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EASY FUNCTIONALIZATION OF C(17) IN THE DESETHYLEBURNAMONINE SERIES

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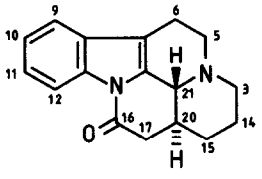
Abstract - A new and interesting C(17)-functionalized desethyleburnamonine derivative 3 was synthesized. When subjected to different reducing conditions this dicarbonyl compound afforded compounds 4-7.

We recently described a synthetic method where under mild reaction conditions (60-70°C, EtOH, argon) indoloquinolizidine enamines are converted to N(b)-substituted 1-oxo-1,2,3,4-tetrahydro-β-carbolines.[1,2]

In the course of our synthetic studies on eburnamine-vincamine type compounds[3-6] we synthesized the desethyl-20-epi-eburnamonine 1.[5,7] We have now found that, under the mild reaction conditions noted above, the corresponding enamine 2 can easily be converted to compound 3. This new and interesting dicarbonyl compound with a long chromophore would appear to be a good synthon for the preparation of new derivatives in the eburnamonine and/or 20-epi-eburnamonine series.



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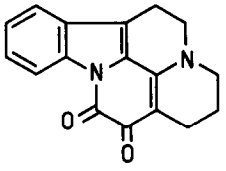
2 $\Delta^{20(21)}$



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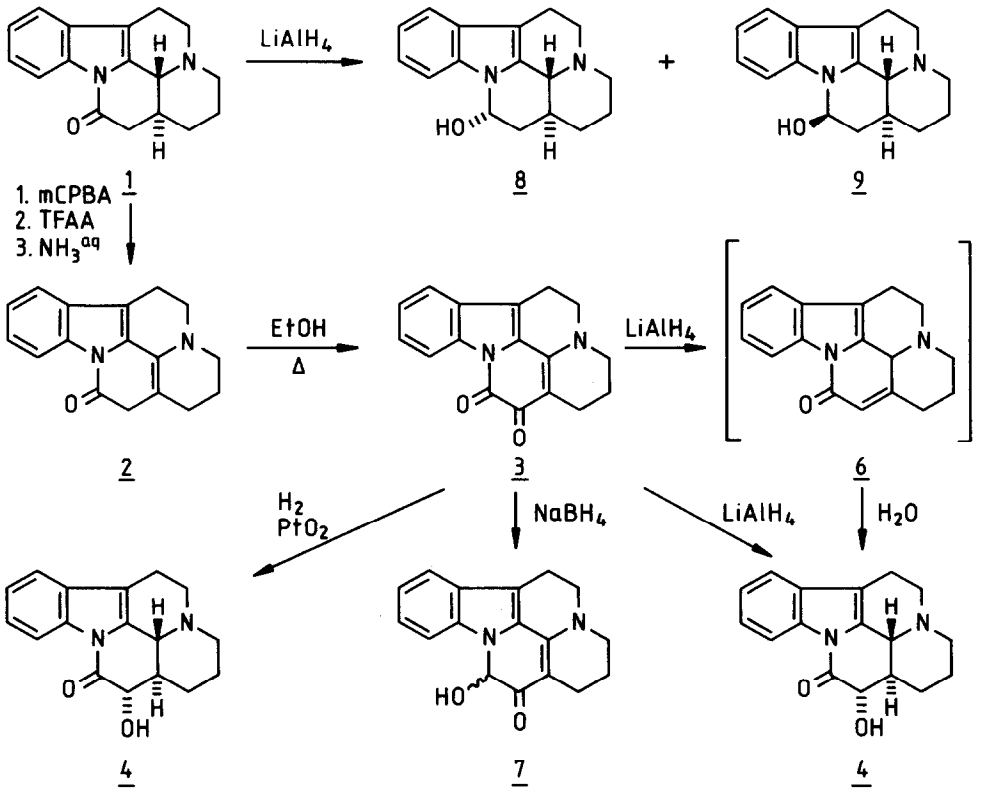
RESULTS AND DISCUSSION

The enamine 2 was synthesized as follows: The N-oxide of compound 1 (for preparation of compound 1 see ref. 5) was subjected to the modified Polonovski reaction conditions.[8] The iminium ion that formed was isolated as its perchlorate salt, and this under basic conditions was converted to the enamine 2.

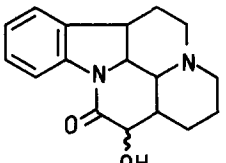
When the mild reaction conditions (60-70°C, EtOH, argon) used in our earlier work[1,2] were applied to 2, a different kind of oxidation product was formed. No ring opening took place, but a C(17) carbonyl compound with an intense orange color was formed instead (Scheme 1, compound 3). This method thus affords an easy way to functionalize C(17) in the desethyleburnamonine series.

To obtain model compounds and useful ^{13}C NMR data for further studies compound 3 was subjected to various reducing conditions (Scheme 1).



Scheme 1

Treatment of compound 3 with H_2/PtO_2 yielded compound 4 [C(20)H - C(21)H trans] where the C(17) hydroxyl group is in equatorial position. Traces of the other C(17) isomer were observed. When the reaction time was increased (vide infra), the indole double bond was slowly reduced to afford compound 5 (one isomer).



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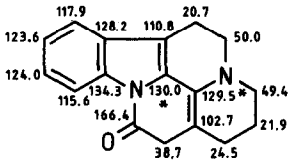
In analogy to earlier work,[9,10] and according to mass spectral data, $LiAlH_4$-reduction of compound 3 in dry THF[11] led to a compound for which the structure 6 is tentatively proposed. However, this compound was easily hydrated (during the purification procedure) to a compound identical with compound 4 formed under catalytic hydrogenation (vide supra).

In the $NaBH_4$-reduction of compound 3, the main product isolated after PLC was compound 7 (mainly one isomer), where only the C(16) lactam carbonyl was reduced.

For purposes of comparison, compound 1 was reduced with $LiAlH_4$ to give compounds 8 (vineburnol, known from its effects on cerebral insufficiency[12-14]) and 9 (Scheme 1).

^{13}C NMR data of all the compounds formed are given in Fig. 1.



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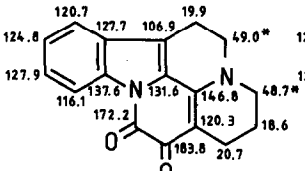

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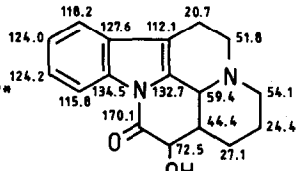

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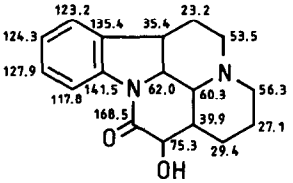
$(CDCl_3/MeOH\text{-}d_4, 1:1)$



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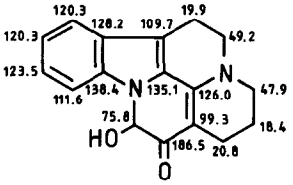

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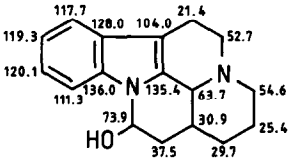
$(DMSO\text{-}d_6)$



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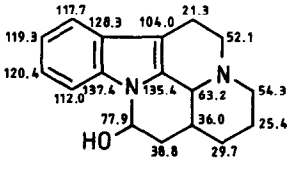
$(DMSO\text{-}d_6)$



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$(DMSO\text{-}d_6)$

Fig. 1

The formation of compound 3 is of great interest, because we now have a very convenient way to functionalize C(17) in the desethyleburnamonine series. The applicability of this reaction to syntheses of eburnamonine and/or 20-epi-eburnamonine derivatives is under investigation.

EXPERIMENTAL

UV spectra were recorded on a Perkin-Elmer Lambda 15 UV/VIS spectrophotometer. IR spectra (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer 700 spectrophotometer, using liquid film between NaCl crystals. ^1H and ^{13}C NMR spectra were measured on 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 $CDCl_3$ if not otherwise stated. Chemical shift data are given in ppm downfield from TMS. For ^{13}C NMR data see Fig. 1. Mass spectrometry (EIMS and HRMS) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compound 2
To the cooled solution (0°C, Ar-atm) of compound 1[5] (448 mg, 1.68 mmol) in dry CH_2Cl_2 (40 ml) m-chloroperbenzoic acid (mCPBA) (410 mg, 2.38 mmol) in dry CH_2Cl_2 (10 ml) was added during 15 min. Stirring was continued for 2 h. The solution was cooled to - 15°C and trifluoroacetic anhydride (TFAA) (0.61 ml, ~ 2.5 equiv.) was added during 10 min. The mixture was stirred for another 2h (-15°C ⟶ 0°C) and evaporated to dryness. The iminium salt formed was isolated as its perchlorate salt.
The perchlorate salt was dissolved in CH_2Cl_2 (30 ml) and stirred with 10% NH_3^{aq}. After the usual work-up the enamine 2 was obtained. Y: 402 mg, 90%.
IR: 1695 (C=O), 1615 (C=C).
^1H NMR: 7.17 - 7.47 (3H, m, arom. H), 8.29 (1H, m, H-12).
MS: 264 (M^+, 100 %), 263, 236; exact mass: 264.1263 (calc. for $C_{17}H_{16}N_2O$: 264.1263).

Preparation of compound 3
Compound 2 (400 mg, 1.52 mmol) in ethanol (99.5%, 50 ml) was gently refluxed for 48 h under argon and then evaporated to dryness. The crude product was purified by column chromatography (alumina, CH_2Cl_2 - MeOH, 98:2) to yield compound 3. Y: 168 mg, 40%. Mp: 234 - 236°C (dec.)
UV [EtOH 99.5%(ε)] λ_{max} 212 (31000), 280 (12800), 289 (11200), 339 (9400), 382 (8300), 448 (5500)nm.
IR: 1700 (>N-C=O), 1650 (>N-C=C-C=O), 1605 (C=C).
^1H NMR: 7.26 - 7.52 (3H, m, arom. H), 8.21 (1H, m, H-12).
MS: 278 (M^+), 250 (100%), 222, 221; exact mass: 278.1049 (calc. for $C_{17}H_{14}N_2O_2$: 278.1055).

Preparation of compounds 4 and 5
Catalytic hydrogenation (PtO_2) of compound 3 (81 mg, 0.29 mmol) afforded compounds 4 and 5 in various ratios depending on the reaction time (18-48 h). Total yield: ~ 58 mg, ~ 70%. The compounds were separated by preparative TLC on silica (CH_2Cl_2 - MeOH, 9:1). Trace amounts of the C(17) isomer of compound 4 (M^+ 282) were isolated as well.
Compound 4:
IR: 3350 (OH), 2820 and 2770 (Bohlmann bands), 1650 (C=O).
^1H NMR: 7.06-7.50 (3H, m, arom. H), 8.19 (1H, m, H-12).
MS: 282 (M^+, 100%), 281, 264, 209; exact mass: 282.1365 (calc. for $C_{17}H_{18}N_2O_2$: 282.1368).
Compound 5:
IR: 3400 (OH), 2830 and 2780 (Bohlmann bands), 1650 (C=O).
^1H NMR: 7.05 - 7.44 (3H, m, arom. H), 8.19 (1H, m, H-12).
MS: 284 (M^+, 100%), 126; exact mass: 284.1521 (calc. for $C_{17}H_{20}N_2O_2$: 284.1525).

Preparation of compound 4 via compound 6
$LiAlH_4$ (150 mg) in dry THF (25 ml) was refluxed for 15 min (Ar-atm). After cooling the mixture, compound 3 (90 mg, 0.32 mmol) in dry THF (15 ml) was added during 20 min. The mixture was stirred for 3.5 h at room temperature. Saturated Na_2SO_4 solution and ether were added and the inorganic precipitate was filtered off. The organic fraction was dried over Na_2SO_4 and evaporated under vacuum. For the main product the structure 6 (M^+ 264) was tentatively proposed (vide supra). Crude yield: 58 mg, 68%. However, during work-up (TLC, silica, CH_2Cl_2-MeOH, 9:1) hydration took place and compound 4 was formed. Analytical data were identical with those given for

compound 4 formed under catalytic reduction conditions (vide supra). In addition traces of a compound where the lactam carbonyl was reduced (M^+ 284) were detected.

Preparation of compound 7
$NaBH_4$ (200 mg) was added to a solution of compound 3 (122 mg, 0.44 mmol) in MeOH - H_2O (30 ml, 5:1). Stirring was continued for 4.5 h. Water was added and the mixture extracted several times with CH_2Cl_2. Crude yield: 61 mg, 50%. The product was purified by preparative TLC on silica (CH_2Cl_2-MeOH, 9:1).
IR: 3300 (OH), 1660 (C=O).
^1H NMR (DMSO-d_6): 7.18 - 7.70 (4H, m, arom. H).
MS: 280 (M^+, 100%), 279, 263, 224; exact mass: 280.1216 (calc. for $C_{17}H_{16}N_2O_2$: 280.1212).

Preparation of compounds 8 and 9
$LiAlH_4$ (450 mg) in dry THF (10 ml) was refluxed for 15 min (Ar-atm). To the cooled mixture compound 1 (150 mg, 0.56 mmol) in dry THF (7 ml) was added. The mixture was stirred for 2 h at room temperature. After the usual work-up a mixture of isomers 8 and 9 was isolated (2:3). Total yield: 127 mg, 85%. Almost pure 8 and 9 (slightly contaminated with each other) were obtained after preparative TLC on silica (CH_2Cl_2-MeOH, 9:1).
Compound 8:
IR (KBr): 3400 (OH).
^1H NMR (DMSO-d_6): 6.84 - 7.55 (4H, m, arom. H).
MS: 268 (M^+), 267, 250, 249(100%), 206; exact mass: 268.1570 (calc. for $C_{17}H_{20}N_2O$: 268.1576).
Compound 9:
IR (KBr): 3200 (OH).
^1H NMR (DMSO-d_6): 6.81 - 7.60 (4H, m, arom. H).
MS: 268 (M^+), 267, 250, 249(100%), 206; exact mass: 268.1570 (calc. for $C_{17}H_{20}N_2O$: 268.1576).

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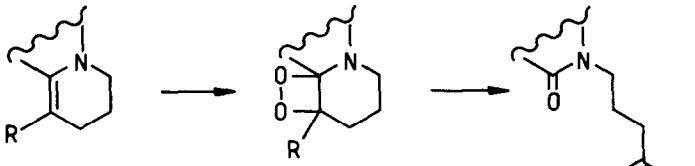
2. Reinvestigation of the reaction conditions (60-70°C, EtOH, argon) indicated the presence of a small amount of free oxygen in the reaction mixture, leading us to propose the following revised reaction mechanism (i→ii→iii). Jokela, R.; Lounasmaa, M. 9th Nordic Symposium on Natural Products Chemistry, Hirtshals, Denmark, 13.-18. June, 1988.



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11. If the THF used is not dry enough the reaction proceeds directly to compound 4 [C(20) protonation followed by reduction of formed iminium and ketonic carbonyl functions] (Scheme 1).

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