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# A MILD NOVEL SYNTHESIS OF SIMPLE 1-OXO-β-CARBOLINES

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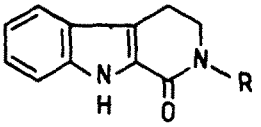
Abstract - A new route using very mild reaction conditions is described for the transformation of indoloquinolizidines 4 and 5 to the 1-oxo-1,2,3,4-tetrahydro-β-carbolines 2 and 3.

The simple β-carboline alkaloids include many pharmacologically active compounds.[1] The corresponding but not so common 1-oxo derivatives have also been shown to possess active properties. Strychnocarpine 1 (1-oxo-N(b)-methyl-1,2,3,4-tetrahydro-β-carboline), a constituent of Strychnos elaeocarpa and of S. floribunda (Loganiaceae), has turned out to be a weak muscle relaxant and 5-hydroxytryptamine receptor stimulant.[2,3]

Several N(b)-substituted 1-oxo-1,2,3,4-tetrahydro-β-carbolines have been synthesized and used for instance for the preparation of quinazolinocarboline alkaloids.[4-11] In two cases in the literature, the starting compound for the preparation of the N(b)-substituted 1-oxo-β-carboline has been a 1-ethyl-1-hydroxymethyl-indoloquinolizidine.[8,11] Under strongly oxidizing conditions this indoloquinolizidine was converted to the N(b)-substituted 1-oxo-1,2,3,4-tetrahydro-β-carboline 3.

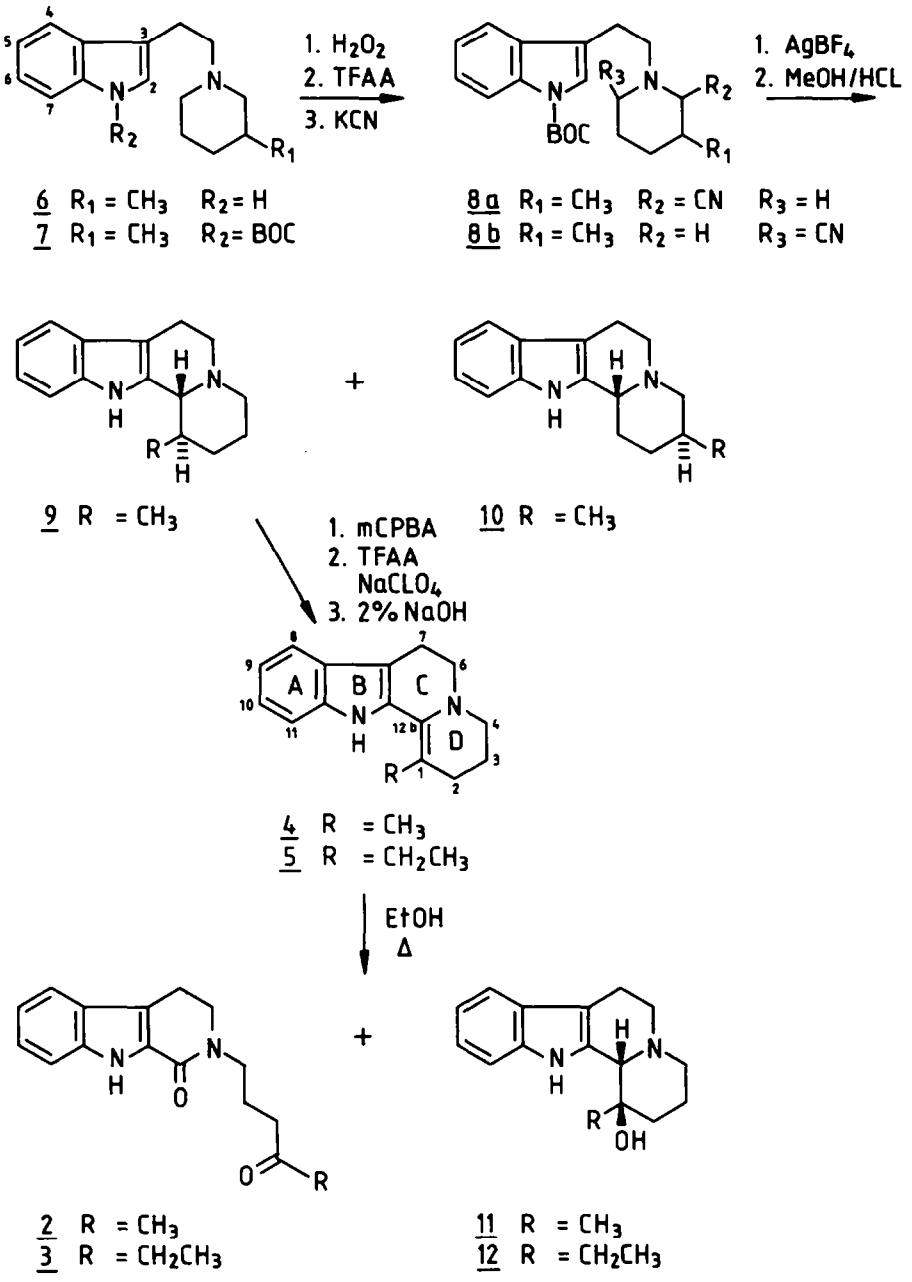


1 R = $CH_3$

2 R = $(CH_2)_3\overset{O}{\overset{\|}{C}}CH_3$

3 R = $(CH_2)_3\overset{O}{\overset{\|}{C}}CH_2CH_3$

We have developed a new method which permits the transformation of the two indoloquinolizidines 4 and 5 in 20% yields to the 1-oxo-1,2,3,4-tetrahydro-β-carbolines 2 and 3, respectively, under very mild reaction conditions.



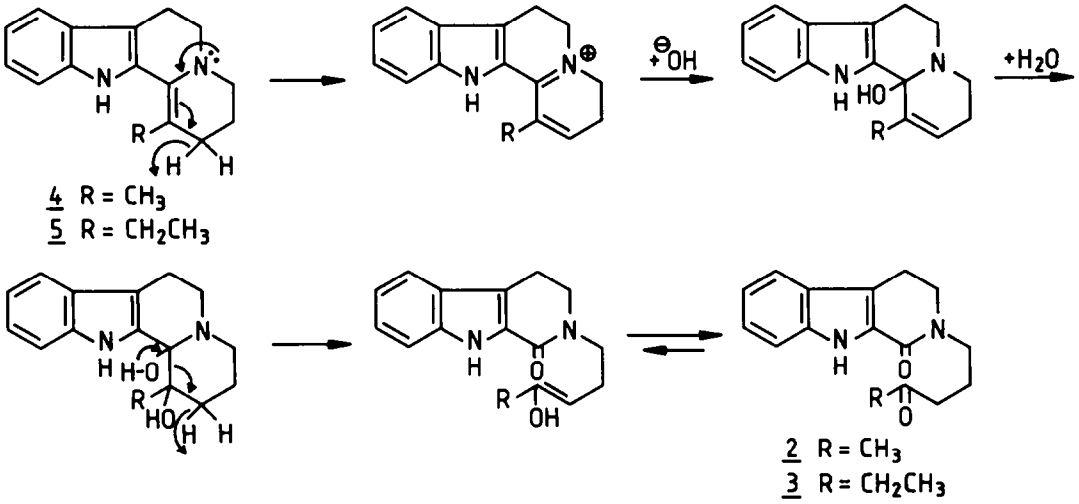

Scheme 1

## RESULTS AND DISCUSSION

The indoloquinolizidines 4 and 5 were obtained as follows. Compound 5, otherwise known as Wenkert's enamine, was synthesized by our recently described versatile method.[12] Several alternative syntheses are described in the literature.[13-16] The corresponding methyl derivative 4 (Scheme 1) was prepared starting from 1-[2-(3-indolyl)ethyl]-3-methylpyridinium bromide. After hydrogenation, yielding compound 6, and subsequent BOC-protection the indole N protected compound 7 was obtained. N-Oxide formation and subsequent modified Polonovski reaction followed by cyano trapping afforded the nitriles 8a and 8b as a 1:1 mixture.[17] Treatment of the mixture of compounds 8a and 8b with $AgBF_4$ and then with MeOH/HCl yielded the indoloquinolizidines 9 and 10 (main isomers) as well as the two other possible isomers in trace amounts (see Ref. 18, compounds

1-4). Compound 9 was treated with mCPBA and then with TFAA to yield the corresponding iminium compound, which was isolated as its perchlorate salt. Basification of the salt in dichloromethane with 2% NaOH afforded the corresponding methylenamine 4, which was immediately used in the next step.

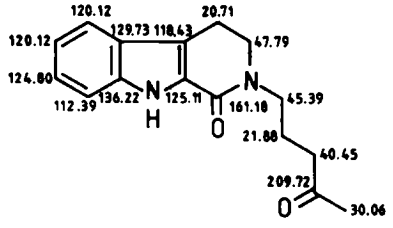
Heating the alkylenamines 4 and 5 in ethanol (99.5%) at 60-70° under argon gave the 1-oxo-1,2,3,4-tetrahydro-β-carbolines 2 and 3, respectively. Under these mild reaction conditions with only a trace of water present, ring D of the indoloquinolizidines 4 and 5 was cleaved to afford the 1-oxo-1,2,3,4-tetrahydro-β-carbolines 2 and 3, respectively. Two further compounds, 11 (traces) and 12, were formed under these reaction conditions, 12 being identical with the compound prepared by us earlier (Ref. 12, compound 21b).




Scheme 2

The formation of compounds 2 and 3 can be explained as follows (Scheme 2; Formally corresponding to the liberation of two moles of hydrogen). Nitrogen assisted cleavage[19] of a hydride ion at C-2 of compounds 4 and 5 gives the corresponding iminium salt with a $\Delta^1$ double bond. Attack of a hydroxide ion at C-12b and subsequent addition of water at the $\Delta^1$ double bond gives the corresponding diole. Ring opening and loss of a hydride ion affords the N(b)-substituted 1-oxo-1,2,3,4-tetrahydro-β-carboline existing mainly in the keto form (2 or 3).

Our new method thus affords a very simple way to synthesize N(b)-substituted 1-oxo-1,2,3,4-tetrahydro-β-carbolines from easily accessible starting compounds. The transformation of indoloquinolizidines 4 and 5 to the corresponding 1-oxo-1,2,3,4-tetrahydro-β-carbolines 2 and 3 under mild reaction conditions might have some biogenetic interest, although it is generally accepted that the biogenetic routes to the indoloquinolizidines and β-carbolines are different.[20]

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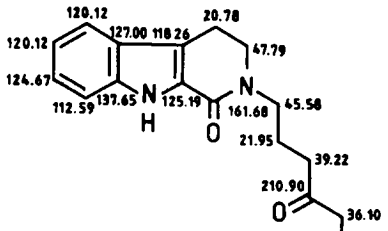


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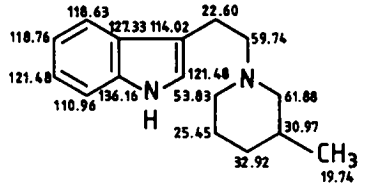


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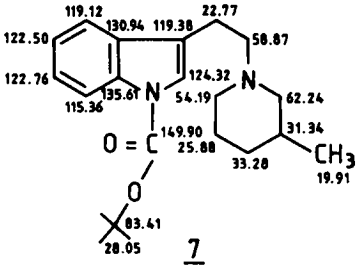


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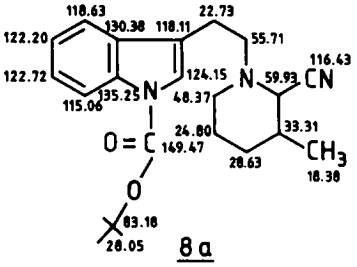
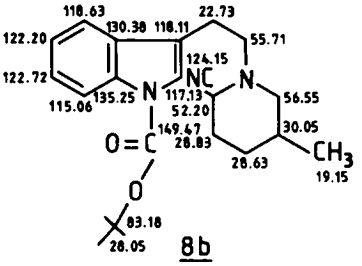
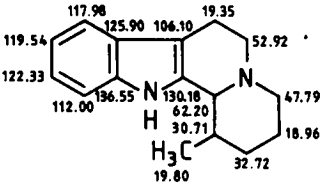



8a




8b




9

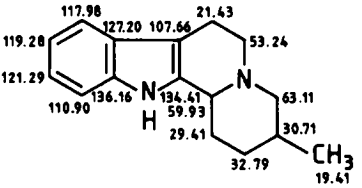



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Fig. 1

## EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 700 spectrophotometer using liquid film between NaCl crystals. $^{1}H$ and $^{13}C$ NMR spectra were recorded in $CDCl_3$ on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz ($^{1}H$ NMR) and 15.04 MHz ($^{13}C$ NMR). Chemical shift data are given in ppm downfield from TMS. Mass spectrometry (EIMS and HRMS) were performed on a Jeol DX 303 / DA 5000 instrument.

1-Oxo-N(b)-4-oxohexyl-1,2,3,4-tetrahydro-β-carboline 3 and 1β-ethyl-1α-hydroxy-1,2,3,4,6,7,12,12bβ-octahydroindolo[2.3-a]quinolizine 12: Wenkert's enamine[12] (300 mg, 0.85 mmol) (as its perchlorate salt) in $CH_2Cl_2$ (30 ml) was stirred with 2% NaOH. After the usual work-up the free base 5 (210 mg, 0.83 mmol) in ethanol (50 ml, 99.5%) was gently refluxed for 15 h under argon and then evaporated to dryness. The crude product was purified by preparative TLC on silica ($CHCl_3$/MeOH, 90:10) to afford compounds 3 (Y:20%) and 12 (Y:15%).

Compound 3:
IR: 3300 (NH), 1715 (C=O), 1640 (C=O, lactam).
$^1$H NMR: 1.00 (3H, t, J = 7 Hz, $-CH_3$), 1.94 (2H, m, $-CH_2-$), 2.40 (2H, q, J = 7 Hz, $-CO-CH_2CH_3$), 2.51 (2H, t, J = 7 Hz, $-CH_2CO-$), 3.16 (2H, t, J = 7 Hz, $-CH_2-$), 3.60 (2H, t, J = 7 Hz, $-CH_2-$), 3.71 (2H, t, J = 7 Hz, $-CH_2-$), 7.05-7.63 (4H, m, arom. H), 10.08 (1H, br s, NH).
$^{13}$C NMR: see Fig. 1.
MS: 284 ($M^+$) 213, 212, 199 (100%), 157, 144, 143, 129; exact mass: 284.1522 (calc. for $C_{17}H_{20}N_2O_2$: 284.1524).
Compound 12:
For analytical data see Ref. 12, comp. 21b.

1-[2-(3-Indolyl)ethyl]-3-methylpiperidine 6: 1-[2-(3-Indolyl)ethyl]-3-methylpyridinium bromide (6.0 g, 18.9 mmol) (prepared in the usual manner from tryptophyl bromide and 3-methylpyridine (Merck)) was dissolved in 100 ml of MeOH and hydrogenated at rt over $PtO_2$ (0.7 g) for 20 h. After the usual work-up, compound 6 (4.09 g, 90%) was obtained as a semisolid oil.
$^1$H NMR: 0.89 (3H, d, J = 6 Hz, $-CH_3$), 6.89 (1H, s, ind. α-H), 7.16-7.65 (4H, m, arom. H), 8.66 (1H, br s, NH).
$^{13}$C NMR: see Fig. 1.
MS: 242 ($M^+$), 144, 130, 113, 112 (100%); exact mass: 242.1780 (calc. for $C_{16}H_{22}N_2$: 242.1783).

1-[2-(3-(N-BOC)indolyl)ethyl]-3-methylpiperidine 7: 50% aq NaOH (30 ml) was added to compound 6 (3.45 g, 14.3 mmol) in 50 ml of toluene containing tetrabutylammonium hydrogen sulphate (1.39 g). The two-phase system was stirred under argon for 5 min. Di-t-butyl dicarbonate (6.20 g, 2 equiv.) in toluene (15 ml) was added during 10 min and stirring was continued for 15 min. The organic layer was separated and the aqueous layer was washed with $CH_2Cl_2$ several times. The combined organic layers were washed with $H_2O$, dried over $Na_2SO_4$ and evaporated to dryness to yield essentially pure 7 (4.79 g, 98%).
IR: 1740 (C=O).
$^1$H NMR: 0.87 (3H, d, J = 6 Hz, $-CH_3$), 1.65 (9H, s, $-C(CH_3)_3$), 7.40 (1H, s, ind. α-H), 8.11 (1H, m, ind. H-7).
$^{13}$C NMR: see Fig. 1.
MS: 342 ($M^+$), 327, 285, 269, 144, 143, 130, 113, 112 (100%); exact mass: 342.2311 (calc. for $C_{21}H_{30}N_2O_2$: 342.2307).

1-[2-(3-(N-BOC)indolyl)ethyl]-2-cyano-3- and 5-methylpiperidines 8a and 8b: Compound 7 (4.50 g, 13.2 mmol) was reacted with $H_2O_2$ (30%, 3 ml) in $CHCl_3$-MeOH (1:1) (60 ml, 60°C, 2d) to afford after the usual work-up the corresponding N-oxide in 91% yield. This was used immediately in the next step. N-Oxide (4.28 g, 12.0 mmol) in dry $CH_2Cl_2$ (30 ml) was stirred at 0°C (Ar-atm) and TFAA (4.2 ml, 2.5 equiv.) was added during 15 min. Stirring was continued for 1 h at 0°C and thereafter 15 min at rt. KCN (1.17 g, 1.5 equiv.) in $H_2O$ (15 ml) was added and the pH of the aqueous layer was adjusted to pH 5 by the addition of NaOAc. The mixture was stirred at rt for 0.5 h, basified to pH 10 with 10% aq. $Na_2CO_3$ and extracted with $CH_2Cl_2$ several times. The organic layer was washed with $H_2O$, dried over $Na_2SO_4$ and evaporated to dryness. Aminonitriles 8a and 8b were obtained as a mixture (1:1) by purification of the crude product through a short column of alumina ($CH_2Cl_2$-hexane, 4:6), Y:73%. TLC was used to get pure samples for spectroscopical analysis.
Compound 8a:
IR: 2270 (CN), 1740 (C=O).
$^1$H NMR: 0.94 (3H, d, J = 7 Hz, $-CH_3$), 1.65 (9H, s, $-C(CH_3)_3$), 3.87 (1H, br s, -CHCN), 7.44 (1H, s, ind. α-H), 8.13 (1H, m, ind. H-7).
$^{13}$C NMR: see Fig. 1.
MS: 367 ($M^+$), 340, 137 (100%), 110; exact mass: 367.2254 (calc. for $C_{20}H_{29}N_3O_2$: 367.2260).
Compound 8b:
IR: 2270 (CN), 1740 (C=O).
$^1$H NMR: 0.88 (3H, d, J = 7 Hz, $-CH_3$), 1.65 (9H, s, $-C(CH_3)_3$), 7.44 (1H, s, ind. α-H), 8.13 (1H, m, ind. H-7).
$^{13}$C NMR: see Fig. 1.
MS: 367 ($M^+$), 340, 137 (100%), 110; exact mass: 367.2257 (calc. for $C_{22}H_{29}N_3O_2$: 367.2260).

1β-and 3β-Methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2.3-a]quinolizines 9 and 10: The mixture of compounds 8a and 8b (1:1) (5.24 g, 14.3 mmol) was dissolved in dry THF (50 ml). $AgBF_4$ (3.0 g, 15.4 mmol) in dry THF (10 ml) was added during 20 min and stirring was continued for 2 h. The mixture was evaporated to dryness. MeOH (300 ml) presaturated with dry HCl gas was added and the mixture was stirred for 2.5 d. After neutralization with $NaHCO_3$ and the usual work-up 3.10 g (90%) of a mixture of 1β- and 3β-methyl-1,2,3,4,6,7,12,12bβ-octahydroindolo[2.3.a]-quinolizines 9 and 10 (major products) and the two other possible isomers[18] (minor products) were obtained. The two major isomers 9 and 10 were separated by preparative TLC on silica ($CH_2Cl_2$-MeOH, 90:10).
Compound 9:
IR: 2830 and 2775 (vw) (Bohlmann bands).
$^1$H NMR: 1.25 (3H, d, J = 6 Hz, $-CH_3$), 3.70 (1H, m, H-12b), 7.03-7.48 (4H, m, arom. H), 9.90 (1H, br s, NH).
$^{13}$C NMR: see Fig. 1.
MS: 240 ($M^+$), 239 (100%), 197, 184, 170, 169; exact mass: 240.1629 (calc. for $C_{16}H_{20}N_2$: 240.1626).
Compound 10:
IR: 2820 and 2780 (Bohlmann bands).
$^1$H NMR: 0.86 (3H, d, J = 6 Hz, $-CH_3$), 7.03-7.49 (4H, m, arom. H), 8.34 (1H, br s, NH).
$^{13}$C NMR: see Fig. 1.
MS: 240 ($M^+$), 239 (100%), 197, 184, 170, 169; exact mass: 240.1628 (calc. for $C_{16}H_{20}N_2$: 240.1626).

1-Oxo-N(b)-4-oxopentyl-1,2,3,4-tetrahydro-β-carboline 2 and 1β-methyl-1α-hydroxy-1,2,3,4,6,7,12,12bβ-octahydroindolo[2.3-a]quinolizine 11: 1.22 g (5.1 mmol) of the mixture of compounds 9 and 10 was dissolved in dry $CH_2Cl_2$ (35 ml) (0°C, Ar-atm). mCPBA (1.20 g, 5.8 mmol) was added and the mixture was stirred at 0°C for 1.5 h. Then it was cooled to -15°C and TFAA (1.8 ml, 2.5 equiv.) was added. Stirring was continued for 2 h (-15°C → 0°C). The mixture was evaporated to dryness and isolated as its perchlorate salt (Y:95%). The transformation of the salt to the β-carboline 2 was performed as described for β-carboline 3 (vide infra). Two compounds were obtained 2 (Y:20%) and 11 (traces).

Compound 2:
IR: 3250 (NH), 1715 (C=O), 1640 (C=O, lactam).
$^1$H NMR: 2.12 (3H, s, $-CH_3$), 2.54 (2H, t, J = 7 Hz, $-CH_2CO-$), 3.05 (2H, t, J = 7 Hz, $-CH_2-$), 3.60 (2H, t, J = 7 Hz, $-CH_2-$), 3.71 (2H, t, J = 7 Hz, $-CH_2-$), 7.11-7.60 (4H, m, arom. H), 9.69 (1H, bs s, NH).
$^{13}$C NMR: see Fig. 1.
MS: 270 ($M^+$), 212, 199 (100%), 157, 144, 143, 129; exact mass: 270.1379 (calc. for $C_{16}H_{18}N_2O_2$: 270.1368).

Compound 11:
IR: 2830, 2780 (Bohlmann bands).
MS: 256 ($M^+$), 171 (100%); exact mass: 256.1581 (calc. for $C_{16}H_{20}N_2O$: 256.1576).

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