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AZA- AND OXA-EBURNAMONINE[+]

(REACTIONS WITH INDOLE DERIVATIVES, PART XLVII[1])

HEINZ HAMMER and EKKEHARD WINTERFELDT*

Institut für Organische Chemie der Universität Hannover,
Schneiderberg 1B, D-3000 Hannover, West Germany

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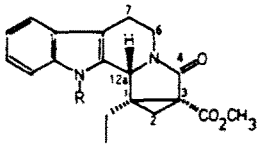
Abstract - Ring opening reactions of cyclopropane intermediates give rise to pentacyclic eburnamonines with a nitrogen or oxygen atom at position 15.

As an intermediate for a stereoselective synthesis of eburnamonine we recently prepared lactam (1)[2] in a highly stereoselective manner.

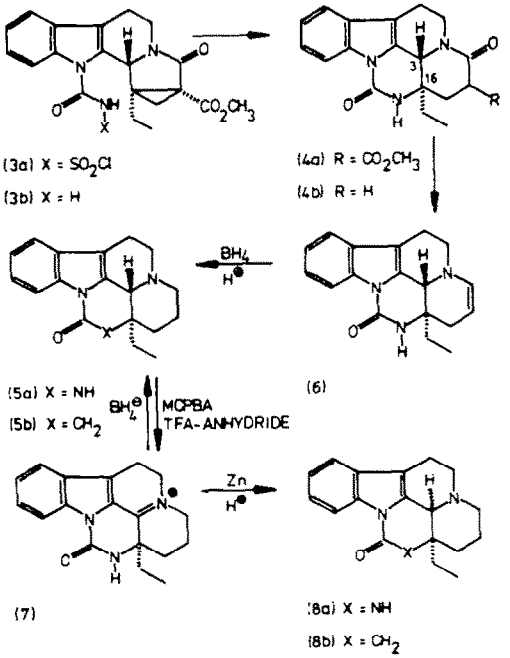


(1) R = H
(2) R = CO-CH_2-CO_2CH_3

While nucleophilic ring opening reactions at carbon atom (2) prove to be very efficient and easily give rise to intermediates en route to vinca alkaloids[3] the quarternary carbon atom (1) is not attacked at all, even if this is tried in an intramolecular way as for instance shown in the malonic ester derivative (2). Treating this compound even with very strong non-nucleophilic proton acceptors like sodium-hydride does not give rise to any cyclisation products, loss of the malonic acid residue being the only result under forcing reaction conditions.

One explanation of this failure could be the electron-overlap plane of the enolate anion being in plane with the indole moiety and thus perpendicular to the C_1-C_3-bond which is to be broken. To investigate the dependance of this process on stereochemical demands of the nucleophile we decided to choose the more flexible and easy to make urea derivative (3b) which in connection with another investigation in our laboratory had proven to efficiently attack cyclopropanes[4].

On treatment of (1) with CSI (chloro-sulfonyl -isocyanate) in methylene chloride a quite unpolar and unstable reaction product was noted in TLC [- presumably the acid chloride (3a) -]



[+]Dedicated with best wishes to Professor Dr. W.Reif at the occasion of his 60th birthday.

but on base-catalysed hydrolysis and work-up this was efficiently transformed into a stable acyl-indole (UV!) as the final reaction product.

Spectroscopic data of this compound however, immediately excluded the ring-open urea structure (3b). Proton resonance spectra completely lack the generally easy to locate cyclopropane protons[2]. Further evidence for the aza-eburnamonine type structure (4a) was gained from decarboxylation experiments as contrary to compounds of type (1) this material easily loses the ester group forming (4b) on treatment with lithiumiodide. Finally this decarboxylation product in ^{13}C-NMR-spectroscopy besides a dublet at 55.3 ppm (C_3) clearly shows a singulet at 56.3 ppm indicating the nitrogen bearing quarternary carbon-atom (C_{16}).

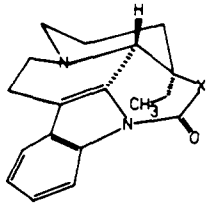
The structures of these pentacyclic products prove the intramolecular nucleophilic ring opening of the cyclopropane in this case to be a very efficient process and as the urea nitrogen turns out to be the active nucleophile a purely nucleophilic attack without any prior formation of a carbenium ion has to be considered (see below). A still open question at this stage however, is the configuration at C_3 and C_{16}, the relative configuration given in (4a) and (4b) being the most probable one on the basis of the assumption that no change in relative location of hydrogen and ethyl group in space occurs during the opening of the three membered ring.

To prove this the reduction of the lactam group was studied aiming at the corresponding indoloquinolizidines and expecting their NMR and infrared spectra to disclose the conformation and configuration of these compounds, particularly by comparison to the well studied carbon analogue eburnamonine (8b)[5].

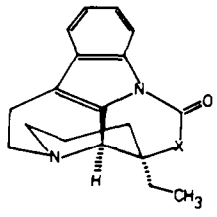
While Dibah reduction[6] stopped at the aldehyde-ammonia state and gave rise to enamine (6) on work-up, which needed further borohydride reduction to complete the process and to generate (5a), the Borch-reduction procedure[7] immediately yielded 90% of this product as crystalline material.

To also prepare the C_3-stereoisomer (8a) which is expected to represent the 15-aza-analogue of eburnamonine (8b), (5) was transformed into the iminium salt (7) via its N-oxide and subsequent Polonovsky elimination[8]. Simple borohydride reduction regenerates exclusively (5a), indicating already its trans-quinolizidine structure. On reduction with zinc in acetic-acid however, (8a) turns out to be the main reaction-product.

The configurations of (5a) and (8a) as given in Scheme 2 can be established by comparing spectroscopic data of these compounds to those of their carbon analogues (5b) and (8b). (8a) as was shown for eburnamonine is lacking Bohlmann bands[9] and accordingly the signal of the C_3-proton is recorded at 5.78 τ [1], while the CH_3-resonance appears at 8.95 τ [3] [(8b): 9.07 τ]. The corresponding resonance in epi-eburnamonine (5b) owing to its closer proximity to the aromatic system (see 5') is appearing at higher field (9.1-9.3 τ) and in good comparison (5a) is showing this signal at 9.1-9.28 τ. Additionally Bohlmann bands are recorded in (5a) as well as in (5b), and as may be expected with a trans-quinolizidine the protons at C_3 are hidden at τ-values higher than 6.6.[10]



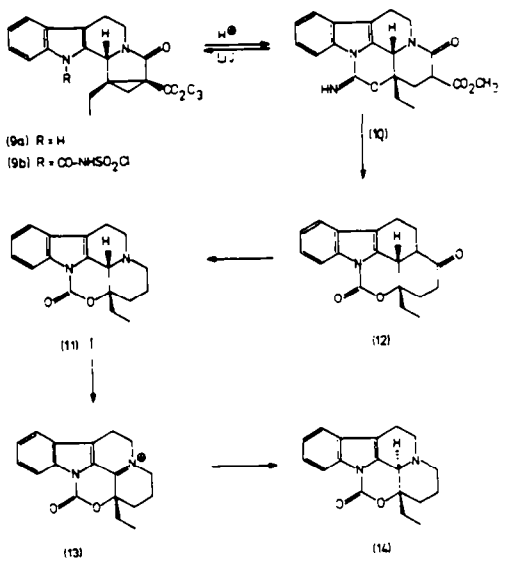
(5')



(8')

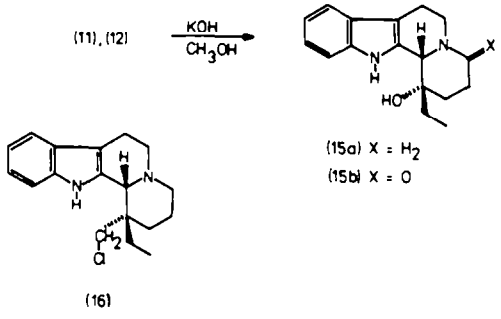
To investigate the stereospecifity of the cyclopropane cleavage we next looked into the same reaction starting from lactam (9a) which in intermolecular ring opening had proven to be particularly slow and was not attacked at the CH_2-group of the cyclopropane under these conditions at all[3]. So quite a different behaviour was to be predicted for this compound and this is true already for the primary addition with CSI [see (9b)].

In this case the sulfonic-acid chloride (9b) turns out to be comparatively stable against base and if heated in soda solution simply loses the urea group completely. Acid stability is very remarkable, too. Heating the compound in a 1:1-mixture of dry methylene chloride and trifluoro acetic acid is of no effect whatsoever, and it needs heating overnight in concentrated trifluoro acetic acid containing



a trace of water to convert (9b) into the imino compound (10). This cyclopropane cleavage with C-O-bond formation is indicated by spectral data, particularly by the ^{13}C-resonance of the quarternary carbon atom. While N-substitution gave rise to a signal at 56.3 ppm in (4b), this o-substituted product is showing a singulet at 79.3 ppm, comparable with tert.butyl esters which reveal resonances at 77-81 ppm.[11]
Competently in line with this structure assignment is the formation of the cyclic urethane (12) on further heating in aqueous trifluoro acetic acid, which can be explained by hydrolysis of ester as well as imino group and subsequent decarboxylation. The nucleophilic attack by the oxygen atom of the urea in this particular ring cleavage is obviously due to preceding proton catalysed formation of a cation which is captured by the urea. As noticed before in interactions of amides with cations it generally turns out to be the oxygen of an amide group that combines to the center of positive charge.[12]
One additional reaction of the imine (10) worth mentioning is the regeneration of the cyclopropane ring on treatment with lithium iodide in dimethylformamide. Instead of estersplitting nucleophilic displacement of the oxygen occurs with simultaneous hydrolysis of the urea to yield the starting material (9a).
As intramolecular capture of a cation is involved in the formation of (10), a cis-configuration as given in the formula is to be expected.

To prove this (12) by using the Borch procedure[7] was reduced to the corresponding oxa-eburnamonine (11). Spectral data of this compound which lacks Bohlmann bands and shows the quinolizidine proton at 5.73 τ is in accordance with this assignment. Additionally the CH_3-resonance is recorded at 8.98 [3] tr (J = 7 Hz). By using the N-oxide-Polonovsky sequence the preparation of iminium salt (13) was attempted. Unfortunately, in the oxa series regioselectivity is not as satisfactory as before, two comparatively unpolar enamines appearing together with the iminium salt in TLC-analysis. Without investigating their structure they were extracted from the water solution and the remaining iminium salt reduced with borohydride. The only product obtained this way turned out to be much less polar than the starting quinolizidine (11), which already indicates configuration (14). Definite proof is obtained from the strong Bohlmann bands in the infrared spectrum, the absence of the quinolizidine proton at τ-values lower than 6.6 and a methyl signal at 9.0-9.2 [3] m.
Having the cyclic urethanes (11) and (12) available their transformation into the hydroxy-indolo-quinolizidine (15a) was studied next. On treatment with base in methanol (11) and (12) gave rise to (15a) and (15b), respectively.



Both may be very useful intermediates in indole-alkaloid chemistry. On alkylation with Meerwein reagent and subsequent borohydride reduction (15b) is cleanly converted into (15a) the stereochemistry of which can be safely secured by comparing its spectral data to those of the well studied compound (16).[13]

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Infrared spectra were taken on Perkin-Elmer 457 and UV spectra on a Beckman DB-GT. ^{1}H-NMR spectra were taken with tetramethylsilane as reference on a Varian HA 100 and mass spectra were recorded on a CH-5 instrument at the temperatures indicated. Melting points were determined on a Kofler bank.

15-Aza-19oxo-18-carbomethoxy-isoeburnamonine (4a)

1 g of lactam (1) in a dried flask is dissolved in 80 ml of dry methylene chloride and at 0°C a solution of 0.27 ml CSI in 5 ml methylene chloride is added. After 4 h at room temperature the solvent is evaporated and the residue dissolved in a mixture of 70 ml acetone and 10 ml water, treated with saturated sodium bicarbonate solution. After 2 h the mixture is extracted with methylene chloride. After evaporation of the solvent the residue is crystallized from acetone and yields 450 mg of crystals. Purification of the mother liquor yields an additional 200 mg of the pure product. Yield 59%, m.p. 203°C; UV (CH_3OH): 295, 280 sh., 265, 230 nm; IR: 3300, 1745, 1710, 1660 cm^{-1}; NMR ($CDCl_3$): τ = 1.73-1.89 [1] m, 2.43-2.77 [3] m, 5.14 [1] s, 5.17-5.42 [1] m, 6.17 [3] s, 9.1 [3] m; MS: m/e 367 (M^+, 64), 338 (43). Found: C, 65.31; H, 5.85; N, 11.39. Calc.for $C_{20}H_{21}N_3O_4$: C, 65.36; H, 5.77; N, 11.44.

15-Aza-19oxo-isoeburnamonine (4b)

300 mg (4a) and 110 mg LiJ are heated in 30 ml dry dimethylformamide under reflux for 3.5 h. For workup the mixture is poured into sodium bicarbonate solution, extracted with methylene chloride, evaporated and the residue crystallized from acetone. Yield 79%, m.p. 271°C; UV: as in (4a); IR: 3400, 1710, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$): τ = 1.76-1.91 [1] m, 2.45-2.78 [3] m, 5.05-5.26 [2] m; ^{13}C-NMR (ppm): 6.5, 22.4, 56.3, 55.3, 19.6, 110.1, 130.1, 113.9, 123.6, 122.3, 118.7, 128.2, 168.4; MS: m/e 309 (M^+, 13), 308 (46). Found: C, 69.60; H, 6.30; N, 13.47. Calc. for $C_{18}H_{19}N_3O_2$: C, 69.75; H, 6.18; N, 13.55.

15-Aza-Δ18,19-isoeburnamonine (6)

A solution of 100 mg (4b) in 20 ml dry toluene is at 0°C treated with a 20% solution of Dibah in toluene. After 3 h at room temperature workup is done as given for (4b) and reaction product crystallized from acetone. Yield 84%, m.p. 199°C; UV: as in (4a); IR: 3420, 3250, 1700, 1660, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$): τ = 1.69 -1.87 [1] m, 2.47-2.81 [3] m, 3.96 [1] d, tr (J = 8 Hz, J = 1.3 Hz), 5.52 [1] m, 5.11 [1] s; MS: m/e 294 (M^+, 35), 293 (77). Found: 293.1527 (mass spectroscopy). Calc.for $C_{18}H_{21}N_3O$: 293.1528.

Treatment of (6) with borohydride in acetic acid at 0°C gives rise to (5a) which is also obtained on Borch reduction (see below).

15-Aza-isoeburnamonine (5a)

200 mg (4b) are dissolved in 10 ml dry methylene chloride, are treated with 700 mg triethyloxonium hexafluorophosphate. After 3 h at room temperature 10 ml of dry monoglyme are added at 0°C followed by 180 mg dry sodium borohydride. After 10' 5 ml methanol are added and the mixture left for 2 h at room temperature. Workup see under (4b). The evaporation residue crystallized from acetone. Yield 90%, m.p.231°C; UV: as in (4a); IR: 3420, 2800, 2750, 1700, 1660 cm^{-1}; ^{1}H-NMR ($CDCl_3$): τ = 1.75-1.92 [1] m, 2.47-2.86 [3] m, 9.10-9.28 [3] m; MS: m/e 296 (M^+, 16), 295 (69). Found: C, 73.00; H, 7.23; N, 14.14. Calc.for $C_{18}H_{19}N_3O$: C, 73.18; H, 7.17; N, 14.22

15-Aza-eburnamonine (8a)

100 mg of (5a) in 10 ml dry methylene chloride are treated at 0°C with 90 mg m-chloroperbenzoic acid, dissolved in 5 ml dry methylene chloride. After 1 h at room temperature the mixture is poured into soda solution, extracted with methylene chloride and evaporated. The residue is redissolved in 25 ml dry methylene chloride and mixed with a solution of 1 ml trifluoro acetic acid anhydride. After 1 h at room temperature the solvent is evaporated and the remaining residue dissolved in 10 ml acetic acid. 500 mg zinc dust are added in two portions and after 10' the reaction mixture is poured into sodium bicarbonate solution and extracted with methylene chloride. The reaction product remaining after evaporation of the solvent is separated by TLC and (8a) is thus obtained in 44% yield, m.p. 191°C; UV: as in (4a); IR: 3420, 1700, 1638 cm^{-1}; ^{1}H-NMR ($CDCl_3$): τ = 1.67-1.81 [1] m, 2.48-2.85 [3] m, 4.28 [1] s, 5.78 [1] s, 8.95 [3] tr (J = 7 Hz); MS: m/e 295 (M^+, 33), 294 (68). Found: 295.1684 (mass spectroscopy). Calc.for $C_{18}H_{19}N_3O$: 295.1684.

CSI adduct (9b)

In a nitrogen flushed flask 1 g (9a) is dissolved in 80 ml dry methylene chloride. At 0°C a solution of 0.27 ml CSI in 10 ml dry methylene chloride is slowly added. After standing overnight at room temperature ice-cold saturated sodium bicarbonate solution is added. After extraction with methylene chloride and evaporation of the solvent 950 mg of pure material are obtained. Yield 70%, m.p. 208°C (decomp.); UV: 210, 257, 309 nm; IR: 3420, 1740, 1660, 1550 cm^{-1}. Found: 465.0760 (mass spectroscopy). Calc. for $C_{20}H_{20}N_3O_6SCl$: 465.0761.

15-Oxa-19-imino-18-carbomethoxy-eburnamonine (10)

300 mg of (9b) are refluxed in trifluoro acetic acid for 8 to 12 h (reaction time dependant on moisture in trifluoro acetic acid). The solution is poured on ice and extracted with methylene chloride. After washing with saturated sodium bicarbonate solution and saturated sodium chloride solution. The solvent is evaporated and the residue crystallized from acetone. Yield 200 mg (80%), m.p. 198°C; UV: 212, 235, 265 (sh.), 271, 288, 295 nm; IR: 3450, 1740, 1660, 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$): τ = 1.49-1.65 [1] m, 2.47-2.84 [3] m, 5.15 [1] m, 5.38 [1] s, 6.33 [3] s, 7.96 [2] q (J = 7.5 Hz), 8.84 [3] tr (J = 7.5 Hz); ^{13}C-NMR 79.3 ppm and general signals for indolo-quinolizidine carbon atoms as given under (4b); MS: m/e 367 (M^+, 19), 366 (100). Found: C, 65.31; H, 5.77; N, 11.21. Calc. for $C_{20}H_{21}N_3O_4$: C, 65.36; H, 5.77; N, 11.43.

15-Oxa-19oxo-eburnamonine (12)

500 mg (9b) are refluxed in a mixture of 7 ml trifluoro acetic acid and 3 ml water. After 2 h water is added and the substance extracted with methylene chloride. After evaporation of the solvent and crystallisation of the residue from acetone 260 mg of pure crystals are obtained. Yield 65%, m.p. 229°C; UV: as given under (9b); IR: 1730, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$): τ = 1.70-1.88 [1] m, 2.47-2.84 [3] m, 4.98-5.16 [1] m, 5.28 [1] s, 8.80 [3] tr (J = 7.5 Hz); MS: m/e 310 (M^+, 39), 309 (100). Found: C, 69.66; H,

6.01; N, 9.01. Calc.for $C_{18}H_{18}N_2O_3$: C, 69.65; H, 5.85; N, 9.03.

15-Oxa-eburnamonine (11)

As described for the preparation of (5a) (12) is reduced to yield 83% of (11), m.p. 178°C; UV: as given under (9b); IR: 1735, 1645 cm^{-1}; ^{1}H-NMR ($CDCl_3$): τ = 1.69-1.81 [1] m, 2.45-2.75 [3] m, 5.73 [1] s, 8.98 [3] tr (J = 7 Hz); ^{13}C-NMR: (ppm) 7.3, 16.3, 22.4, 29.0, 29.4, 44.3, 50.4, 54.4, 86.8; MS: m/e 296 (M^+, 83), 223 (100). Found: C, 72.68; H, 6.82; N, 9.49. Calc.for $C_{18}H_{20}N_2O_2$: C, 72.93; H, 6.81; N, 9.45.

15-Oxa-isoeburnamonine (14)

N-Oxide formation and Polonovsky reaction are done as given under (8a). The residue remeining after evaporation is dissolved in 5 ml isopropanol, 10 ml of water are added and this solution twice extracted with ether which is discarded. After this 100 mg sodium borohydride are added in two portions at 0°C. After 15' 20 ml soda solution are added and the mixture extracted with methylene chloride. The residue remaining after evaporation of solvent is purified by TLC. Yield 38%, m.p. 196°C; UV: as given under (9b); IR: 2805, 2780, 1738, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$): τ = 1.71-1.90 [1] m, 2.47-2.79 [3] m, 9.0-9.2 [3] m. Found: 296.1522 (mass spectroscopy). Calc.for $C_{18}H_{20}N_2O_2$: 296.1525.

Hydroxy-indolo-quinolizidine (15b)

100 mg (12) are dissolved in 20 ml methanol, 10 ml of a 20% KOH solution are added and the mixture left overnight at room temperature. After dilution with water and extraction with methylene chloride the solvent is evaporated and the residue crystallized from acetone. Yield 76%, m.p. 198°C; IR: 3440, 1625 cm^{-1}; ^{1}H-NMR (DMSO-d_6): τ = -0.3 [1] s, 2.43-3.16 [4] m, 4.87 [1] s, 5.18-5.36 [2] m, 8.98 [3] tr (J = 7 Hz); MS: m/e 284 (M^+, 55), 171 (100). Found: C, 71.55; H, 7.19; N, 9.91. Calc.for $C_{17}H_{20}N_2O_2$: C, 71.79; H, 7.09; N, 9.85.

Hydroxy-indolo-quinolizidine (15a)

100 mg of (11) treated as given above give rise to 80% of the carbinol (15a); m.p. 186°C; IR: 3500, 3450, 2850, 2810, 2780 cm^{-1}; ^{1}H-NMR ($CDCl_3$): τ = 2.58-3.10 [4] m, 6.07 [1] s, 8.07 [2] q (J = 7 Hz), 8.96 [3] tr (J = 7 Hz); MS: m/e 270 (M^+, 43), 171 (100). Found: 270.1730 (mass spectroscopy). Calc.for $C_{17}H_{22}H_2O$: 270.1732.

REFERENCES

[1] This paper forms Part XLVII of the series Reactions with Indole Derivatives. Part XLVI: E.Bölsing and E.Winterfeldt, Chem.Ber.114,1932 (1981).

[2] R.Becker, G.Benz, M.Rösner, U.Rosentreter, and E.Winterfeldt, Chem.Ber.112, 1879 (1979).

[3] E.Bölsing, F.Klatte, U.Rosentreter, and E.Winterfeldt, Chem.Ber.112, 1902 (1979).

[4] Unpublished work Ph.D. paper H.Hammer, University Hannover, 1981.

[5] D.L.Coffen, D.A.Katonag, and F.Wong, J.Am. Chem.Soc.96, 3966 (1974).

[6] E.Winterfeldt, Synthesis 1975, 617.

[7] R.F.Borch, Tetrahedron Lett.1968, 61.

[8] A.Ahond, A.Cavé, C.Kanfan, H.P.Husson, J.de Rostolan, and P.Potier, J.Am.Chem.Soc.90, 5622 (1969).

[9] F.Bohlmann, Chem.Ber.91, 2157 (1958).

[10] M.Uskokovic, H.Bruderer, C.v.Planta, T.Williams, and A.Brossi, J.Am.Chem.Soc.86, 3364 (1964).

[11] S.W.Pelletier, Z.Djarmati, and C.Pape, Tetrahedron 32, 995 (1976).

[12] Y.J.Pocker, J.Chem.Soc. [London] 1959, 2319.

[13] P.Pfäffli, W.Oppolzer, R.Wenger, and H.Hauth, Helv.Chim.Acta 58, 1131 (1975).