Tetrahedron Vol 46, No 7, pp 2633–2650, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

STEREOCHEMICAL COURSE OF THE ALKALINE DECARBOALKOXYLATIVE CYCLIZATION OF C(4)- , C(5)- AND C(4),C(5)-SUBSTITUTED 1-[2-(3-INDOLYL)ETHYL]-3-METHOXYCARBONYL-1,4,5,6-TETRAHYDROPYRIDINES TO C(2)- , C(3)- AND C(2),C(3)-SUBSTITUTED INDOLO[2,3-a]QUINOLIZIDINES

MAURI LOUNASMAA*, REIJA JOKELA, PIRJO MÄKIMATTILA and BIRGIT TIRKKONEN

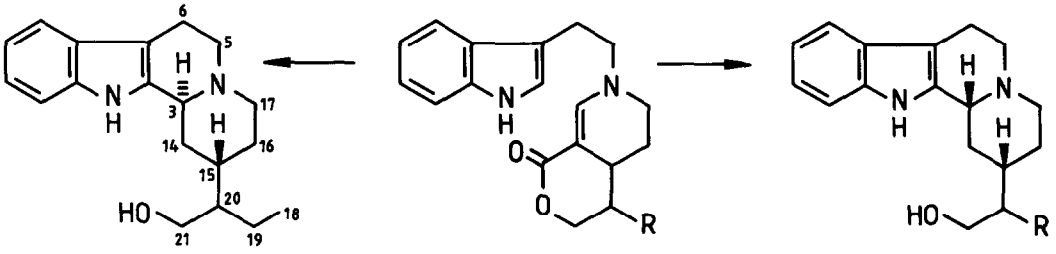
Laboratory for Organic and Bioorganic Chemistry,
Technical University of Helsinki, SF-02150 Espoo, Finland

(*Received in UK* 18 *December* 1989)

Abstract - Alkaline decarboalkoxylative cyclization of C(4)-monosubstituted 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridines 1a and 1d leads mainly to C(2)-monosubstituted indolo[2,3-a]quinolizidines 2a and 2d possessing the C(12b)H-C(2)H cis relationship [corresponding to the C(3)H-C(15)H cis relationship when the biogenetic numbering of indole alkaloids is used].
The C(5)-monosubstituted 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine 1e yields almost exclusively C(3)-monosubstituted indolo[2,3-a]quinolizidine 3e [C(12b)H-C(3)H trans relationship]. In the case of the C(4),C(5)-disubstituted analogues 1f and 1g, the C(12b)H-C(2)H relationship is strongly influenced by the C(4)H-C(5)H relationship (cis or trans) of the original 1,4,5,6-tetrahydropyridine. Thus 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-4-methyl-5-ethyl-1,4,5,6-tetrahydropyridine 1f [C(4)H-C(5)H cis relationship] leads to 2-methyl-3-ethylindolo[2,3-a]quinolizidines 3f and 2f [C(12b)H-C(2)H trans and cis relationships, respectively] in about 98:2 ratio, whereas 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-4-methyl-5-ethyl-1,4,5,6-tetrahydropyridine 1g [C(4)H-C(5)H trans relationship] yields exclusively 2-methyl-3-ethylindolo[2,3-a]quinolizidine 2g [C(12b)H-C(2)H cis relationship].

More than a decade ago we showed[1] that the alkaline decarboalkoxylative cyclization (alkaline hydrolysis followed by decarboxylation and cyclization)[2-5] of 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-4-methyl-1,4,5,6-tetrahydropyridine 1a leads to 2-methylindolo[2,3-a]quinolizidine 2a possessing the C(12b)H-C(2)H cis relationship.[1] In this connection we expressed doubts concerning the preparation of dl-18,19-dihydroantirhine 3b

[C(3)H-C(15)H trans relationship when the biogenetic numbering[6] is used, corresponding to the C(12b)H-C(2)H trans relationship in IUPAC numbering] by alkaline decarboalkoxylative cyclization of 1,4,5,6-tetrahydropyridine 1b, as claimed by Wenkert et al.[7] (Scheme 1).



3b 1b R = CH_2-CH_3 2b R = CH_2-CH_3

1c R = CH_3 2c R = CH_3

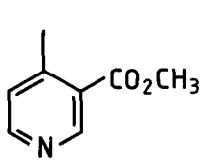
Scheme 1

In connection with our recent stereoselective syntheses of dl-18,19-dihydroantirhine 3b and dl-3-epi-18,19-dihydroantirhine 2b, we repeated the alkaline decarboalkoxylative cyclization of 1,4,5,6-tetrahydropyridine 1b.[8] As expected, we found that the product formed was not dl-18,19-dihydroantirhine 3b as claimed by Wenkert et al.[7] but dl-3-epi-18,19-dihydroantirhine 2b. We further confirmed our findings by showing that the alkaline decarboalkoxylative cyclization of 1,4,5,6-tetrahydropyridine 1c leads to dl-3-epi-18-nor-18,19-dihydroantirhine 2c (Scheme 1).[9]

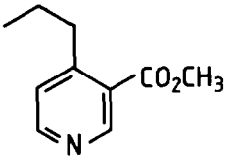
In view of the criticism of our conclusions regarding the general stereochemical course of the alkaline decarboalkoxylative cyclization of C(4)-substituted 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridines to C(2)-substituted indolo[2,3-a]quinolizidines and the claim of ubiquitous C(12b)H-C(2)H trans product formation, presented by Wenkert et al.[4,5,7,10,11], we have now examined the reaction in more detail.

RESULTS AND DISCUSSION

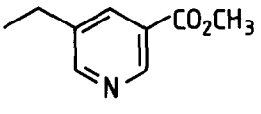
Treatment of nicotinic acid methyl esters 4a[12], 4d[12], 4e[13] and 4f[4] with tryptophyl bromide[14] yielded 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl



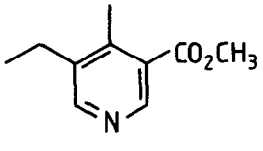
4a



4d

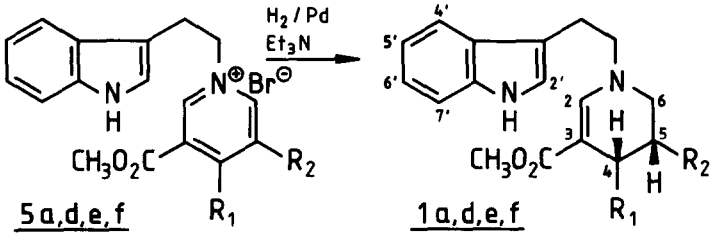


4e



4f

pyridinium bromides 5a, 5d, 5e and 5f, respectively, which were transformed by catalytic hydrogenation (Pd, Et_3N) to the corresponding 1,4,5,6-tetrahydropyridines 1a, 1d, 1e and 1f (Scheme 2).



a, $R_1 = CH_3$; $R_2 = H$

d, $R_1 = CH_2-CH_2-CH_3$; $R_2 = H$

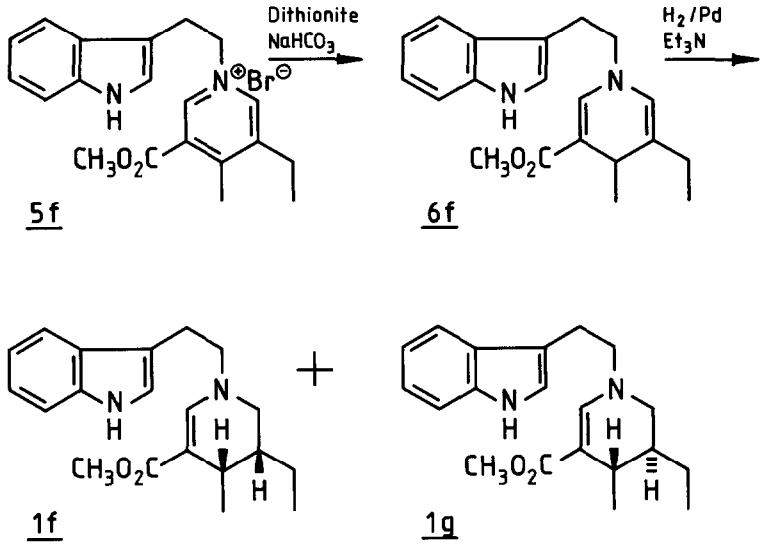
e, $R_1 = H$; $R_2 = CH_2-CH_3$

f, $R_1 = CH_3$; $R_2 = CH_2-CH_3$

Scheme 2

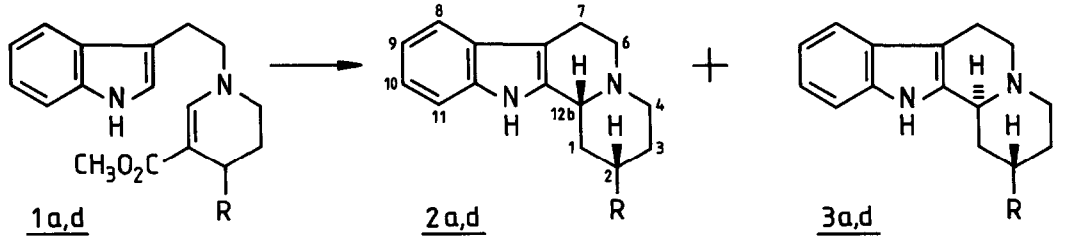
Sodium dithionite reduction[12,15-19] of 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl pyridinium bromide 5f using $NaHCO_3$ buffer afforded the corresponding 1,4-dihydropyridine 6f. Catalytic hydrogenation (Pd, Et_3N) of the 1,4-dihydropyridine 6f led to a 70:30 mixture of 1,4,5,6-tetrahydro-

pyridines 1f (vide supra) and 1g (Scheme 3).



Scheme 3

Reinvestigation of the alkaline decarboalkoxylative cyclization of 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-4-methyl-1,4,5,6-tetrahydropyridine 1a[1] to 2-methylindolo[2,3-a]quinolizidine 2a revealed the simultaneous formation in small amount (3%) of the isomeric 2-methylindolo[2,3-a]quinolizidine 3a (Scheme 4).



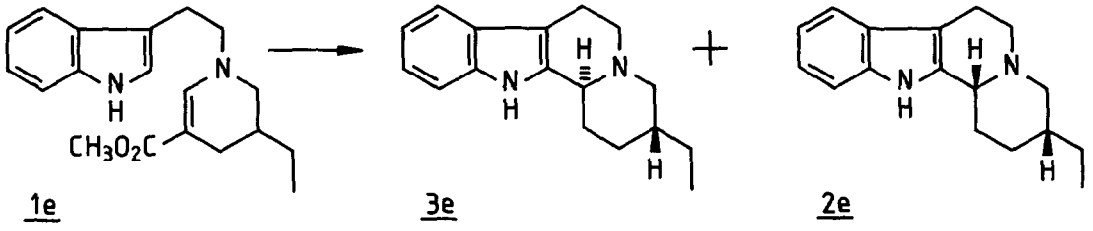
a, R = CH_3

d, R = CH_2-CH_2-CH_3

Scheme 4

Alkaline decarboalkoxylative cyclization of 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-4-propyl-1,4,5,6-tetrahydropyridine 1d afforded 2-propylindolo[2,3-a]quinolizidine 2d as the main product, together with 6% of the isomeric 2-propylindolo[2,3-a]quinolizidine 3d (Scheme 4).

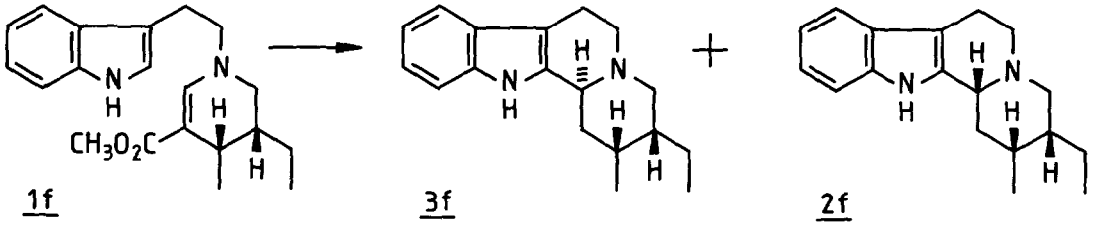
Alkaline decarboalkoxylative cyclization of C(5)-monosubstituted 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine 1e led to 3-ethylindolo[2,3-a]quinolizidines 3e and 2e in about 98:2 ratio (Scheme 5).



1e 3e 2e

Scheme 5

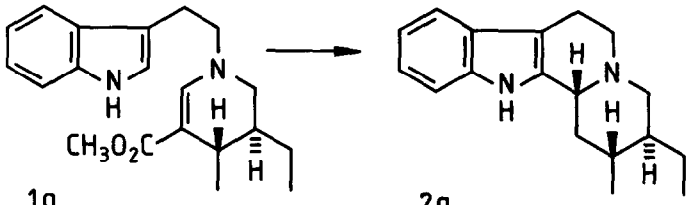
In the case of C(4),C(5)-disubstituted 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridines 1f and 1g, the final C(12b)H-C(2)H relationship is strongly influenced by the C(4)H-C(5)H relationship (cis or trans) of the original 1,4,5,6-tetrahydropyridine. Thus 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-4-methyl-5-ethyl-1,4,5,6-tetrahydropyridine 1f led to 2-methyl-3-ethylindolo[2,3-a]quinolizidines 3f and 2f in about 98:2 ratio (Scheme 6), whereas 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-



1f 3f 2f

Scheme 6

4-methyl-5-ethyl-1,4,5,6-tetrahydropyridine 1g yielded exclusively 2-methyl-3-ethylindolo[2,3-a]quinolizidine 2g[20] (Scheme 7).

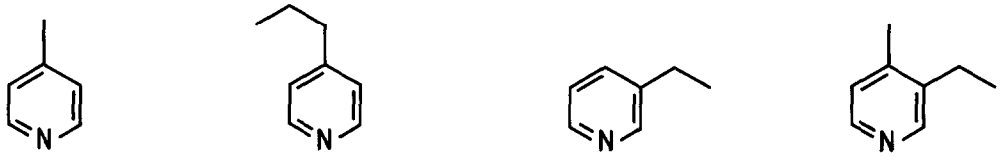


1g 2g

Scheme 7

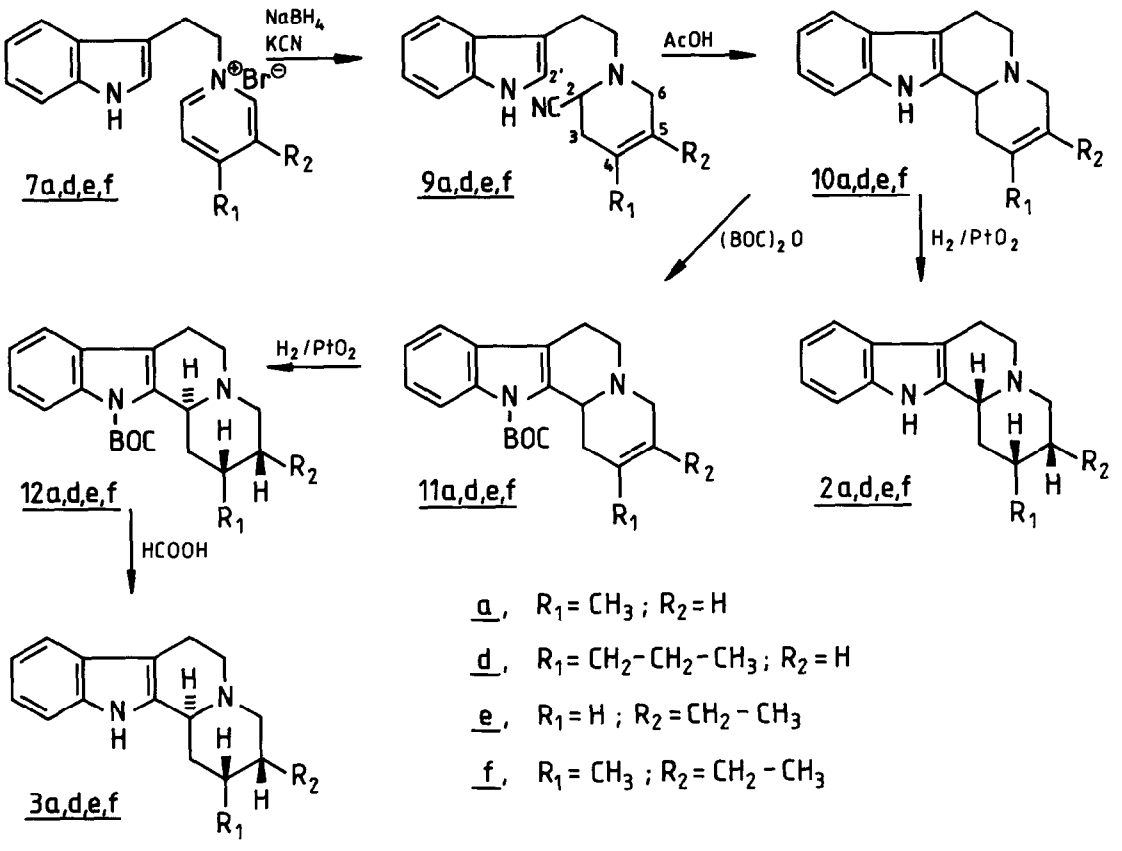
For purposes of comparison, compounds 2a, 2d, 2e, 2f, 3a, 3d, 3e and 3f were also synthesized (vide infra) by an alternative route, using our recently developed method for stereoregulation in the preparation of C(1)- , C(2)- , C(3)- and C(2),C(3)-substituted indolo[2,3-a]quinolizidines.[8,21-23]

Pyridinium salts 7a, 7d, 7e and 7f (prepared from tryptophyl bromide[14] and pyridine derivatives 8a[24], 8d[25], 8e[26] and 8f[27], respectively) were



8a 8d 8e 8f

transformed by $NaBH_4$ reduction and cyanide trapping to α-aminonitriles 9a, 9d, 9e and 9f, which by acid treatment yielded indolo[2,3-a]quinolizidines 10a, 10d, 10e and 10f, respectively. Parts of the compounds 10a, 10d, 10e and 10f were transformed with di-t-butyl dicarbonate [$(BOC)_2O$] to the corresponding BOC-protected indolo[2,3-a]quinolizidines 11a, 11d, 11e and 11f (Scheme 8).



Scheme 8

Catalytic hydrogenation (PtO_2) of compounds 10a, 10d, 10e and 10f afforded compounds 2a, 2d, 2e[28] and 2f, whereas the same treatment of the BOC-protected compounds 11a, 11d, 11e and 11f led, via compounds 12a, 12d, 12e and 12f,[29] to compounds 3a, 3d, 3e and 3f, respectively (Scheme 8).[30]

The ^{13}C NMR data of compounds 1d, 1e, 1f, 6f, 1g, 2d, 2f, 2g, 3d, 3f, 9d, 9f, 10d, 10f, 11d, 11f, 12d and 12f are given in Fig. 1. For those of compounds 1a and 2a, see Ref. 1 (compounds 1b and 5d), for those of compounds 3a, 9a, 10a, 11a and 12a, see Ref. 21 (compounds 7b, 2b, 3b, 5b and 6b), for those of compounds 9e, 10e, 11e and 12e, see Ref. 31 (compounds 2, 3, 5 and 9) and for those of compounds 2e and 3e, see Ref. 32 (compounds 3 and 4).

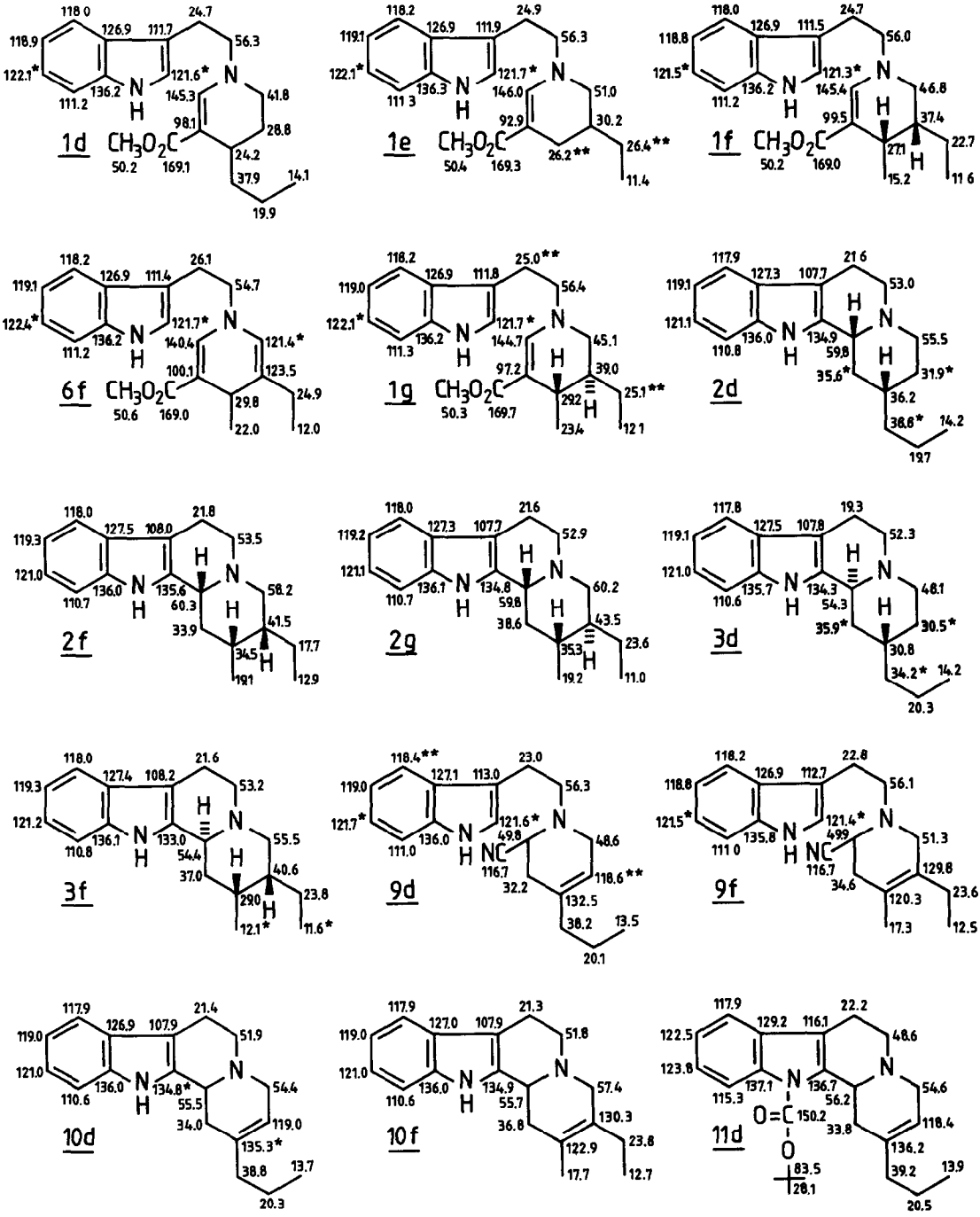


Fig. 1

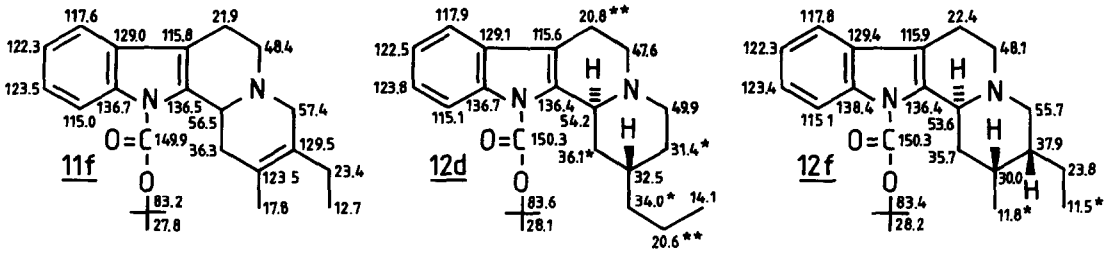


Fig. 1 (continued)

Comparison of the chemical shifts found for compounds 2d, 2f, 2g, 3d, 3f, 10d, 10f, 11d, 11f, 12d and 12f with those given earlier,[21,31,32] taking into account the conformational considerations relevant for indolo[2,3-a]quinolizidines,[21,33] provides clear evidence for the stereostructures depicted in the formulae.

CONCLUSIONS

The alkaline decarboalkoxylative cyclization of C(4)-monosubstituted 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridines 1a and 1d leads preponderantly to indolo[2,3-a]quinolizidines 2a and 2d possessing the C(12b)H-C(2)H cis relationship. The C(5)- monosubstituted 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridine 1e yields nearly exclusively indolo[2,3-a]quinolizidine 3e possessing the C(12b)H-C(3)H trans relationship. The preponderance of the C(12b)H-C(3)H trans relationship seems to be the dominating stereochemical feature also in the transformation of C(4),C(5)-disubstituted 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridines 1f and 1g to indolo[2,3-a]quinolizidines 3f and 2g by the alkaline decarboalkoxylative cyclization, and seems to determinate thereby that the C(12b)H-C(2)H relationship in 3f and 2g becomes trans and cis, respectively.

The present results clearly show that the claim of ubiquitous C(12b)H-C(2)H trans product formation [= C(3)H-C(15)H trans product formation when the biogenetic numbering[4] is used] in the alkaline decarboalkoxylative cyclization of C(4)-substituted 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridines (and similar compounds) to C(2)-substituted

indolo[2,3-a]-quinolizidines, presented by Wenkert et al.[4,5,7,10,11], is an oversimplification that cannot be accepted.

EXPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 700 spectrophotometer in $CHCl_3$, if not otherwise stated. ^1H and ^{13}C NMR spectra were measured with a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^1H NMR) and 15.04 MHz (^{13}C NMR). The spectra were recorded in $CDCl_3$. Chemical shift data are given in ppm downfield from TMS. Abbreviations s, d, t, q, m, br and def are used to designate singlet, doublet, triplet, quartet, multiplet, broad and deformed, respectively. For the ^{13}C NMR data, see above. Mass spectrometry (EIMS and HRMS) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compounds 1a, 1d, 1e and 1f from compounds 5a, 5d, 5e and 5f

Pyridinium salt 5a, 5d, 5e or 5f (3.0 mmol) in methanol (90 ml)/Et_3N (0.56 ml) was hydrogenated (Pd/C, 10%, 0.33 g) for 24-48 h. Usual work-up afforded a crude product which was purified by column chromatography (alumina, CH_2Cl_2).

Compound 1a:

Y. 63%. Mp. 137-138°C (MeOH) (lit.[1] Mp. 137-138°C).

Analytical data were identical with those described earlier.[1]

Compound 1d:

Y. 61%. Viscous oil.

IR: 3320 (NH), 1670 (C=O).

^1H NMR: 0.98 (3H, def, $-CH_2-CH_2-\underline{CH_3}$), 3.64 (3H, s, $-CO_2CH_3$), 6.85 (1H, d, J=2.4 Hz, H-2'), 7.35 (1H, s, H-2), 7.16-7.44 (4H, m, H-4', 5', 6', 7'), 8.88 (1H, br s, NH).

MS: 326 (M^+), 295, 283, 196 (100%), 144, 130; exact mass: 326.2000 (calculated for $C_{20}H_{26}N_2O_2$: 326.1990).

Compound 1e:

Y. 53%. Viscous oil.

IR: 3300 (NH), 1660 (C=O).

^1H NMR: 0.91 (3H, def, $-CH_2-\underline{CH_3}$), 3.66 (3H, s, $-CO_2CH_3$), 6.89 (1H, d, J=2.4 Hz, H-2'), 7.37 (1H, s, H-2), 7.03-7.54 (4H, m, H-4', 5', 6', 7'), 8.64 (1H, br s, NH).

MS: 312 (M^+), 281, 182 (100%), 144, 130; exact mass: 312.1851 (calc. for $C_{19}H_{24}O_2N_2$: 312.1838).

Compound 1f:

Y. 45%. Viscous oil.

IR: 3300 (NH), 1660 (C=O).
^{1}H NMR: 0.90 (3H, t, J=7.0 Hz, $-CH_2-\underline{CH_3}$), 1.08 (3H, d, J=7.0 Hz, $-CH_3$), 3.65 (3H, s, $-CO_2CH_3$), 6.79 (1H, d, J=2.4 Hz, H-2'), 7.32 (1H, s, H-2), 6.98-7.57 (4H, m, H-4', 5', 6', 7'), 8.92 (1H, br s, NH).
MS: 326 (M^+), 295, 196 (100%), 144, 130; exact mass: 326.2021 (calc. for $C_{20}H_{26}N_2O_2$: 326.1990).

Preparation of compound 6f

$Na_2S_2O_4$ (31.00 mmol) was added during 45 min to a stirred mixture of 5f (5.51 mmol), $NaHCO_3$ (8.61 g), MeOH (80 ml) and H_2O (40 ml). Stirring was continued for 22 h (rt, Ar-atm). The mixture was filtered and the filtrate concentrated. The residue was extracted several times with CH_2Cl_2. The extracts were washed with H_2O and dried over Na_2SO_4. The crude product was purified by column chromatography (alumina, CH_2Cl_2).
Y. 73%. Amorphous material.
IR: 3340 (NH), 1670 (C=O).
^{1}H NMR: 0.96 (3H, t, J=6.0 Hz, $-CH_2-\underline{CH_3}$), 1.05 (3H, d, J=6.0 Hz, $-CH_3$), 2.02 (2H, q, J=6.0 Hz, $-\underline{CH_2}-CH_3$), 3.65 (3H, s, $-CO_2CH_3$), 6.87 (1H, d, J=2.4 Hz, H-2'), 7.06 and 7.18 (2H, two s, H-2 and H-6), 7.02-7.59 (4H, m, H-4', 5', 6', 7'), 8.56 (1H, br s, NH).
MS: 324 (M^+), 309, 293, 144 (100%); exact mass: 324.1820 (calc. for $C_{20}H_{24}N_2O_2$: 324.1838).

Preparation of compounds 1f and 1g from compound 6f

Compound 6f (1.5 mmol) in MeOH (90 ml)/Et_3N (0.3 ml) was hydrogenated (Pd/C, 10%, 175 mg) for 8 h. Usual work-up afforded a 70:30 mixture of compounds 1f and 1g (Y. 58%). TLC was used to get pure samples for spectroscopical analysis. Otherwise the mixture was used as such in the next step (vide infra).
Compound 1f:
Analytical data were identical with those described above for compound 1f.
Compound 1g:
IR: 3310 (NH), 1660 (C=O).
^{1}H NMR: 0.89 (3H, t, J=7.0 Hz, $-CH_2-\underline{CH_3}$), 1.03 (3H, d, J=7.0 Hz, $-CH_3$), 3.65 (3H, s, $-CO_2CH_3$), 6.94 (1H, d, J=2.4 Hz, H-2'), 7.30 (1H, s, H-2), 7.04-7.64 (4H, m, H-4', 5', 6', 7'), 8.31 (1H, br s, NH).
MS: 326 (M^+), 295, 196 (100%), 144, 130; exact mass: 326.1987 (calc. for $C_{20}H_{26}N_2O_2$: 326.1990).

Preparation of compounds 2a, 3a, 2d and 3d by alkaline decarboalkoxylative cyclization

Compound 1a or 1d (1.50 mmol) was dissolved in MeOH (35 ml). KOH (5.50 g) and H_2O (23 ml) were added. The mixture was refluxed for 48 h (Ar-atm). MeOH was evaporated and H_2O added. The solution was extracted several times with CH_2Cl_2 and dried over Na_2SO_4.

A mixture of two isomers 2a and 3a (~ 90:10) or 2d and 3d (~ 80:20) was obtained. The crude product was purified by TLC.

Compound 2a:

Y. 30%. Mp. 165-166°C (MeOH) (lit.[1] Mp. 165-166°C).

Analytical data were identical with those described earlier.[1]

Compound 3a:

Y. 3%. Mp. 154-155°C (C_6H_6, petroleum ether addition) (lit.[21] 154-155°C).

Analytical data were identical with those described earlier.[21]

Compound 2d:

Y. 27%. Mp. 80-81°C (EtOH).

IR: 3430 (NH), 2830 and 2770 (Bohlmann bands).

^1H NMR: 0.91 (3H, t, J=6.0 Hz, $-CH_3$), 6.97-7.52 (4H, m, H-8, 9, 10, 11), 8.17 (1H, br s, NH).

MS: 268 (M^+), 267 (100%), 225, 197, 170, 169; exact mass: 268.1913 (calc. for $C_{18}H_{24}N_2$: 268.1939).

Compound 3d:

Y. 6%. Amorphous material.

IR: 3440 (NH).

^1H NMR: 0.93 (3H, def, $-CH_3$), 3.92 (1H, m, H-12b), 7.01-7.54 (4H, m, H-8, 9, 10, 11), 8.08 (1H, br s, NH).

MS: 268 (M^+), 267 (100%), 225, 197, 170, 169; exact mass: 268.1919 (calc. for $C_{18}H_{24}N_2$: 268.1939).

Preparation of compounds 3e and 2e by alkaline decarboalkoxylative cyclization

Compounds 3e and 2e were prepared from compound 1e using the same procedure (*vide supra*) as described for the preparation of compounds 2a, 3a, 2d and 3d (reaction time 64 h).

Compound 3e:

Y. 90%. Mp. 159-161°C (EtOH) (lit. Mp. 159-161°C[31], 160-161°C[34], 157°C[35]).

Analytical data were identical with those described earlier[31,34,35].

Compound 2e:

Y. 2%. Amorphous material.

Analytical data were identical with those described earlier.[22]

Preparation of compounds 3f and 2f by alkaline decarboalkoxylative cyclization

Compounds 3f and 2f were prepared from 1f using the same procedure (vide supra) as described for the preparation of compounds 2a, 3a, 2d and 3d (reaction time 192 h).

Compound 3f:

Y. 59%. Amorphous material.

IR: 3440 (NH), 2850 and 2780 (Bohlmann bands).

^{1}H NMR: 0.91 (3H, def, $-CH_2-\underline{CH_3}$), 0.95 (3H, d, J=7.0 Hz, $-CH_3$), 3.52 (1H, m, H-12b), 6.99-7.44 (4H, m, H-8, 9, 10, 11), 7.98 (1H, br s, NH).

MS: 268 (M^+), 267 (100%), 170, 169; exact mass: 268.1908 (calc. for $C_{18}H_{24}N_2$: 268.1939).

Compound 2f:

Y. 1-2%. Amorphous material.

IR: 3440 (NH), 2830 and 2780 (Bohlmann bands).

^{1}H NMR: 0.89 (3H, def, $-CH_2-\underline{CH_3}$), 0.94 (3H, d, J=7.0 Hz, $-CH_3$), 6.97-7.52 (4H, m, H-8, 9, 10, 11), 7.72 (1H, br s, NH).

MS: 268 (M^+), 267 (100%), 170, 169; exact mass: 268.1927 (calc. for $C_{18}H_{24}N_2$: 268.1939).

Preparation of compounds 3f, 2f and 2g by alkaline decarboalkoxylative cyclization

Compounds 3f, 2f and 2g were prepared from the 70:30 mixture of 1f and 1g using the same procedure (vide supra) as described for the preparation of compounds 2a, 3a, 2d and 3d (reaction time 192 h).

Compound 3f:

Y. 41%. Amorphous material.

Analytical data were identical with those described above for compound 3f.

Compound 2f:

Y. 1%. Amorphous material.

Analytical data were identical with those described above for compound 2f.

Compound 2g:

Y. 18%. Amorphous material.

IR: 3430 (NH), 2830 and 2780 (Bohlmann bands).

^{1}H NMR: 0.97 (3H, def, $-CH_2-\underline{CH_3}$), 0.97 (3H, def, $-CH_3$), 6.98-7.53 (4H, m, H-8, 9, 10, 11), 8.08 (1H, br s, NH).

MS: 268 (M^+), 267 (100%), 170, 169; exact mass: 268.1927 (calc. for $C_{18}H_{24}N_2$: 268.1939).

Preparation of compounds 9a, 9d, 9e and 9f

Compounds 9a, 9d, 9e and 9f were prepared by $NaBH_4$ reduction and cyanide trapping from the corresponding pyridinium salts 7a, 7d, 7e and 7f, respectively, using the procedure described in Ref. 21.

Compound 9a:

Y. 93%. Amorphous material.

Analytical data were identical with those described earlier.[21]

Compound 9d:

Y. 90%. Amorphous material.

IR: 3440 (NH), 2290 (CN).

^1H NMR: 0.87 (3H, t, J=7.0 Hz, $-CH_3$), 3.89 (1H, m, H-2), 5.39 (1H, br s, H-5), 6.88 (1H, d, J=2.4 Hz, H-2'), 7.05-7.63 (4H, m, H-4', 5', 6', 7'), 8.05 (1H, br s, NH).

MS: 293 (M^+), 266, 163, 144, 138 (100%), 136, 130; exact mass: 293.1866 (calc. for $C_{19}H_{23}N_3$: 293.1892).

Compound 9e:

Y. 90%. Viscous oil.

Analytical data were identical with those described earlier.[31]

Compound 9f:

Y. 62%. Viscous oil.

IR: 3440 (NH), 2260 (CN).

^1H NMR: 0.96 (3H, t, J=7.0 Hz, $-CH_2-\underline{CH_3}$), 1.61 (3H, s, $-CH_3$), 1.88 (2H, q, J=7.0 Hz, $-\underline{CH_2}-CH_3$), 3.84 (1H, m, H-2), 6.83 (1H, d, J=2.4 Hz, H-2'), 6.99-7.64 (4H, m, H-4', 5', 6', 7'), 8.09 (1H, br s, NH).

MS: 293 (M^+), 266, 251, 163, 144 (100%), 138, 130; exact mass: 293.1895 (calc. for $C_{19}H_{23}N_3$: 293.1892).

Preparation of compounds 10a, 10d, 10e and 10f

Compounds 10a, 10d, 10e and 10f were prepared by AcOH treatment from compounds 9a, 9d, 9e and 9f, respectively, using the procedure described in Ref. 21.

Compound 10a:

Y. 54%. Amorphous material.

Analytical data were identical with those described earlier.[21]

Compound 10d:

Y. 47%. Mp. 70-71°C (EtOH).

IR: 3430 (NH).

^1H NMR: 0.86 (3H, t, J=6.0 Hz, $-CH_3$), 5.43 (1H, br s, H-3), 7.08-7.55 (4H, m, H-8, 9, 10, 11), 7.93 (1H, br s, NH).

MS: 266 (M^+), 265, 170 (100%), 169; exact mass: 266.1779 (calc. for $C_{18}H_{22}N_2$: 266.1783).

Compound 10e:

Y. 44%. Mp. 146-148°C (EtOH) (lit. 143-145°C[37]; 147-148°C[38]; 146-148°C[31]). Analytical data were identical with those described earlier.[31]

Compound 10f:

Y. 45%. Mp. 178-179°C (MeOH).

IR: 3440 (NH).

^1H NMR: 0.97 (3H, t, J=7.0 Hz, $-CH_2-\underline{CH_3}$), 1.62 (3H, s, $-CH_3$), 2.02 (2H, q, J=7.0 Hz, $-\underline{CH_2}-CH_3$), 7.02-7.54 (4H, m, H-8, 9, 10, 11), 7.72 (1H, br s, NH).

MS: 266 (M^+), 265, 170 (100%), 169; exact mass: 266.1759 (calc. for $C_{18}H_{22}N_2$: 266.1783).

Preparation of compounds 2a, 2d, 2e and 2f from compounds 10a, 10d, 10e and 10f

Catalytic hydrogenation (PtO_2) of compounds 10a, 10d, 10e and 10f afforded compounds 2a, 2d, 2e and 2f, respectively.

Compound 2a:

Y. 72%. Mp. 165-166°C (EtOH) (lit.[1] Mp. 165-166°C).

Analytical data were identical with those of compound 2a described above.

Compound 2d:

Y. 70%. Mp. 80-81°C (EtOH).

Analytical data were identical with those of compound 2d described above.

Compound 2e:

Y. 60%. Amorphous material.

Analytical data were identical with those described earlier.[22]

Compound 2f:

Y. 95%. Amorphous material.

Analytical data were identical with those of compound 2f described above.

Preparation of compounds 11a, 11d, 11e and 11f

Compounds 11a, 11d, 11e and 11f were prepared by di-t-butyl dicarbonate [$(BOC)_2O$] treatment from compounds 10a, 10d, 10e and 10f, respectively, using the procedure described in Ref. 21.

Compound 11a:

Y. 95%. Viscous oil.

Analytical data were identical with those described earlier.[21]

Compound 11d:

Y. 90%. Viscous oil.

IR: 1730 (C=O).
^{1}H NMR: 0.90 (3H, t, J=6.0 Hz, -CH_3), 1.65 (9H, s, -$C(CH_3)_3$), 4.08 (1H, br d, H-12b), 5.48 (1H, br s, H-3), 7.14-7.51 (3H, m, H-8, 9, 10), 8.08 (1H, m, H-11).
MS: 366 (M^+), 310, 309, 214 (100%), 170, 169; exact mass: 366.2319 (calc. for $C_{23}H_{30}N_2O_2$: 366.2307).
Compound 11e:
Y. 90%. Viscous oil.
Analytical data were identical with those described earlier.[31]
Compound 11f:
Y. 90%. Viscous oil.
IR: 1720 (C=O).
^{1}H NMR: 1.00 (3H, t, J=7.0 Hz, -CH_2-CH_3), 1.63 (12 H, s, -CH_3 and -$C(CH_3)_3$), 2.05 (2H, q, J=7.0 Hz, -CH_2-CH_3), 4.03 (1H, br d, H-12b), 7.12-7.39 (3H, m, H-8, 9, 10), 8.08 (1H, m, H-11).
MS: 366 (M^+), 310, 309, 214 (100%), 170, 169; exact mass: 366.2310 (calc. for $C_{23}H_{30}N_2O_2$: 366.2307).

Preparation of compounds 12a, 12d, 12e and 12f
Catalytic hydrogenation (PtO_2) of compounds 11a, 11d, 11e and 11f afforded compounds 12a, 12d, 12e and 12f, respectively.
Compound 12a:
Y. 85%. Amorphous material.
Analytical data were identical with those described earlier.[21]
Compound 12d:
Y. 95%. Viscous oil.
IR: 1730 (C=O).
^{1}H NMR: 0.91 (3H, def, -CH_3), 1.67 (9H, s, -$C(CH_3)_3$), 4.47 (1H, m, H-12b), 7.12-7.34 (3H, m, H-8, 9, 10), 7.95 (1H, m, H-11).
MS: 368 (M^+), 312, 311 (100%), 267, 215; exact mass: 368.2472 (calc. for $C_{23}H_{32}N_2O_2$: 368.2464).
Compound 12e:
Y. 75%. Viscous oil.
Analytical data were identical with those described earlier.[31]
Compound 12f:
Y. 73%. Viscous oil.
IR: 1730 (C=O).
^{1}H NMR: 0.91 (3H, t, J=7.0 Hz, -CH_2-CH_3), 1.06 (3H, d, J=7.0 Hz, -CH_3), 1.67 (9H, s, -$C(CH_3)_3$), 4.28 (1H, br d, H-12b), 7.01-7.48 (3H, m, H-8, 9, 10), 7.94 (1H, m, H-11).

MS: 368 (M^+), 312, 311 (100%), 267, 215; exact mass: 368.2409 (calc. for $C_{23}H_{32}N_2O_2$: 368.2464).

Preparation of compounds 3a, 3d, 3e and 3f from compounds 12a, 12d, 12e and 12f

Compounds 3a, 3d, 3e and 3f were prepared by HCOOH treatment from compounds 12a, 12d, 12e and 12f, respectively, using the procedure described in Ref. 21.

Compound 3a:

Y. 95%. Mp. 154-155°C (C_6H_6, petroleum ether addition) (lit.[21] Mp. 154-155°C).

Analytical data were identical with those described above for compound 3a.

Compound 3d:

Y. 95%. Amorphous material.

Analytical data were identical with those described above for compound 3d.

Compound 3e:

Y. 80%. Mp. 159-161°C (EtOH) (lit. Mp. 159-161°C[31], 160-161°C[34], 157°C[35]).

Analytical data were identical with those described above for compound 3e.

Compound 3f:

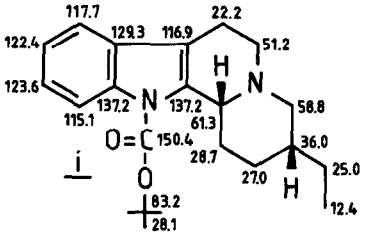
Y. 90%. Amorphous material.

Analytical data were identical with those described above for compound 3f.

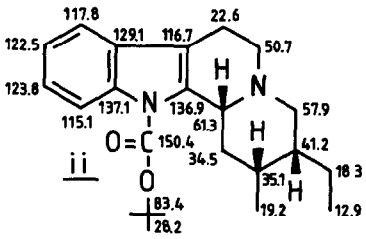
REFERENCES AND NOTES

1. Lounasmaa, M.; Jokela, R. Tetrahedron 1978, 34, 1841.
2. Lounasmaa, M.; Johansson, C.-J.; Svensson, J. Acta Chem. Scand. 1976, B30, 251.
3. Lounasmaa, M.; Hämeilä, M. Tetrahedron 1978, 34, 437.
4. Wenkert, E.; Dave, K.G.; Haglid, F. J. Am. Chem. Soc. 1965, 87, 5461.
5. Wenkert, E.; Dave, K.G.; Lewis, R.G.; Sprague, P.W. J. Am. Chem. Soc. 1967, 89, 6741.
6. LeMen, J.; Taylor, W. Experientia 1965, 21, 508.
7. Wenkert, E.; Sprague, P.W.; Webb, R.L. J. Org. Chem. 1973, 38, 4305.
8. Lounasmaa, M.; Jokela, R. Tetrahedron 1989, 45, 7449.
9. Lounasmaa, M.; Jokela, R. The results were first presented as part of a series of lectures at the Technical University of Helsinki (Autumn 1989).
10. Wenkert, E.; Han, A.-L.; Michelotti, E.L. Croatica Chem. Acta 1985, 58, 737.
11. Wenkert, E.; Moeller, P.D.R.; Shi, Y.-J. J. Org. Chem. 1988, 53, 2383.
12. Lounasmaa, M.; Johansson, C.-J. Tetrahedron 1977, 33, 113.
13. Jokela, R.; Tamminen, T.; Lounasmaa, M. Heterocycles 1985, 33, 1707.
14. Hoshino, T.; Shimodaira, K. Liebigs Ann. Chem. 1935, 520, 19.
15. Lounasmaa, M.; Juutinen, P.; Kairisalo, P. Tetrahedron 1978, 34, 2529.
16. Lounasmaa, M.; Merikallio, H; Puhakka, M. Tetrahedron 1978, 34,2995.
17. Lounasmaa, M.; Jokela, R. Tetrahedron Lett. 1978, 3609.

18. Frostell, E.; Jokela, R.; Lounasmaa, M. Acta Chem. Scand. 1981, B35, 671.
19. Jokela, R.; Lounasmaa, M. Tetrahedron 1982, 38, 1015.
20. The exclusive formation of 2-methyl-3-ethylindolo[2,3-a]quinolizidine 2g [C(12b)H-C(2)H cis relationship = C(3)H-C(15)H cis relationship when the biogenetic numbering[4] of indole alkaloids is used] using 1,4,5,6-tetrahydropyridine 1g [C(4)H-C(5)H trans relationship = C(15)H-C(20)H trans relationship when the biogenetic numbering of indole alkaloids is applied in sensu lato to the 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl-1,4,5,6-tetrahydropyridines] is of special interest when compared with the statement (Ref. 4, Note 22): "The uniform formation of 3,15-trans compounds in the cyclization of 2,3-seco-3-dehydro substances is consistent with a similar observation in the case of a 15,20-trans compound". See also, Ref. 10, Equation b.
21. Lounasmaa, M.; Jokela, R. Tetrahedron 1989, 45, 3975.
22. Lounasmaa, M.; Jokela, R.; Tirkkonen, B.; Tamminen, T. Tetrahedron 1989, 45, 7615.
23. Lounasmaa, M.; Jokela, R. Tetrahedron (in press).
24. Aldrich, Compound 23,961-5.
25. K&K, Compound 217169.
26. Aldrich, Compound 14,239-5.
27. Fluka, Compound 535642.
28. Small amounts of compound 3e were also formed (cf. Ref. 22).
29. In the case of compounds 12e and 12f, the small amounts of the formed C(12b) epimers i (cf. Ref. 31, compound 11) and ii were separated.



i



ii

After reconsideration of the ^{13}C NMR spectrum of compound 11 in Ref. 31 (= compound i) we have interchanged the C(12b) and C(4) signals. A similar interchange for compound 14 in Ref. 22 is obvious.

30. It should be noted that Scheme 8 is drawn in such a way that optical antipodes of compounds 10a,d,e,f are involved in the formation of compounds 2a,d,e,f and 12a,d,e,f.
31. Tamminen, T.; Jokela, R.; Tirkkonen, B.; Lounasmaa, M. Tetrahedron 1989, 45, 2683.
32. Lounasmaa, M.; Jokela, R.; Tamminen, T. Heterocycles 1985, 23, 1367. See also, Ref. 31, Note 15, and Ref. 36, Note 15.
33. Lounasmaa, M. in "Studies in Natural Products Chemistry", ed. Atta-ur-Rahman, Vol. 1, Stereoselective Synthesis (Part A), Elsevier, Amsterdam, 1988, pp. 89-122.
34. Yamanaka, E.; Narushima, M.; Inukai, K.; Sakai, S.-I. Chem. Pharm. Bull. 1986, 34, 77.
35. Massiot, G.; Oliveira, F.S.; Levy, J. Bull. Soc. Chim. France II 1982, 185.
36. Jokela, R.; Karvinen, E.; Tolvanen, A.; Lounasmaa, M. Tetrahedron 1988, 44, 2367.
37. Wenkert, E.; Massy-Westropp, R.A.; Lewis, R.G. J. Am. Chem. Soc. 1962, 84, 3732.
38. Fry, E.M.; Beisler, J.A. J. Org. Chem. 1970, 35, 2809.