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MODELS OF FOLATE COFACTORS 18.[1] APPLICATION IN AN APPROACH TO THE SYNTHESIS OF INDOLOQUINOLIZINE ALKALOIDS

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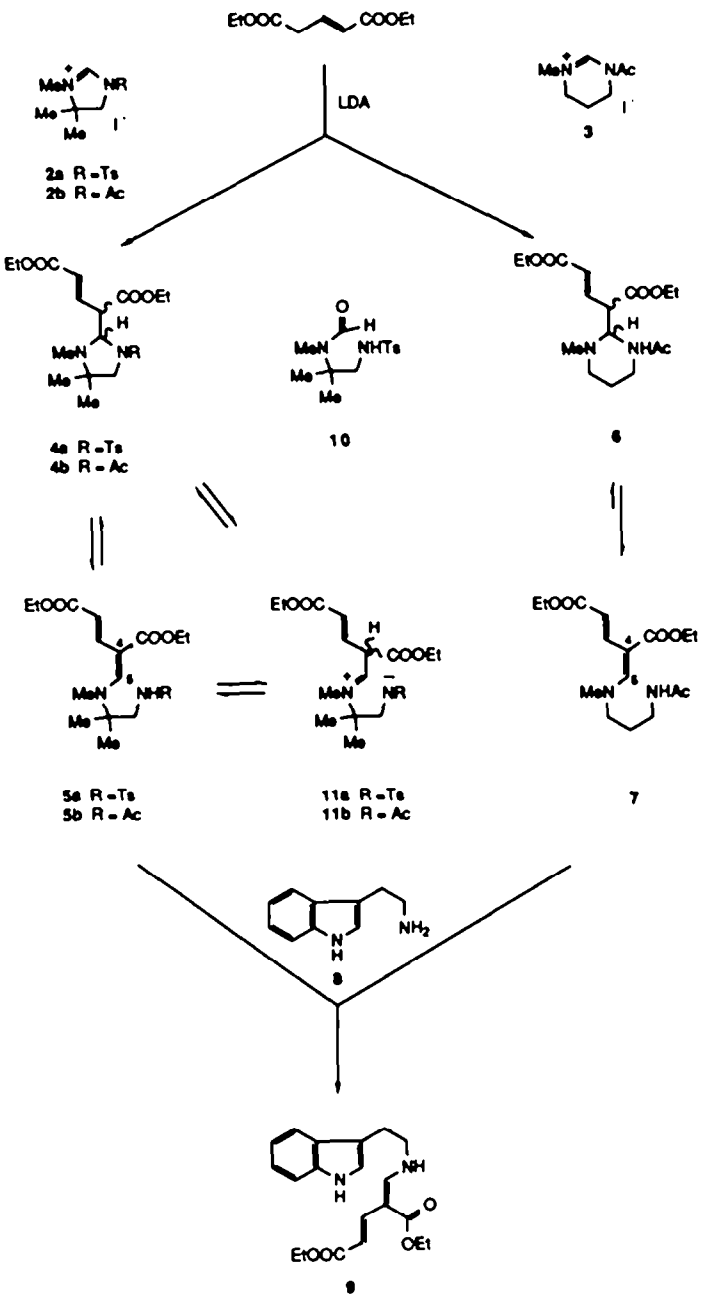
Abstract - The substituted 5,10-methylenetetrahydrofolate models 5b and 7, prepared by the addition of glutaconate ester anion to 1-acetyl-3,4,4-trimethyl-2-imidazolinium iodide (2b) and 1-acetyl-3-methyl-1,4,5,6-tetrahydropyrimidinium iodide (3) transfer the C(2)-carbons with the attached functional groups to give an indole derivative which serves as a convenient precursor for the synthesis of nor-deplancheine (21) and nor-epigeissoschizoate (27).

The chemistry of N,N-unsymmetrically substituted imidazolidines is of special interest in view of the analogy which the heterocycles bear to the functional moiety of the cofactor 5,10-methylenetetrahydrofolate (5,10-CH_2-H_4folate). Appropriately substituted imidazolidines, that is 5,10-CH_2-H_4folate models, exhibit group transfer reactions which constitute crucial steps in the synthesis of several heterocyclic systems,[3a,b] notably those related to β-carboline alkaloids.[4a,b] As a part of our continued interest in the synthetic application of the folate cofactor models, we now report a convenient approach to the synthesis of the indoloquinolizine alkaloids nor-deplancheine (21) and nor-epigeissoschizoate (27). A preliminary report on this has been published earlier.[5]

The chosen strategy envisaged the transfer of a functionalized carbon fragment, from a suitable 5,10-CH_2-H_4folate model, to tryptamine, to result in the formation of an intermediate which could be readily elaborated to the desired indoloquinolizine system. The "reagents" capable of conveniently delivering the required carbon fragment were recognized in the folate models 4a,b and 6 formed by the addition of glutaconate ester anion (1, Scheme I) to imidazolinium and tetrahydropyrimidinium salts 2a,b[6] and 3, respectively. The initially formed products 4a,b and 6 undergo ring-opening to the corresponding enamine esters (5a,b and 7, respectively). The E-configuration of these esters is based upon the chemical shift of the C(5)-protons. For 5a,b and 7 the C(5)-protons resonate at δ 8.04, 8.05 and 7.47, respectively. These are significantly deshielded by the C(4)-ester function, in comparison to the analogous proton (δ 6.35, J = 13.6) in the related compound 9 (to be described in the sequel), in which the Z-geometry is assumed on grounds of earlier work.[3,4]

The projected transfer of the six-carbon fragment from the three models, to tryptamine, reveals some interesting differences. Whereas, reactions of 5b and 7 with tryptamine, under the standard conditions (AcOH, MeCN, 60°C) result in high yields (85%) of the expected diester 9, a similar reaction of 5a leads to the quantitative formation of product 10[6] and glutaconate ester. To explain this, it has to be assumed that under the reaction conditions, 5a reverts back to 4a, which fragments into glutaconate ester and salt 2a. Hydrolysis of the latter salt constitutes the source of 10. The difference in the behaviours of 5a and 5b has its roots in the difference in the pK_a's of the tosylamide (pK_a 10) and the acyl amide (pK_a 15) groups.[7] From these pK_a values it follows that in the tautomeric equilibrium of 5 ⇌ 11, the ratio 11a/5a will be much higher than 11b/5b.


EtOOC
COOEt
LDA
MeN
NR
Me
Me
I⁻
2a R = Ts
2b R = Ac
MeN
NAc
I⁻
3
EtOOC
COOEt
H
MeN
NR
Me
Me
4a R = Ts
4b R = Ac
O
H
MeN
NHTs
Me
Me
10
EtOOC
COOEt
H
MeN
NHAc
6
EtOOC
COOEt
MeN
NHR
Me
Me
5a R = Ts
5b R = Ac
EtOOC
H
COOEt
MeN
NR
Me
Me
11a R = Ts
11b R = Ac
EtOOC
COOEt
MeN
NHAc
7
NH2
N
H
8
NH
O
OEt
EtOOC
N
H
9

Scheme 1

Intermediate 11a obviously lies, via 4a, on the route to 10. In comparing 4b ⇌ 5b with 6 ⇌ 7, it should be remarked that the transfer reaction via 7, to 8, is appreciably faster than via 5b. This is presumably due to the higher concentration of 7 in the equilibrium mixture (6 ⇌ 7); the cyclic form being relatively disfavoured owing to entropic effects, arising from a longer (6 versus 5) chain length and the absence of the gem-dialkyl (Thorpe-Ingold) effect.[8a,b]

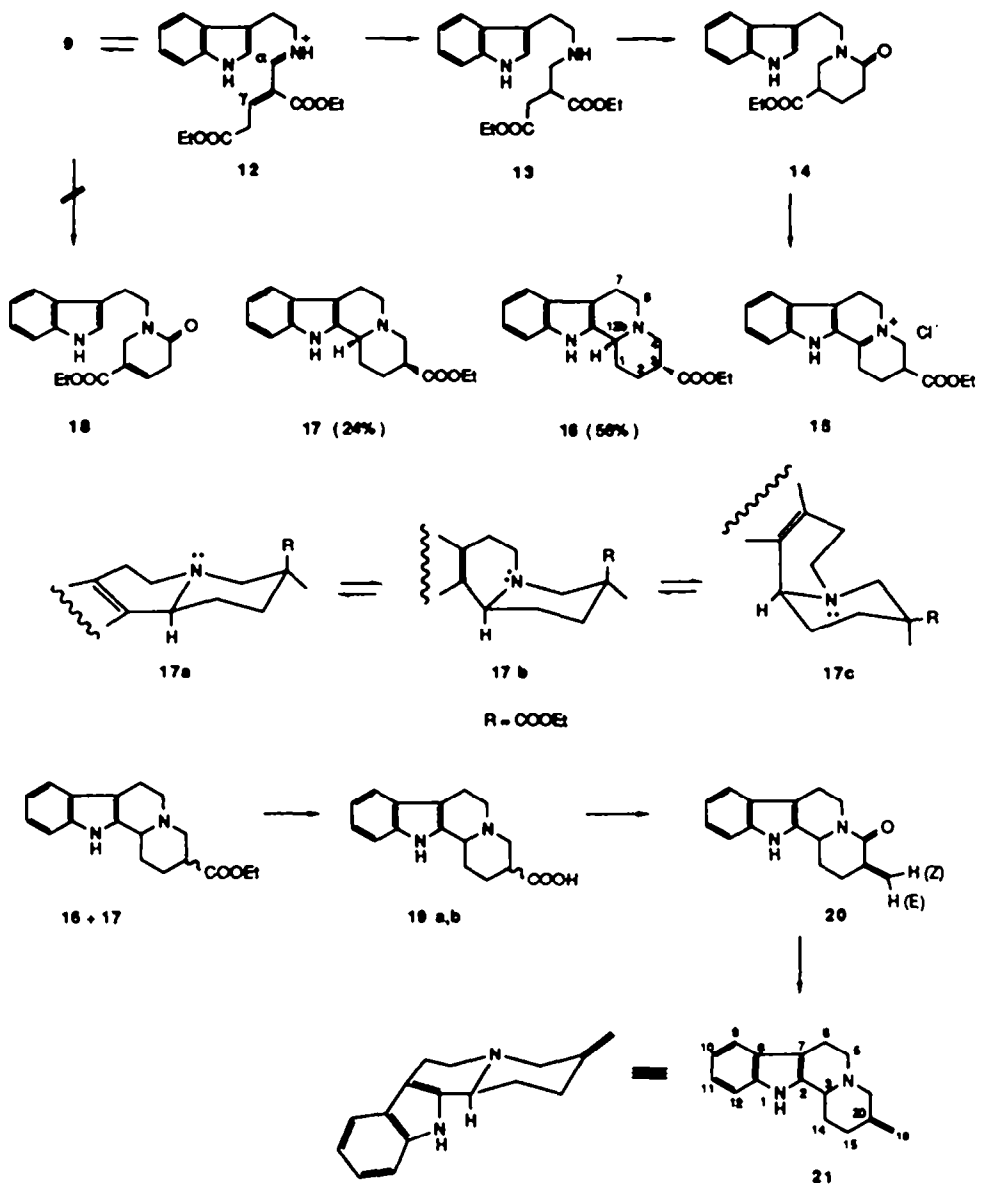
Reduction of dienamine diester 9 by $NaCNBH_3$, in the presence of acetic acid, followed by heating (60°C, 24 h) resulted in the formation of piperidone (14) in 80% yield. The latter obviously arises from the intramolecular aminolysis of the initially formed amino diester 13. From the structure of 14 it can be assumed that the reduction process involves a hydride addition to C(γ) of the conjugated iminium salt 12 to give the corresponding enamine, which is protonated and subsequently converted into 13 via a second reduction step. The absence of 18 in the reaction mixture suggests that reduction of 12 does not proceed by an initial C(α)-hydride addition. The observed regioselectivity is in contrast to the $NaCNBH_3/CH_3COOH$ [9] reductions of analogous dienamine esters reported in the literature.[10a,b]

The Bischler-Napieralski cyclization ($POCl_3$, benzene, 80°C, 4h)[11] of 14 gave the expected salt 15, which was reduced ($NaBH_4$) to a mixture of pyridocarbazole esters 16 and 17 in good overall yield (80%). The ^{13}C NMR spectra[12,13a-c] of 16 and 17 throw light upon the conformation of the molecules. Especially relevant in this connection are the chemical shifts of carbons C(1)- to C(4)- in the compounds. In 16 these lie at δ 28.99 [C(1)-], 27.04 [C(2)-], 41.81 [C(3)-] and 57.03 [C(4)-], attesting by comparison with literature data to a trans quinolizine ring system with an equatorial configuration of the ester group. In the case of 17, the same carbons exhibit resonance signals at δ 27.05, 24.38, 40.36 and 54.73, respectively. These values are in complete agreement with those reported for the corresponding axial methyl ester.[13c] However, based upon the expected displacements of chemical shifts for α-, β- and γ-carbons, which are observed upon introduction of an axial substituent in the C(3)-position of the indoloquinolizine skeleton, it can be concluded that 17 consists of an equilibrum mixture of conformational isomers 17a ⇌ 17c. Comparison of the chemical shifts for C(7) in 16 (δ 21.67) and 17 (δ 20.60) reveals that while 16 is completely in the trans-quinolizine form, 17 on the other hand, is a 76:24 mixture of 17a and 17c.[14a,b,15] In line with these data, the weaker Bohlmann bands[16] in 17, compared to those in 16, attest to contribution of the cis-quinolizine conformational isomer 17c.[14b]

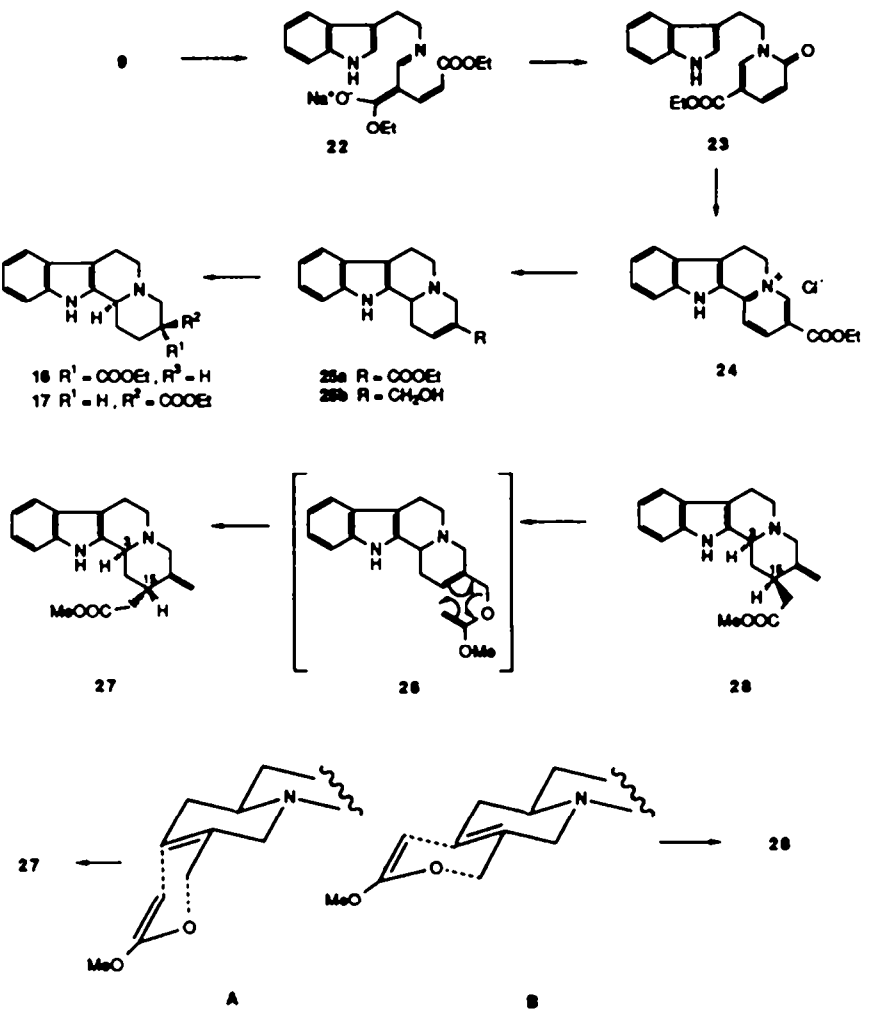
The esters 16 and 17, derived from the carbon-fragment transfer product 9, constitute readily available intermediates for the synthesis of 18-nor-deplancheine (21, Scheme II). The esters were hydrolysed to the corresponding acids 19a,b, which were, subsequently, either apart or as a mixture, subjected to the methylene-lactam rearrangement[18a,b,19,20a-d] by treatment with acetic anhydride. The reaction proceeded smoothly to give the methylene lactam 20 as a crystalline product, in 83% yield. The amide group in 20 could be reduced by diisobutylaluminiumhydride[21a,b] with the formation of 18-nor-deplancheine (21), which is stable under nitrogen but oxidizes when exposed to air. The structure of 21 [17] is derived from ^{13}C-^1H correlation NMR spectra (vide Experimental). Characteristic Bohlmann bands[16] and ^{13}C-shifts[14] for C(3) and C(6) at δ 59.30 and 21.47, respectively, show that the molecule incorporates a trans quinolizine moiety.

The dienamine ester 9 is a versatile intermediate, since it also serves as a starting material for the synthesis of compounds related to geissoschizoate[22] (Scheme III). To this end, 9 was subjected to base-catalyzed cyclization. Using sodium hydride as base, the cyclization reaction was studied in different solvents. In tetrahydrofuran, cyclization was slow and formation of 23 (Scheme III) was incomplete (54%) even after 6 days at 60°C. On the other hand, in benzene (80°C, 3h) 80% 23 [21a,b] was obtained. Presumably, rotational barrier to the formation of the productive conformer 22, accounts for this difference.

Application of the Bischler-Napieralski cyclization to pyridone 23 gave the expected quinolizinium salt 24 [21a] which could be reduced by sodium borohydride, at low temperature (-20°C), in methanol, but not in ethanol, to the unsaturated ester 25a.[21a] The observed influence of the solvent has its origin in the difference between the pK_as of methanol (16) and ethanol (17). Presumably, the dienamine species, formed in the first reduction step[23] is not effectively protonated by ethanol to the iminium intermediate, which serves as the precursor of 25a. When the reduction was



Scheme II


9
22
23
24
16 R¹ = COOEt, R² = H
17 R¹ = H, R² = COOEt
25a R = COOEt
25b R = CH₂OH
27
26
28
A
B

Scheme 8

started in ethanol and after a time methanol was added to the mixture, besides 25a, the fully reduced ester 17 was also formed in the reaction. Significantly, 17 could be obtained in 90% yield from 25a, by reduction with sodium borohydride in ethanol (20°C, 28 h). The stereoselective formation of 17, with an axial ester group is noteworthy. That this is the kinetically formed product is attested by the fact that when 17 is stirred in ethanol, in the presence of catalytic amounts of sodium ethoxide, it is converted (97%) into the thermodynamically favoured isomer 16 with the ester group in the equatorial configuration. In contrast to these results, reduction of 25a by lithium borohydride (in ethanol) proceeds slowly and leads to a mixture of 16 and 17. From an analysis (TLC, NMR) of the reaction mixture formed by the borohydride reduction, it is revealed that during the course of the reaction the axial ester 17 is converted into its equatorial isomer 16 and that this process is responsible for the origin of the major part of 16.

With the ester 25a in hand, the stage was set for the synthesis of a 18-nor-geissoschizoate system, via an approach involving a [3,3]-sigmatropic rearrangement of a suitable allyl vinyl ether.[18b,22,24] Ester 25a was smoothly reduced (92%) by diisobutylaluminium hydride to the corresponding allylic alcohol 25b.[21] When 25b was treated with 1,1,1-trimethoxyethane, in the presence of a catalytic amount of propionic acid (138°C, 150 min), the reaction led to a mixture from which 18-nor-epigeissoschizoate 27 (61%) and 18-nor-geissoschizoate 28 (4%) were isolated. The reaction proceeds via the formation and subsequent rearrangement of intermediate 26. The transition state of this rearrangement is assumed to possess a six-membered chair-like geometry.[18b,25] The closely related case, where such a geometry rationalizes the experimental results, is that of the synthesis of the isomeric isogeissoschizines.[22] In the rearrangement of 26, transition states represented by structures A and B (Scheme III) would have to be invoked to account for the formation of isomers 27 and 28, respectively. A comparison of structures A and B suggests that B would be favoured over A in view of the trans- versus cis-decalin type stereochemistry. Clearly, the formation of 27 as the major product, is not in line with this reasoning. The observed result can, however, be accounted for by taking into consideration the known acid catalyzed isomerization of the cis C(3)-H, C(15)-H to the trans C(3)-H, C(15)-H indolo [2,3-a]quinolizine system.[26] Evidence that this indeed was the case was derived from the experiment in which pure 28 was heated (138°, 150 min) with propionic acid, whereupon the formation of about 50% 27 was observed.

The synthesis of 21 and 27 plus 28 from 9 and that of 17, via 25a, illustrate the application of the folate model mediated functionalized group transfer methodology.

EXPERIMENTAL

All mps are uncorrected. IR spectra were recorded on a Perkin Elmer 257 spectrometer. The absorptions are given in cm^{-1}. PMR spectra were run on a Bruker WM 250 instrument, using TMS as an internal standard. Mass spectra were obtained with a Varian Matt 711 spectrometer. Analyses were carried out at the microanalytical laboratory, Department of Physical Organic and Analytical Chemistry, Organic Chemistry Institute, TNO, Zeist, The Netherlands.

1-Acetyl-3-methyl-1,4,5,6-tetrahydropyrimidinium iodide (3).
To a solution of 8 g (63.5 mmol) of 1-acetyl-1,4,5,6-tetrahydropyrimidine[5] in dry CH_2Cl_2 (150 ml) was added 18 g CH_3I, dissolved in 20 ml CH_2Cl_2 (0°C, N_2). Stirring was continued for 18 hr. The resulting white crystals obtained after filtration were washed with Et_2O.
3: Yield 12.76 g (47.61 mmol, 75%); mp 118-120°C (EtOH). IR (KBr): 1730 (s), 1655 (s), 1360 (s). PMR (DMSO-d_6): 2.06 (2H, q, J = 5.8, $NCH_2\underline{CH_2}CH_2N$), 2,48 (3H, s, $COCH_3$), 3.48 (3H, s, NCH_3), 3.55 and 3.66 (4H, 2xt, J = 5.8, $\underline{NCH_2}CH_2\underline{CH_2}N$), 9.13 (1H, s, C_2H). Found: C, 31.18; H, 4.94; N, 10.40. $C_7H_{13}N_2O_1I_1$ requires C, 31.37; H, 4.89; N, 10.45.

Ethyl 5-[2-(tosylamino-1,1-dimethyl)ethyl methyl]amino-4-ethoxycarbonyl-pentadienoate (5a).
To a stirred solution of 10 mmol LDA in 150 ml THF was added 1.86 g (10 mmol) diethylglutaconate 1 dissolved in 5 ml THF (-78°C, N_2). After an additional stirring for 15 min 3.94 g of 2a (10 mmol) was added to the reaction mixture. The reaction mixture was vigorously stirred for 1 hr at -40°C and 2 hr at 0°C, after which the solvent was evaporated off. The residue was chromatographed using EtOAc on SiO_2. Recrystallization from Et_2O gave 5a as white crystals.
5a: Yield 3.25 g (7.2 mmol, 72%); mp 128-129°C. IR ($CHCl_3$): 3380 (w), 3300-3100 (w), 1690 (s), 1685 (s), 1665 (s), 1652 (s), 1609 (s), 1600 (s), 1585 (s), 1578 (s), 1568 (s), 1162 (s). PMR (C_6O_6): 0.87 (6H, s, $NC(CH_3)_2$), 1.07 (6H, t, J = 7.1, 2x $COOCH_2\underline{CH_3}$), 1.96 (3H, s, $TosCH_3$), 2.57-2.69 (5H, m, NCH_3 and $\underline{CH_2}NH$), 4.01-4.16 (4H, m, 2x $COO\underline{CH_2}CH_3$), 6.01-6.18 (1H, bs, NH), 6.79 (1H, d, J = 15,7, C_2H), 6.91 and 7.86 (4H, 2x d, J = 7.7, TosArH), 8.04 (1H, s, C_5H), 8.15 (1H, d, J = 15.7, C_3H). Found: M^+, 452.1981. $C_{22}H_{32}N_2O_6S_1$ requires M^+, 452.1981.

Ethyl 5-[2-(acetylamino-1,1-dimethyl)ethyl methyl]amino-4-ethoxycarbonyl-pentadienoate (5b).
Procedure was identical with that of 5a (2b was used instead of 2a). After chromatography (Al_2O_3 EtOAc/EtOH 95:5) 5b was obtained as a yellow oil which was crystallised from Et_2O/hexane (white crystals).
5b: Yield 2.41 g (7.10 mmol, 71%); mp 86°C. IR ($CHCl_3$): 3450 (w), 3400-3250 (w), 1690 (s), 1675 (s), 1655 (s), 1610 (s), 1570 (s), 1520 (s). PMR (C_6D_6): 0.77 (6H, s, $NC(CH_3)_2$), 1.07 (6H, t, J = 7.1, 2x $COOCH_2\underline{CH_3}$), 1.70 (3H, s, $COCH_3$), 2.70 (3H, s, NCH_3), 2.99 (2H, d, J = 6.4, $\underline{CH_2}NH$), 4.10-4.21 (4H, m, 2x $COO\underline{CH_2}CH_3$), 5.72 (1H, bs, NH), 6.74 (1H, d, J = 15.6, C_2H), 8.05 (1H, s, C_5H), 8.21 (1H, d, J = 15.6, C_3H). Found: $\underline{M}^+$, 340.1983. $C_{17}H_{28}N_2O_5$ requires $\underline{M}^+$, 340.1998.

Ethyl 5-[3-(acetylaminopropyl)methyl]amino-4-ethoxycarbonyl-pentadienoate (7).
Procedure was identical with that of 5a, except that 3 instead of 2a and a longer reaction time (3 hr at -30°C and 1 hr at 0°C) was used. After removal of the solvent, the residue was chromatographed on Al_2O_3 using EtOAc/EtOH 95:5. Recrystallization from EtOAc gave 7 as white crystals.
7: Yield 2.25 g (6.9 mmol, 69%); mp 82-84°C. IR ($CHCl_3$): 3450 (w), 3400-3300 (w), 1690 (s), 1662 (s), 1600 (s), 1590 (s), 1580 (s). PMR (C_6D_6): 1.02 and 1.07 (6H, 2x t, J = 7.1, 2x $COOCH_2\underline{CH_3}$), 1.23-1.41 (2H, m, $NCH_2\underline{CH_2}CH_2NH$), 1.83 (3H, s, $COCH_3$), 2.09 (3H, s, NCH_3), 2.74-2.80 (2H, m, CH_3NCH_2), 3.10 (2H, q, J = 6.3, $NCH_2CH_2\underline{CH_2}NH$), 4.09 and 4.16 (4H, 2xq, J = 7.1, 2x $COO\underline{CH_2}CH_3$), 6.40-6.50 (1H, bs, NH), 7.08 (1H, d, J = 15.2, C_2H), 7.47 (1H, s, C_5H), 7.91 (1H, d, J = 15.2, C_3H). Found: $\underline{M}^+$, 326.1818. $C_{16}H_{26}N_2O_5$ requires $\underline{M}^+$, 326.1841.

Ethyl 5-[2-(3-indolyl)ethylamino]-4-ethoxycarbonyl-pentadienoate (9).
A mixture of 7 (2.0 g, 5.88 mmol) and 3 eq tryptamine (2.82 g, 17.64 mmol) was stirred in CH_3CN (30 ml) and CH_3COOH (3 ml) under nitrogen (60°C, 150 min). After removal of the solvent, the residue was chromatographed on SiO_2 using EtOAc. Crystallization from Et_2O gave 9 as white crystals (-20°C, 18 hr).
9: Yield 1821 mg (5.12 mmol, 87%); mp 100-101°C. IR ($CHCl_3$): 3490 (s), 3350-3250 (w), 1690 (s), 1662 (s), 1620 (s), 1595 (s). PMR (C_6D_6): 0.97 and 1.10 (6H, 2x t, J = 7.1, 2x $COOCH_2\underline{CH_3}$), 2.41 (2H, t, J = 6.5, $\underline{CH_2}CH_2NH$), 2.69 (2H, q, J = 6.5, $CH_2\underline{CH_2}NH$), 4.03 and 4.24 (4H, 2x q, J = 7.1, 2x $COO\underline{CH_2}CH_3$), 6.35 (1H, d, J = 13.6, C_5H), 6.40 (1H, d, J = 2.4, indole C_2H), 6.51 (1H, d, J = 15.6, C_2H), 6.92-6.94 (1H, bs, indole NH), 7.04-7.24 (m, C_6H_6 and indole (C_5H, C_6H and C_7H)), 7.37 (1H, d, J = 7.5, indole C_4H), 7.76 (1H, d, J = 15.6, C_3H), 8.94-9.04 (1H, bs, NH). Found: $\underline{M}^+$, 356.1720. $C_{20}H_{24}N_2O_4$ requires $\underline{M}^+$, 356.1736.

A mixture of 5b (2.0 g, 6.13 mmol) and tryptamine (2.95 g, 18.4 mmol) was stirred in CH_3CN (30 ml) and CH_3COOH (3 ml) under nitrogen (60°C, 210 min). Identical work-up gave 9 (85%).

5-Ethoxycarbonyl-1-[2-(3-indolyl)ethyl]-piperidine-2-one (14)
A mixture of 9 (1.5 g, 4.21 mmol), 1.06 g $NaBCNH_3$ (16.8 mmol), 40 ml CH_3CN and 4 ml CH_3COOH was vigorously stirred under nitrogen (20°C, 43 hr). The reaction was monitored on SiO_2 using EtOAc as eluent. Stirring was continued for 24 hr at 60°C. The resulting mixture was poured into a concentrated $NaHCO_3$ soln and extracted with Et_2O. The organic layer was treated with a concentrated NaCl soln, dried over Na_2SO_4 and concentrated. Chromatography on SiO_2 with EtOAc gave yellow crystals which where recrystallized from EtOAc.
14: Yield 1.06 g (3.38 mmol, 80%); mp 109-111°C. IR ($CHCl_3$): 3480 (m), 1730 (s), 1630 (s). PMR ($CDCl_3$): 1.23 (3H, t, J = 7.1), $COOCH_2\underline{CH_3}$), 1.77-2.11 (2H, m, $C_4H_{eq,ax}$), 2.31-2.54 (2H, m, $C_3H_{eq,ax}$), 2.61-2.73 (1H, m, C_5H_{ax}), 3.02 (2H, bt, J = 7.6), $\underline{CH_2}CH_2N$), 3.34 (1H, ddd, J = 1.0, J = 5.2, J = 12.2, C_6H_{eq}), 3.47 (1H, dd, J = 8.8, J = 12.2, C_6H_{ax}), 3.66 (2H, bt, J = 7.6, $CH_2\underline{CH_2}N$), 4.12 (2H, q, J = 7.1, $COO\underline{CH_2}CH_3$), 7.03 (1H, d, J = 2.1, indole C_2H), 7.07-7.20 (2H, m, indole (C_5H and C_6H)), 7.34 (1H, d, J = 7.2, indole C_7H), 7.65 (1H, d, J = 7.6, indole C_4H), 8.18 (1H, bs, NH). Found: $\underline{M}^+$, 314.1593. $C_{18}H_{22}N_2O_3$ requires $\underline{M}^+$, 314.1603.

3-Ethoxycarbonyl-1,2,3,4,6,7-12(H)-hexahydroindolo[2,3-a]quinolizinium chloride (15).
A mixture of 14 (1.0 g, 3.18 mmol), 2.33 ml (25.5 mmol, 8 eq) freshly destilled $POCl_3$ and 35 ml benzene was refluxed under nitrogen (4 hr, 80°C). After removal of the solvent, the residue was diluted with dry CH_2Cl_2. Filtration (in soluble material was filtered off) and dilution of the filtrate with EtOAc gave 15 as yellow crystals. Filtration and recrystallization from CH_2Cl_2/EtOAc gave 15 as light yellow crystals.
15: Yield 910 mg (2.73 mmol, 86%); mp 146-150°C. IR (KBr): 3300-2500 (m), 1735 (s), 1720 (s), 1640 (s), 1625 (s), 1570 (s), 1550 (s). PMR ($CDCl_3$): 1.24 (3H, t, J = 7.1, $COOCH_2\underline{CH_3}$), 1.95-2.04 and 2.14-2.25 (2H, 2x m, $C_2H_{eq,ax}$), 3.08-3.38 (5H, m, $C_7H_{eq,ax}$, $C_1H_{eq,ax}$ and C_3H_{ax}), 3.90-4.19 (6H, m, $COOCH_2CH_3$, $C_4H_{eq,ax}$ and $C_6H_{eq,ax}$), 6.98 and 7.25 (2H, 2x t, J = 7.5, C_9H and $C_{10}H$), 7.30 (1H, d, J = 8.2, $C_{11}H$), 7.55 (1H, d, J = 8.5, C_8H), 12.79 (1H, bs, NH).[10] Found: $\underline{M}^+$, 297.1574. $C_{18}H_{21}N_nO_2$ requires $\underline{M}^+$, 297.1603.

3-Ethoxycarbonyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (16, 17).
To a solution of 15 (800 mg, 2.41 mmol) in anhydrous EtOH was added 4x 200 mg $NaBH_4$ (-20°C, under nitrogen). The mixture was stirred for 2 hr (-20°C → 20°C) and diluted with a concentrated NH_4Cl soln. The residue was extracted with Et_2O. The extract was washed with 5% $NaHCO_3$ soln and saturated brine. After drying over Na_2SO_4 and evaporation of the solvent, the crude product was chromatographed on SiO_2 (EtOAc/hexane 1:1). The first product 16 was recrystallized from CH_3OH to give white crystals.
16: Yield 403 mg (1.35 mmol, 56%); mp 169°C. IR ($CHCl_3$): 3478 (m), 2820 (m), 2770 (m), 2740 (m), 1725 (m). PMR ($CDCl_3$): 1.26 (3H, t, J = 7.1, $COOCH_2\underline{CH_3}$), 1.57-1.67 (2H, m, C_1H_{ax}, C_2H_{ax}), 2.11-2.16 (1H, m, C_1H_{eq}), 2.18-2.24 (1H, m, C_2H_{eq}), 2.49 (1H, t, J = 11.3, C_4H_{ax}), 2.62-2.88 (3H, m, C_6H_{ax}, C_7H_{ax}, C_3H_{ax}), 2.91-3.04 (1H, m, C_7H_{eq}), 3.06-3.12 (1H, m, C_6H_{eq}), 3.22 (1H, bd, J = 10.4, $C_{12b}H_{ax}$), 3.27 (1H, ddd, J = 1.6, J = 3.9, J = 11.3, C_4H_{eq}), 4.15 (2H, q, J = 7.1, $COOCH_2CH_3$), 7.04-7.15 (2H, m, C_9H and $C_{10}H$), 7.28 (1H, d, J = 7.8, $C_{11}H$), 7.46 (1H, d, J = 7.5, C_8H), 7.74 (1H, s, NH).[10] ^{13}C NMR (50.32 MHz, $CDCl_3$): 28.99 (C_1), 27.04 (C_2), 41.81 (C_3), 60.49 ($COO\underline{CH_2}CH_3$), 14.18

($COOCH_2CH_3$), 57.03 (C_4), 53.13 (C_6), 21.67 (C_7), 59.44 (C_{12b}), 173.92 (ester CO).[12] Found: 72.67; H, 7.45; N, 9.30. $C_{18}H_{22}N_2O_2$ requires C, 72.50; H, 7.45; N, 9.39.
The second product 17 was recrystallized from CH_3OH to give white crystals.
17: Yield 172 mg (0.58 mmol, 24%); mp 158-159°C. IR ($CHCl_3$): 3478 (s), 2810 (m), 2765 (m), 2730 (w), 1728 (s). PMR ($CDCl_3$): 1.21 (3H, t, J = 7.1, $COOCH_2CH_3$), 1.61-1.74 (1H, m, C_2H_{ax}), 1.87-1.97 (2H, m, $C_1H_{eq,ax}$), 2.09-2.14 (1H, m, C_2H_{eq}), 2.58-2.68 (3H, m, C_4H_{ax}, C_7H_{ax}, C_3H_{eq}), 2.72-2.78 (1H, m, C_6H_{ax}), 2.87-3.00 (1H, m, C_7H_{eq}), 3.03-3.10 (1H, m, C_6H_{eq}), 3.30 (1H, ddd, J = 0.9, J = 5.3, J = 12.3, C_4H_{eq}), 3.45-3.51 (1H, m, $C_{12b}H_{ax}$), 4.06-4.18 (2H, m, ABX_3, $COOCH_2CH_3$).[12] ^{13}C NMR (50.32 MHz, $CDCl_3$): 27.05 (C_1), 24.38 (C_2), 40.36 (C_3), 60.40 ($COOCH_2CH_3$), 14.13 ($COOCH_2CH_3$), 54.73 (C_4), 52.84 (C_6), 20.60 (C_7), 58.43 (C_{12b}), 173.79 (ester CO).[12] Found: M^+, 298.1679. $C_{18}H_{22}N_2O_2$ requires M^+, 298.1681.

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine-3-carboxylate (19a, 19b).
To a solution of ester 16 or 17 (1 mmol, 298 mg) in 4 ml CH_3OH was added 2.5 ml 1% NaOH soln. The mixtures were stirred for 1 hr (45°C). TLC (SiO_2 EtOAc/EtOH 3:2). To the stirred mixtures was added 10% HCl soln (pH ≈ 2.5). The resulting white crystals 19a (eq COOH derivate) were filtered and washed with H_2O.
19a: Yield 255 mg (0.948 mmol, 94%); mp 277-280°C (dec). The solution of 19b was evaporated, dissolved in CH_3OH and in soluble material (NaCl) was filtered off. The filtrate was left for 18 hr (6°C). After filtration white crystals were obtained.
19b: Yield 240 mg (0.89 mmol, 89%); mp 185-192°C (dec). IR (KBr) of both products were identical 3230 (s), 3500-2300 (m), 1710 (s). Found: M^+, 270.1353. $C_{16}H_{18}N_2O_3$ requires M^+, 270.1368. MS (70 eV, m/z (%)), 19b: 270 (97), 269 (100), 226 (12), 197 (14), 184 (7), 170 (64), 169 (37), 156 (16).

3-Methylene-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine-4-one (20)
A solution of 19a (200 mg, 0.74 mmol) and 19b (200 mg, 0.74 mmol) in 8 ml acetic anhydride was refluxed under nitrogen for 2 hr. To the resulting mixture was added a saturated $NaHCO_3$ soln (20°C) and EtOAc. The organic phase was separated and washed with NaCl soln. After drying over Na_2SO_4 the residue upon work-up was chromatographed using EtOAc on SiO_2. Recrystallization from EtOAC gave 20 as white crystals.
20: Yield 310 mg (1.23 mmol, 83%); mp 218-219°C. IR ($CHCl_3$): 3475 (m), 3500-3100 (m), 1655 (s), 1612 (s), 1598 (m), 1309 (s). PMR ($CDCl_3$): 1.84 (1H, ddt, J = 4.1, J = 11.1, J = 13.0, C_1H_{ax}), 2.41-2.58 (1H, m, C_1H_{eq}), 2.69-2.99 (5H, m, $C_2H_{eq,ax}$, $C_7H_{eq,ax}$, C_6H_{ax}), 4.84-4.90 (1H, m, J = 11.1, $C_{12b}H$), 5.15-5.26 (1H, m, C_6H_{eq}), 5.34 (1H, s, $C{=}CH_2$), 6.27 (1H, t, J = 1.9, $C{=}CH_2$), 7.07-7.20 (2H, m, C_9H and $C_{10}H$), 7.32 (1H, d, J = 7.3, $C_{11}H$), 7.50 (1H, d, J = 7.3, C_8H), 8.07 (1H, bs, $N_{12}H$). Found: M^+, 252.1270. $C_{16}H_{16}N_2O_1$ requires M^+, 252.1262.

18-Nor-deplancheine (21).
To a stirred solution of lactam 20 (200 mg, 0.74 mmol) in anhydrous THF (10 ml) was added 1 ml DIBAH (1.5 M soln in toluene). Stirring was continued for 30 min under nitrogen at -50°C. After this to the mixture was added 3 ml EtOAc and a saturated NH_4Cl soln. After being stirred for min at 20°C, the reaction mixture was diluted with 10% KOH soln (pH ≈ 8) and EtOAc. The organic layer was separated and washed with NaCl soln. After drying over Na_2SO_4 the residue upon work-up was chromatographed using EtOAc on SiO_2. After evaporation of the solvent and recrystallization from Et_2O (under nitrogen) white crystals were obtained.
21: Yield 143 mg (0.6 mmol, 75%); mp 166-167°C (106-110°C).[17] IR ($CHCl_3$): 3475 (s), 3078 (w), 3058 (w), 2810 (m), 2780 (m), 1765 (m), 2740 (m), 1656 (m), 905 (s). PMR ($CDCl_3$, under nitrogen): 1.65 (1H, dq, J = 4.4, J = 12.6, $C_{14}H_{ax}$), 2.11-2.21 (1H, m, $C_{14}H_{eq}$), 2.27-2.34 (1H, m, $C_{15}H_{ax}$), 2.48-2.55 (1H, m, $C_{15}H_{eq}$), 2.63-2.75 (2H, m, C_5H_{ax} en C_6H_{ax}), 2.94-3.13 (3H, m, C_5H_{eq}, C_6H_{eq} and $C_{21}H_{ax}$), 3.37-3.46 (2H, m, C_3H_{ax} and $C_{21}H_{eq}$), 4.81 (1H, s, $C_{19}H$), 4.86 (1H, d, J = 1.5, $C_{19}H$), 7.03-7.15 (2H, m, $C_{10}H$ and $C_{11}H$), 7.29 (1H, d, J = 7.1, $C_{12}H$), 7.46 (1H, d, J = 7.1, C_9H), 7.70 (1H, bs, N_1H). ^{13}C NMR (50.32 MHz, $CDCl_3$, ^{13}C-^1H correlation): 134.43 (C_2), 59.30 (C_3), 52.78 (C_5), 21.47 (C_6), 108.13 (C_7), 127.20 (C_8), 118.05 (C_9), 119.25 (C_{10}), 121.24 (C_{11}), 110.68 (C_{12}), 135.92 (C_{13}), 30.59 (C_{14}), 32.40 (C_{15}), 110.00 (C_{19}), 143.22 (C_{20}), 61.53 (C_{21}). Found: M^+, 238.1457. $C_{16}H_{18}N_2$ requires M^+, 238.1470. MS (70 eV, m/z (%)): 238 (72), 237 (100), 223 (12), 209 (14), 170 (9), 169 (26), 156 (26).

Ethyl 1-[2-(3-indolyl)ethyl]-6-oxo-1,6-dihydronicotinate (23).
To a suspension of NaH (6.31 mmol) in anhydrous benzene (25 ml) was added a solution of 9 (1.5 g, 4.21 mmol) in benzene (10 ml). After being refluxed for 3 hr (80°C), the mixture was treated with a saturated NH_4Cl soln. The organic phase was washed with a NaCl soln and dried over Na_2SO_4. The residue upon work-up was chromatographed using EtOAc on SiO_2. The resulting yellow oil was crystallised from CH_3OH (-20°C) to give 23 as white needles.
23: Yield 1045 mg (3.37 mmol, 80%); mp 172-174°C (174°C).[21a] IR ($CHCl_3$): 3480 (m), 3340 (m), 1710 (s), 1662 (s), 1605 (m), 1545 (m), 1298 (s), 838 (m). NMR (CD_3CN): 1.17 (3H, t, J = 7.1, $COOCH_2CH_3$), 3.10 (2H, t, J = 7.0, CH_2CH_2N), 4.10 (2H, q, J = 7.1, $COOCH_2CH_3$), 4.17 (2H, t, J = 7.0, CH_2CH_2N), 6.36 (1H, d, J = 9.5, C_5H), 6.96 (1H, d, J = 2.5, indol C_2H), 6.99 and 7.09 (2H, 2x t, J = 7.6, indol C_5H and C_6H), 7.35 (1H, d, J = 7.6, indol C_7H), 7.53 (1H, d, J = 7.6, indol C_4H), 7.70 (1H, dd, J = 2.4, J = 9.5, C_4H), 7.77 (1H, d, J = 2.4, C_2H), 9.09 (1H, bs, indol NH). Found: M^+, 310.1305. $C_{18}H_{18}N_2O_3$ requires M^+, 310.1317.

18-Nor-epigeissoschizoate (27) and 18-nor-geissoschizoate (28).
To a stirred suspension of 25b (254 mg, 1 mmol) in xylene (20 ml) was added 840 mg (0.89 ml, 7 eq) 1,1,1,trimethoxyethane and a catalytic amount of propionic acid (0.07 mmol, 5.22 µl). The mixture was refluxed at 138°C for 150 min under nitrogen. After evaporation of the solvent, the crude products were chromatographed on SiO_2 using EtOAc/hexane 1:1. The first fraction, consisting of three products, was submitted to additional purification using flash-chromatography on SiO_2 with EtOAc/hexane 1:1 leaving 28 as a light yellow oil.
28: Yield 11.6 mg (0.037 mmol, 4%). IR ($CHCl_3$): 3478 (m), 3040 and 3060 (w), 2810 (m), 2780 (m),

2740 (m), 1730 (s), 1652 (s). PMR ($CDCl_3/C_5D_5N$ 10:1): 1.39 (1H, q, J = 11.9, $C_{14}H_{ax}$), 2.26 (2H, dd, J = 7.7, J = 15.0, $\underline{CH_2}COOCH_3$), 2.43-2.75 (6H, m, C_6H_2, $C_{21}H_{ax}$, $C_{15}H_{ax}$, $C_{14}H_{eq}$ and C_5H_{ax}), 2.98-3.15 (2H, m, C_5H_{eq} and $C_{21}H_{eq}$), 3.43 (1H, bd, J = 11.9, C_3H_{ax}), 3.49 (3H, s, $COOCH_3$), 4.69 and 4.93 (2H, 2x s, $C_{19}H_2$), 6.92-7.58 (m, $CHCl_3$, C_5H_5N and ArH (4x)), 8.57 (1H, bs, N_1). Found: $\underline{M}^+$, 310.1677. $C_{19}H_{22}N_2O_2$ requires $\underline{M}^+$, 310.1681.

As second product was obtained 27 as white amorphous material.

27. Yield 190 mg (0.163 mmol, 61%). IR ($CHCl_3$): 3475 (m), 3080 and 3050 (w), 2810 (m), 2780 (m), 2770 (m), 2740 (m), 1729 (s), 1655 (m). PMR ($CDCl_3$): 1.91-2.11 (2H, m, $C_{14}H_{ax,eq}$), 2.51-2.66 (2H, m, $\underline{CH_2}COOCH_3$), 2.67-2.85 (2H, m, C_5H_{ax} and C_6H_{ax}), 2.90-3.07 (2H, m, C_6H_{eq} and $C_{15}H_{eq}$), 3.10-3.19 (2H, m, C_5H_{eq} and $C_{21}H_{ax}$), 3.33 (1H, d, J = 12.3, $C_{21}H_{eq}$), 3.70 (3H, s, $COOCH_3$), 3.78 (1H, dd, J = 2.6, J = 9.0, C_3H_{ax}), 4.84 and 4.91 (2H, 2x s, $C_{19}H$), 7.04-7.16 (2H, m, $C_{10}H$ and $C_{11}H$), 7.30 (1H, d, J = 7.0, $C_{12}H$), 7.46 (1H, d, J = 7.1, C_9H), 7.85 (1H, s, N_1H). ^{13}C NMR (50.32 MHz, $CDCl_3$): 133.65 (C_2), 54.12 (C_3), 52.15 (C_5), 20.51 (C_6), 108.32 (C_7), 127.28 (C_8), 117.98 (C_9), 119.26 (C_{10}), 121.20 (C_{11}), 110.81 (C_{12}), 135.95 (C_{13}), 34.39 (C_{14}), 36.55 (C_{15}), 37.23 (C_{16}), 51.64 ($COOCH_3$), 172.71 (ester CO), 110.00 (C_{19}), 144.71 (C_{20}), 56.91 (C_{21}). Found: $\underline{M}^+$, 310.1677. $C_{19}H_{22}N_2O_2$ requires $\underline{M}^+$, 310.1681. MS (70 eV, m/z (%)): 238 (72), 237 (100), 223 (12), 209 (14), 170 (9), 169 (25), 156 (26).

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