SYNTHESIS OF NERSECULARININES

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Abstract - The transformation of cularines into N-nersecularine alkaloids using a Cope elimination to cleave the nitrogenated ring is reported.

INTRODUCTION

Our current studies\(^1\) on the chemical components of the Fumariaceae Corydalis claviculata (L.)DC, Sarcoponos enneaphylla (L.)DC and Sarcopnoes crassifolia (Desf.)DC have led us to the isolation of nersecularine\(^2\) (1a), nersecularidine (1b), nersecosarcocapnine (1c) and nersecosarcocapnidine (1d), the first examples of N-nersecularine alkaloids\(^3\).

In order to confirm their structures, previously established on the basis of spectroscopic data\(^2,3\), we embarked on a project aimed at their synthesis from their parent cularines (2), which had previously been isolated from plant material. To this end we have studied different ways of cleaving ring B in the desired manner (Scheme I).

We found that it is more difficult to cleave the ring B of cularines with simultaneous formation of a double bond in position 12-13 than it is the corresponding ring in aporphines\(^4\), a fact undoubtedly due to the former compounds not giving rise to an aromatic ring like that produced in the case of aporphines.

RESULTS AND DISCUSSION

When sarcapnine (2a) was refluxed with Ac\(_2\)O/KOAc, the intermediate quaternary amide did not undergo a C-elimination, but suffered a nucleophilic displacement by acetate on C-1, giving 3a (90%). Hydrolysis of the acetate 3a gave the alcohol 3b in 50% yield, which after dehydration with p-TsOH afforded nersecosarcocapnine (1c), but in very low yield (5%).
By using AcCl as the quaternization agent, ring opening took place in a similar way producing chloride 3c in 60% yield. A similar result was obtained when 3c was reacted with dichlorocarbene, affording formamide 3d (66%). Attempts to dehydrohalogenate derivatives 3c and 3d were not successful. The above results show that the activation of the nitrogen atom with an acyl group leads to substitution at C-1, whereas aporphines readily afford phenanthrene derivatives under such conditions. However, it is important to note that cularine methiodide, in which the nitrogen is quaternized by an alkyl group, undergoes β-elimination by treatment with sodium ethoxide.

In view of these findings, we approached the preparation of norsecocularines by the Cope elimination of cularine N-oxides, a procedure which recently has been used for the cleavage of aporphines.

Treatment of cularines 2a-d with m-CPBA afforded the cularine N-oxides 4a-d in 55-70% yields. Their structures were established on the basis of their spectroscopic data (Table I). Comparison between their chemical shifts and those of their parent cularines (Table II) showed a significant downfield shift of the NHe group and C-1 and C-a hydrogens, which is in agreement with the nitrogen quaternization. Each 1H-nmr signal appeared duplicated due to the formation of two isomeric N-oxides.

### TABLE I. - Spectroscopic data of cularine N-oxides (4a-d)

<table>
<thead>
<tr>
<th>Compound</th>
<th>1H-Nmr (250 MHz, CDCl3)δ</th>
<th>UV,CHC13,λ max(nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>6.97-6.59(m,ArH),5.10(dd, J2=3.2, J2=12.6,H-1),3.68(dd, J2=4.5,J2=16.1,H-α),4.44(dd, J2=4.5,J2=15.4, H-β)</td>
<td>770,1020,1100,1230, 1300,1480,1550,1630, 3000</td>
</tr>
<tr>
<td>4b</td>
<td>7.30-6.30(m,ArH),5.13(dda, H-1),4.44(dd, J2=3.0,J2=15.4, H-α),4.02(dda, H-α),3.87,3.84,3.74, 3.77(4s,4xOME),3.27,3.16(2s,2xNHe)</td>
<td>750,1010,1125,1230, 1480,1530,1630,3000, 3550</td>
</tr>
<tr>
<td>4c</td>
<td>7.09-6.30(m,ArH),5.02(dda, J2=2.6, J2=12.6, H-1),4.46(dd, J2=3.0,J2=15.4, H-α),4.13(dd, J2=2.7,J2=12.6, H-β)</td>
<td>760,840,1080,1130, 1315,1530,1630,2990</td>
</tr>
<tr>
<td>4d</td>
<td>6.86-6.63(m,ArH),5.20(dda, H-1),4.77(dda, H-1),4.00(dd, H-α),4.00,3.96,3.91,3.87,3.85, 3.84(6s,6xOME),3.34,3.09(2s,2xNHe)</td>
<td>770,1110,1305,1470, 1520,1630,2960,3560</td>
</tr>
</tbody>
</table>

a - not resolved
Transformation of cularine N-oxides to N-hydroxy-norsecocularines 5a-d was carried out by refluxing the N-oxides in toluene at 130°C, the yields ranging from 50 to 60%. The products were identified by their spectral data (Table III). All the Ms spectra showed the characteristic peaks of aliphatic amines at m/e 44 (CH2=NHHe) and 60 [CH2=NOHHe], resulting from an α-cleavage of the side chain.

Finally, reduction of the N-hydroxy-norsecocularines 5a-d with zinc powder and sulphuric acid afforded the N-norsecocularines 1a-d in 55-65% yield. Their spectral data were identical with those of the natural products.

### TABLE III. - Spectroscopic data of N-hydroxy-norsecocularines 5a-d

<table>
<thead>
<tr>
<th>Compound</th>
<th>1H-Nmr (250 MHz,CDCl3)</th>
<th>Uv(CHc1, )</th>
<th>Ir(film)</th>
<th>Ms(m/e,%), High Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>formula</td>
<td>δ (ppm)</td>
<td>λ&lt;sub&gt;max&lt;/sub&gt;(nm)</td>
<td>ν(cm&lt;sup&gt;-1&lt;/sup&gt;)</td>
<td>Ms</td>
</tr>
<tr>
<td>5a</td>
<td>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;20&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>6.93,6.68 (ABq;J=8.5,H=4,H=5), 6.90,6.79 (ABq;J=11.5,H=12, H=13),6.01(s,1H,ArH),6.65(s, 1H,ArH),3.99,3.83,3.91(3s,9H, 3xOHe),2.96,2.80(2m,4H,2-x- CH2),1.267(s,3H,NHe)</td>
<td>224,324,3370</td>
<td>357(M&lt;sup&gt;+&lt;/sup&gt;,0.3), 341(a(M&lt;sup&gt;+&lt;/sup&gt;-16), 3),326(a-15, 2),298(M&lt;sup&gt;+&lt;/sup&gt;-59, 9),60(52),44 (100)</td>
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<tr>
<td>5b</td>
<td>C&lt;sub&gt;19&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>6.90,6.84 (ABq;J=8.2,H=4,H=5), 6.64,6.70 (ABq;J=11.4,H=4, H=9),6.01(s,1H,ArH),6.65(s, 1H,ArH),3.95,3.84(2s,6H, 2xOHe),2.90,2.80(2m,4H,2-x- CH2),1.269(s,3H,NHe)</td>
<td>245,322,3350</td>
<td>343(M&lt;sup&gt;+&lt;/sup&gt;,1),327 (a(M&lt;sup&gt;+&lt;/sup&gt;-16, 9), 312(a-15,19), 244(M&lt;sup&gt;+&lt;/sup&gt;-59,7), 60(47),44(100)</td>
</tr>
<tr>
<td>5c</td>
<td>C&lt;sub&gt;18&lt;/sub&gt;H&lt;sub&gt;16&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>6.93,6.84 (ABq;J=8.4,H=4,H=5), 6.81,6.66 (ABq;J=8.5,H=12, H=13),6.76(ABq,2H),4.03,3.91, 3.65(3s,9H,3xOHe),2.90,2.83 (2m,4H,2-x-CH2),2.68(s,3H,NHe)</td>
<td>246,325,3360</td>
<td>357(M&lt;sup&gt;+&lt;/sup&gt;,3),341 (M&lt;sup&gt;+&lt;/sup&gt;-16,19),298 (M&lt;sup&gt;+&lt;/sup&gt;-59,100,60 (19),44(64)</td>
</tr>
<tr>
<td>5d</td>
<td>C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;15&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;</td>
<td>6.98-6.50(9,6H,ArH),3.95,3.90 (2s,6H,2xOHe),2.92,2.83(2m,2H, -CH2),2.67(s,3H,NHe)</td>
<td>242,319,3460</td>
<td>343(M&lt;sup&gt;+&lt;/sup&gt;,4),327 (a(M&lt;sup&gt;+&lt;/sup&gt;-16,22), 312(a-15,5,284 (M&lt;sup&gt;+&lt;/sup&gt;-59,16),60 (11),44(100)</td>
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</table>
EXPERIMENTAL

Material and Techniques

Melting points were determined with a Büchi apparatus and are uncorrected. IR spectra were taken in film with a Pye Unicam SP-1100 spectrometer. UV-visible spectra were determined on a Pye Unicam SP-1700 spectrophotometer. $^1$H-NMR spectra were recorded on a Brucker WH-250 spectrometer; chemical shifts are reported in parts per million (ppm) dowfield (δ) from internal tetramethylsilane; the solvent was deuteriochloroform. Routine mass spectra were obtained using a Kratos MS-25 instrument operating at 70 ev. High resolution Mss spectra were determined on a Kratos MS9/50 spectrometer.

All reactions were monitored by thin layer chromatography (tlc) carried out on 60 GF-254 silica gel plates using uv light and iodine vapour as the developing agent. Preparative tlc (ptlc) was performed on 0.5 mm layers of Merck 60 GF-254 silica gel.

13-Acetoxy-12,13-dihydro-N-acetyl-norsecosarcocapnine (3a)

To a solution of 256 mg (0.777 mmol) of sarcocapnine (2c) in 7 ml of AcOH, 304 mg (3.108 mmol) of KOAc was added and the mixture was refluxed for 4 h. The solvent was evaporated and water was added to the dry residue, which was extracted with CH$_2$Cl$_2$. The organic extracts were dried (Na$_2$SO$_4$) and evaporated to dryness. The residue obtained was purified by ptc on silica gel using 5% MeOH/CH$_2$Cl$_2$ as developing solvent to provide acetamide 3a (310 mg, 90%). UV (EtOH)λ max (log ε): 212 (4.04) and 285 (3.18). IR(film)ν max: 1010, 1090, 1230, 1640, 1730, 2920 cm$^{-1}$. $^1$H-NMR (CDCl$_3$, 250 MHz,δ): (signals appear duplicated due to the presence of two rotamers) 6.96 and 6.87 (ABq, J=6.5 Hz, H-4 and H-5), 6.90 and 6.81 (ABq, J=8.4 Hz, H-4 and H-5), 6.79 and 6.65 (ABq, J=8.5 Hz, H-10 and H-11), 6.76 and 6.55 (ABq, J=8.5 Hz, H-11 and H-10), 6.75 and 6.65 (ABq, J=8.5 Hz, H-11 and H-10), 6.50 and 6.20 (2m, H-13), 3.99, 3.92 and 3.85 (3s, 3xOHe), 2.96 and 2.93 (2s, NHMe), 2.07 and 1.99 (2s, OAc), 1.99 and 1.84 (2s, Ac). Ms m/z (%): 443.1939 (calculated for C$_{24}$H$_{29}$N$_{0}$O$_{7}$ : 443.1944) (M$^+$, 0.1), 383 (12), 297 (9), 86 (8), 44 (100), 43 (49).

Hydrolysis of 3a

Acetamide 3a (310 mg) dissolved in MeOH (15 ml) was treated with aqueous sodium hydroxide solution (50%, 15 ml) and refluxed for 4 h. Solvent was evaporated off to leave a small volume and water was added to the residue, which was extracted with CH$_2$Cl$_2$ (3x40 ml). The organic extracts were dried (Na$_2$SO$_4$) and evaporated to dryness. The residue obtained was purified by ptc on silica gel (10% MeOH/CH$_2$Cl$_2$) to provide alcohol 3b (126 mg, 50%). UV(CHCl$_3$)λ max: 246 and 284 nm; ir(film)ν max: 1150, 1260, 1500, 2940, 3350 cm$^{-1}$. $^1$H-NMR (CDCl$_3$, 250 MHz,δ): 6.97 and 6.66 (ABq, J=6.4 Hz, H-4 and H-5), 6.90 and 6.66 (ABq, J=8.3 Hz, H-10 and H-11), 5.20 (dd, J$_1$=6.3, J$_2$=2.8, H-13), 3.95, 3.94 and 3.85 (3s, 3xOHe), 3.40 (dd, J$_1$=2.6, J$_2$=13.7, H-12), 3.13 (dd, J$_1$=6.3, J$_2$=13.7, H-12'), 2.30 (s, NHMe). Ms m/z (%): 359.1713 (calculated for C$_{20}$H$_{25}$NO$_{5}$: 359.1732)(M$^+$,1), 341 (a)(M$^+$-H$_2$O,17), 316 (17), 296 (a-43, 19), 44 (CH$_2$=NHMe, 100).
To a solution of 150 mg of sarcocapnine (2c) in 1.5 ml of Ac2O, 0.1 ml of AcCl was added and the mixture was refluxed for 2 h. The mixture was evaporated to dryness and water was added to the residue, which was basified with 5% NaOH and extracted with CH2Cl2. The organic extracts were dried and evaporated to give an oily residue that was purified as above to afford acetamide (110 mg, 60%). Uv (CHCl3) λ max: 246 and 288 nm. Ir(film) ν max: 1110, 1280, 1500 and 1650 cm⁻¹. 1H-Nmr (CDCl3, 250 MHz, δ): (signals appear duplicated due to the presence of two rotamers in the ratio 3:1) 7.10 and 6.74 (ABq, J=8.5, H-4 and H-5), 7.05 and 6.73 (ABq, J=8.5, H-4 and H-5), 6.97 and 6.86 (ABq, J=8.4, H-10 and H-11), 4.47 (dd, J1=5.7, J2=8.0, H-13), 4.22 (dd, J1=4.0, J2=8.0, H-13), 4.07, 3.93 and 3.89 (3s, 3xOHe), 2.97 and 2.93 (2s, NHe), 2.09 and 1.94 (2s, AcI). Ms m/z (%): 419.1492 (calculated for C22H26N05: 419.1499).

General procedure for the m-CPBA oxidation of curarine alkaloids 2a-4

To a chloroform solution of the curarine alkaloids 2a-d, was added a three molar excess of m-CPBA in one portion at room temperature, with magnetic stirring maintained for 4 h. In order to remove the m-CPBA in excess and the m-chlorobenzoic acid, the mixture was put on a silica gel preparative-layer and chromatographed using 5% MeOH/CH2Cl2 as eluent. The spectroscopic data of the curarine N-oxides are shown in Table I. The yields were 55, 70, 60 and 65% for 4a-d, respectively. The signals of the Ms spectra always appeared impurificated with those of the β-elimination products, due to the easy they undergo a Cope Elimination by heating, so these data did not consider.

General procedure for the Cope Elimination of curarine N-oxides 4a-d

Each of the curarine N-oxides 4a-d (25 mg) was dissolved in a mixture of toluene/MeOH (6 ml: 0.5 ml) and heated to reflux. Solvent was evaporated to dryness and the residue was purified as above. The yields were 52, 60, 55 and 57% for 5a-d, respectively. Their spectroscopic data are shown in Table III.
General procedure for the reduction of N-hydroxy norsecocullarines 5a-d

Each of the N-hydroxy norsecocullarines 5a-d (15 mg) was dissolved in a mixture H2SO4(20%)/MeOH (4ml:0.5ml). An excess of zinc powder (200 mg) was added at room temperature and the mixture was maintained with magnetic stirring for 4 h. The mixture was filtered and the filtrate was basified with 5% NaOH and extracted with CHCl3. The organic extracts were dried and evaporated to dryness to give a residue that was purified as above. The spectral data of the reaction products (yields were 55, 60, 65 and 58% for 1a-d, respectively) were identical to those of the natural products.

ACKNOWLEDGEMENTS

We thank the CAICYT (Spain) for its financial support and Prof. Maurice Shamma of the Pennsylvania State University (USA) for the high resolution mass spectra.

REFERENCES


Received, 31st March, 1988