_2O_3$ 328.1786; IR ($CHCl_3$): 1720, 1638, 1560; PMR ($CDCl_3$)*: δ 1.39 (s, 6H, 2 × CH_3), 2.98 (t, 2H, J = 7, Ar-CH_2), 3.40-3.60 (m, 2H, -CH_2NH-), 4.94 (d, 1H, J = 7.5, =CHCO), 6.65 (dd, 1H, NHCH=CH, $J_{CH=CH}$ = 7.5, J_{NH-CH} = 12), 6.95 [d, 1H, indole C(2)-H].

8. **9**: oil (70%), MS: Found 303.1489, Calc. for $C_{17}H_{21}NO_4$ 303.1470; IR ($CHCl_3$): 1695, 1655, 1629; PMR ($CDCl_3$)*: δ 1.39 (s, 6H, 2 × CH_3), 2.88 (t, 2H, J = 7, Ar-CH_2), 3.88 (t, 2H, J = 7, CH_2-N), 5.39 (d, 1H, J = 8, =CHCO), 6.90 (d, 1H, J = 8, N-CH=).

9. **10**: mp 114-115°C (70%), MS: Found 282.1345, Calc. for $C_{17}H_{18}N_2O_2$ 282.1368; IR ($CHCl_3$): 1695, 1655, 1629; PMR ($CDCl_3$)*: δ 1.39 (s, 6H, 2 × CH_3), 3.10 (t, 2H, J = 7, ArCH_2), 3.93 (t, 2H, J = 7, CH_2N), 5.26 (d, 1H, J = 7.2, =CHCO), 6.78 (d, 1H, J = 7.2, NCH=), 6.97 [d, 1H, J = 2.5, indole C(2)-H].

10. **2**: mp 168°C (70%); MS: Found 303.1460, Calc. for $C_{17}H_{21}NO_4$ 303.1470; IR ($CHCl_3$): 1725, 1640, 1510; PMR (DMSO-d_6)*: δ 1.25 (s, 3H, CCH_3), 1.28 (s, 3H, CCH_3), 2.67-2.93 (m, 4H), 3.75 (s, 6H, 2 × OCH_3), 6.78 (s, 1H, Ar-H), 6.90 (s, 1H, Ar-H).

11. **3**: mp 214-215°C (70%); MS: Found 282.1345, Calc. for $C_{17}H_{18}N_2O_2$ 282.1368; IR ($CHCl_3$): 1725, 1645, 1465, 1430; PMR (DMSO-d_6)*: δ 1.28 (s, 3H, CCH_3), 1.29 (s, 3H, CCH_3), 2.71-3.05 (m, 4H, 7.01, 7.10, 7.37, 7.46 (dt, dt, d, d respectively, 4H, Ar-H).

12. **11**: mp 258-260°C (70%); IR ($CHCl_3$): 1690, 1620, 1605; PMR (DMSO-d_6)*: δ 1.35 (s, 6H, 2 × CH_3), 3.09 (t, 2H, J = 6.4, Ar-CH_2), 4.07 (t, 2H, J = 6.4, CH_2N), 6.08 (s, 1H, =CHCO).

*characteristic chemical shifts.

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