SYNTHESIS OF NORSECOCULARINES

Emilia Tojo, Domingo Domínguez, and Luis Castedo*

Departamento de Química Orgánica de la Facultad de Química y Sección de Alcaloides del CSIC. Santiago de Compostela, Spain

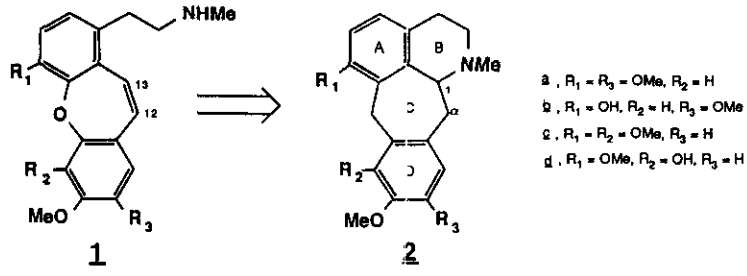
Abstract - The transformation of cularines into N-norsecocularine alkaloids using a Cope elimination to cleave the nitrogenated ring is reported.

INTRODUCTION

Our current studies[1] on the chemical components of the Fumariaceae Corydalis claviculata (L.)DC, Sarcocapnos enneaphylla (L.)DC and Sarcocapnos crassifolia (Desf.)DC have led us to the isolation of norsecocularine[2] (1a), norsecocularidine (1b), norsecosarcocapnine (1c) and norsecosarcocapnidine (1d), the first examples of N-norsecocularine 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).

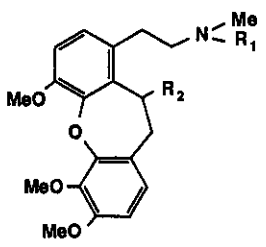
We found that it is more difficult to cleave the ring B of cularines with simultaneous formation of a double bond in position 12-13 than it is the corresponding ring in aporphines[4], a fact undoubtedly due to the former compounds not giving rise to an aromatic ring like that produced in the case of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



SCHEME 1

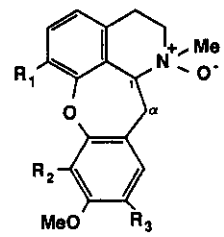
RESULTS AND DISCUSSION

When sarcocapnine (2c) was refluxed with Ac_2O/KOAc, the intermediate quaternary amide did not undergo a β-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 norsecosarcocapnine (1c), but in very low yield (5%).



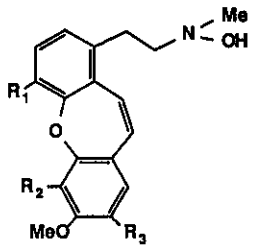
3

a , R_1 = Ac, R_2 = OAc
b , R_1 = H, R_2 = OH
c , R_1 = Ac, R_2 = Cl
d , R_1 = CHO, R_2 = Cl



4

a , R_1 = R_3 = OMe, R_2 = H
b , R_1 = OH, R_2 = H, R_3 = OMe
c , R_1 = R_2 = OMe, R_3 = H
d , R_1 = OMe, R_2 = OH, R_3 = H



5

a , R_1 = R_3 = OMe, R_2 = H
b , R_1 = OH, R_2 = H, R_3 = OMe
c , R_1 = R_2 = OMe, R_3 = H
d , R_1 = OMe, R_2 = OH, R_3 = H

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 2c 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[5,6]. 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[7].

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[8].

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 NMe group and C-1 and C-α hydrogens, which is in agreememt with the nitrogen quaternization. Each ^{1}H-nmr signal appeared duplicated due to the formation of two isomeric N-oxides.

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

Compound	^{1}H-Nmr (250 MHz, $CDCl_3$) δ	Ir, ν(cm^{-1})	Uv, $CHCl_3$, λ_{max}(nm)
4a	6.97-6.59(m,ArH),5.10(dd,J_1=3.2, J_2=12.6,H-1),4.64(dd[a],H-1),4.35(dd, J_1=3.2,J_2=15.7,H-αα),4.00(dd,J_1=5.0, J_2=16.1,H-αα),3.92,3.89,3.88, 3.87,3.84,3.78(6s,6xOMe),3.33, 3.17(2s,2xNMe)	770,1020,1120,1230, 1300,1480,1550,1630, 3000	242,287
4b	7.30-6.30(m,ArH), 5.13(dd[a],H-1),4.44 (dd[a],H-1),4.08(dd,J_1=3.0,J_2=15.4, H-αα),4.02(dd[a],H-αα), 3.87,3.84,3.74, 3.77(4s,4xOMe),3.27,3.06(2s,2xNMe)	750,1010,1125,1230, 1480,1530,1630,3000, 3550	244,291
4c	7.09-6.30(m,ArH),5.02(dd,J_1=2.6,J_2=12.6, H-1),4.46(dd[a],H-1),4.39(dd,J_1=2.6, J_2=15.4,H-αα),4.13(dd,J_1=2.7,J_2=12.6, H-αα),4.04,3.95,3.94,3.88,3.85, 3.84(6s,6xOMe),3.34,3.09(2s,2xNMe)	760,840,1080,1130, 1315,1530,1630,2990	244,284
4d	6.96-6.63(m,ArH),5.20(dd[a],H-1),4.77 (dd[a],H-1),4.42(dd[a],H-αα),4.00(dd[a], H-αα),3.96,3.91,3.87,3.86(4s,4xOMe), 3.40,3.24(2s,2xNMe)	770,1110,1305,1470 1520,1630,2960,3560	244,283

a.- not resolved

TABLE II. - ^{1}H-Nmr chemical shifts for cularines and their N-oxides

	NMe	H-1	H-αα
2a	2.59	4.46	3.28
4a	3.33,3.17	5.10,4.64	4.35,4.00
2b	2.56	4.28	3.20
4b	3.27,3.06	5.13,4.44	4.08,4.02
2c	2.58	4.33	3.24
4c	3.34,3.09	5.02,4.46	4.39,4.32
2d	2.60	4.48	3.35
4d	3.40,3.24	5.20,4.77	4.42,4.00

Transformation of cularine N-oxides to N-hydroxynorsecocularines 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 (CH_2=$\overset{+}{N}$HMe) and 60 [CH_2=$\overset{+}{N}$(OH)Me], resulting from an α-cleavage of the side chain.

Finally, reduction of the N-hydroxynorsecocularines 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

Compound formula	^{1}H-Nmr (250 MHz,$CDCl_3$) δ(ppm)	Uv($CHCl_3$) λ_{max}(nm)	Ir(film) ν(cm^{-1})	Ms(m/e,%)	High Resolution Ms
5a $C_{20}H_{23}NO_5$	6.93,6.86(ABq,J=8.5,H-4,H-5), 6.90,6.79(ABq,J=11.5,H-12, H-13),6.91(s,1H,ArH),6.65(s, 1H,ArH),3.89,3.84,3.91(3s,9H, 3xOMe),2.98,2.80(2m,4H,2x-CH_2-),2.67(s,3H,NMe)	224,324	3370	357(M^+,0.3), 341(a)(M^+-16, 3),326(a-15, 2),298(M^+-59, 9),60(52),44 (100)	f:357.1569 c:357.1576
5b $C_{19}H_{21}NO_5$	6.90,6.84(ABq,J=8.2,H-4,H-5), 6.84,6.70(ABq,J=11.4,H-12, H-13),6.86(s,1H,ArH),6.63(s, 1H,ArH),3.86,3.84(2s,6H, 2xOMe),2.90,2.80(2m,4H,2x-CH_2-),2.69(s,3H,NMe)	245,322	3350	343(M^+,1),327 (a)(M^+-16,9), 312(a-15,19), 284(M^+-59,7), 60(47),44(100)	f:343.1411 c:343.1419
5c $C_{20}H_{23}NO_5$	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, 3.85(3s,9H,3xOMe),2.90,2.83 (2m,4H,2x-CH_2-),2.68(s,3H,NMe)	246,325	3360	357(M^+,3),341 (M^+-16,19),298 (M^+-59,100),60 (19),44(64)	f:357.1554 c:357.1576
5d $C_{19}H_{21}NO_5$	6.98-6.60(m,6H,ArH),3.95,3.90 (2s,6H,2xOMe),2.92,2.83(2m,2H, -CH_2-),2.67(s,3H,NMe)	242,319	3460	343(M^+,4),327 (a)(M^+-16,22), 312(a-15,5),284 (M^+-59,16),60 (11),44(100)	f:343.1408 c:343.1419

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 WM-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. and the High resolution Ms spectra were determined on a Kratos MS9/50 spectrometer.

All reactions were monitored by thin layer chromatrography (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 Ac_2O, 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_2Cl_2. The organic extracts were dried (Na_2SO_4) and evaporated to dryness. The residue obtained was purified by ptlc on silica gel using 5% MeOH/CH_2Cl_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=8.5 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-11 and H-10), 6.76 and 6.65 (ABq, J=8.5 Hz, H-11 and H-10), 6.30 and 6.20 (2m, H-13), 3.99, 3.92 and 3.85 (3s, 3xOMe), 2.96 and 2.93 (2s, NMe), 2.07 and 1.99 (2s, OAc), 1.99 and 1.84 (2s, Ac). Ms m/z (%): 443.1939 (calculated for $C_{24}H_{29}NO_7$: 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_2Cl_2 (3x40 ml). The organic extracts were dried (Na_2SO_4) and evaporated to dryness. The residue obtained was purified by ptlc on silica gel (10% MeOH/CH_2Cl_2) to provide alcohol 3b (126 mg, 50%). Uv($CHCl_3$)λ_{max}: 246 and 284 nm; ir(film)ν_{max}: 1150, 1280, 1500, 2940, 3350 cm^{-1}. ^{1}H-Nmr ($CDCl_3$, 250 MHz,δ): 6.97 and 6.68 (ABq, J=8.4 Hz, H-4 and H-5), 6.90 and 6.86 (ABq, J=8.3 Hz, H-10 and H-11), 5.20 (dd, J_1=6.3, J_2=2.6, H-13), 3.95, 3.94 and 3.83 (3s, 3xOMe), 3.48 (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, NMe). Ms m/z (%): 359.1713 (calculated for $C_{20}H_{25}NO_5$: 359.1732)(M^+,1), 341 (a)(M^+-H_2O,17), 316 (17), 298 (a-43, 19), 44 (CH_2=$\overset{+}{N}$HMe, 100).

13-Chloro-12,13-dihydro-N-acetyl-norsecosarcocapnine (3c)

To a solution of 150 mg of sarcocapnine (2c) in 1.5 ml of Ac_2O, 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 CH_2Cl_2. The organic extracts were dried and evaporated to give an oily residue that was purified as above to afford acetamide 3c (110 mg, 60%). Uv ($CHCl_3$) λ_{max}: 246 and 288 nm. Ir(film) ν_{max}: 1110, 1280, 1500, 1650 and 2940 cm^{-1}. ^{1}H-Nmr ($CDCl_3$, 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, J_1=3.2, J_2=8.0, H-13), 4.22 (dd, J_1=4.0, J_2=8.0, H-13), 4.07, 3.93 and 3.89 (3s, 3xOMe), 2.97 and 2.93 (2s, NMe), 2.09 and 1.94 (2s,Ac). Ms m/z (%): 419.1492 (calculated for $C_{22}H_{26}NO_5$: 419.1499)(M^+, 0.1), 383 (M^+-HCl, 29), 370 (66), 310 (44), 297 (46), 269 (29), 44 (100).

13-Chloro-12,13-dihydro-N-formyl-norsecosarcocapnine (3d)

140 mg of sarcocapnine (2c) in 75 ml of $CHCl_3$ were stirred with 7 ml of 50% NaOH and a catalytic amount of TBAC at room temperature. After 5 h, the organic phase was decanted, washed with 10% HCl, dried and evaporated to dryness. The residue obtained was purified as above to give formamide 3d (110 mg, 66%). Uv ($CHCl_3$) λ_{max}: 246 and 288 nm. Ir(film) ν_{max}: 1110, 1280, 1500, 1670 and 2930 cm^{-1}. ^{1}H-Nmr ($CDCl_3$, 250 MHz,δ): (signals appear duplicated due to the formation of two rotamers in the ratio 1:1.5) 8.05 and 7.83 (2s, CHO), 7.08 and 6.73 (ABq, J=8.5, H-4 and H-5), 7.04 and 6.72 (ABq, J=8.5, H-4 and H-5), 6.86 (ABq, H-10 and H-11), 6.97 and 6.85 (ABq, J=8.4, H-10 and H-11), 4.50 (dd, J_1=5.7, J_2=7.9, H-13), 4.20 (dd, J_1=5.1, J_2=8.5, H-13), 4.06, 3.92 and 3.89 (3s, 3xOMe), 2.94 and 2.90 (2s, NMe). Ms m/z (%): 405.1316 (calculated: 405.1343)(M^+, <0,1), 369 (17), 356 (70), 310 (3), 297 (28), 269 (31), 72 (24), 44 (100).

General procedure for the m-CPBA oxidation of cularine alkaloids 2a-d

To a chloroform solution of the cularine 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 chromatographied using 5% MeOH/CH_2Cl_2 as eluent. The spectroscopic data of the cularine 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 cularine N-oxides 4a-d

Each of the cularine 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-hydroxynorsecocularines 5a-d

Each of the N-hydroxynorsecocularines 5a-d (15 mg) was dissolved in a mixture H_2SO_4(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 $CHCl_3$. 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

1. For previous work see: a/J.M. Boente, L. Castedo, D. Domínguez, and A.R. de Lera, Tetrahedron Lett., 1986, 27, 5535; b/L. Castedo, D. Domínguez, S. López, A.R. de Lera, E. Tojo, and C. Villaverde, Heterocycles, 1987, 26, 29.
2. J.M. Boente, D. Domínguez, and L. Castedo, Heterocycles, 1986, 24, 3359.
3. L. Castedo, D. Domínguez, S. López, E. Tojo, and C. Villaverde, Heterocycles, 1987, 26, 591.
4. M. Shamma, "The Isoquinoline Alkaloids", Academic Press, London, 1972.
5. S.R. Johns, J.A. Lamberton, and A.A. Sioumis, Aust. J. Chem., 1966, 19, 2339.
6. L. Castedo, J.L. Castro, and R. Riguera, Heterocycles, 1982, 19, 209.
7. J.M. Boente, L. Castedo, D. Domínguez, A. Fariña, A.R. de Lera, and M.C. Villaverde, Tetrahedron Lett., 1984, 25, 889.
8. Sheng-Teh Lu and Yang-Chang Wu, Heterocycles, 1985, 23, 3085.

Received, 31st March, 1988