*Tetrahedron* Vol 42, No. 24, pp. 6669 to 6672, 1986
Printed in Great Britain

0040-4020/86 $3.00 + .00
Pergamon Journals Ltd.

# SYNTHESIS OF SECOISOQUINOLINE ALKALOIDS

## TOTAL SYNTHESIS OF CRYPTOPLEUROSPERMINE

MARIA D. ROZWADOWSKA* and MARIA CHRZANOWSKA

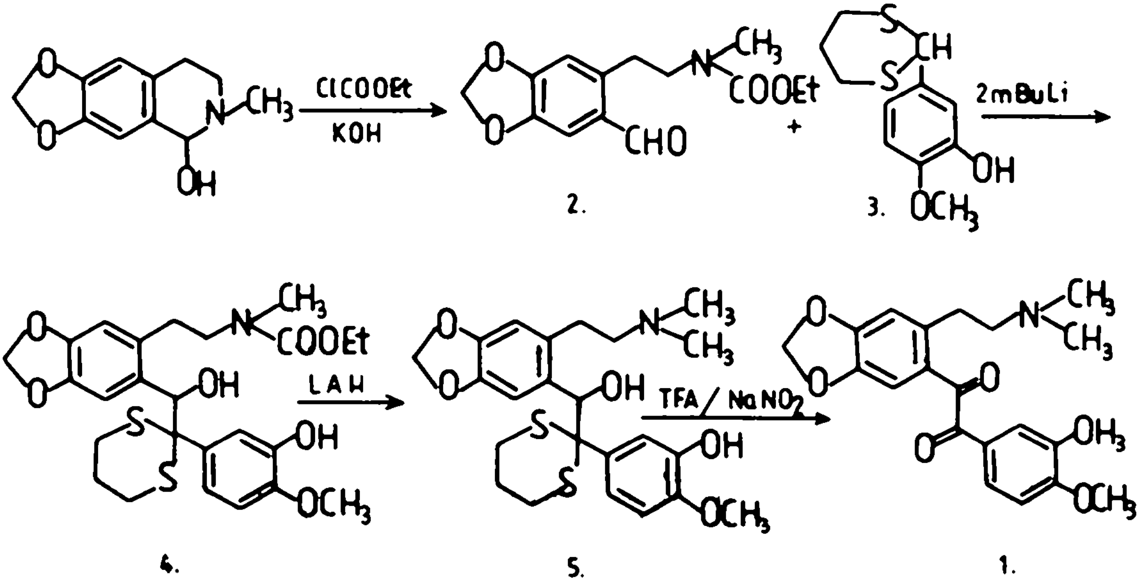
Faculty of Chemistry, Adam Mickiewicz University,
60-780 Poznań, Grunwaldzka 6, Poland

(*Received in U.K.* 13 *October* 1986)

Abstract - Cryptopleurospermine (1), a 1,2-secobenzylisoquinoline alkaloid was synthesized from hydrastinine derivative 2 and isovanillin 1,3-propylene dithioacetal 3. The formation of C-C bond between these two synthons involved addition of dilithio salt of dithian 3 to aldehyde group in 2. Reduction and hydrolysis of the masking group in addition product 4 furnished the synthesis.

Cryptopleurospermine (1), a 1,2-secobenzylisoquinoline alkaloid has been isolated from the bark of Cryptocarya pleurosperma White and Francis (Lauraceae) by Jones et al.[1]. Spectroscopic and degradative studies have shown that cryptopleurospermine (1) is a substituted benzil, containing the N,N-dimethylaminoethyl side chain characteristic of many of the secoisoquinoline alkaloids.

Following our model experiments[2], in result of which we worked out a general method of synthesis of 1,2-secobenzylisoquinoline alkaloids, we performed the synthesis of cryptopleurospermine (1). As substrates we applied aromatic aldehydes: hydrastinine derivative 2 and isovanillin. To form C-C bond between these two aldehydes we adapted isovanillin to nucleophilic acylation by transforming it into dithioacetal 3. Under the action of two molar equivalents of butyllithium in THF at -76°C dithioacetal 3 was transformed into dianion which reacted readily with derivative 2 giving α-hydroxythioacetal 4 in 67% yield.



IR spectrum of compound 4 exhibited an absorption characteristic of urethane carbonyl at 1665 cm$^{-1}$. The PMR spectrum showed signals for amide N-methyl group (2.87δ), one methoxy group (4.00δ) and one methylenedioxy substituent (6.00δ), five aromatic proton multiplet (6.62-7.58δ) and one triplet (1.23δ) together with one quartet (4.03δ) characteristic of ethoxycarbonyl group protons. Methylene groups of dithian ring and those from aminoethyl chain superimposed on each other forming a broad multiplet within the range 1.93-3.50δ . The EI MS showed a M-18 ion peak and two peaks at m/z 241 (100 %) and m/z 280 (44 %) owing to the cleavage of the molecule into two parts by fission of the bond between the two benzylic carbon atoms.

Lithium aluminum hydride reduction of compound 4 caused a transformation of the urethane function into N,N-dimethyl-aminoethyl substituent, yielding amine 5 in 72 % yield. The IR spectrum of amine 5 did not exhibit the presence of carbonyl group. Both PMR and mass spectrum revealed the presence of N,N-dimethylaminoethyl group in the form of six-proton singlet at 2.20δ and base peak at m/z = 58 coming from $CH_2{=}N(CH_3)_2^+$ ion, respectively. Moreover, the structure of compound 5 was confirmed by the presence of molecular ion in the mass spectrum at m/z = 463.

Deblocking of the dithian masking group in amine 5 was carried out by using two independent methods. The application of both systems: $CF_3COOH/NaNO_2$[3] and formalin in $CF_3COOH$[4] led directly to cryptopleurospermine (1) in yields 42 % and 63 %, respectively. It is evident that the deblocking process was accompanied by autoxidation of expected benzoin to benzil. A similar process was observed also in our model experiments[2].

The over-all yield of our synthesis attained 28 % and the prepared cryptopleurospermine (1) after crystallisation from acetone or/and methylene chloride formed yellow needles of m.p. 183-184°C. Furthermore, spectra of our alkaloid correspond in their general characteristic to those reported for the natural product[1]. Since the m.p. was a bit lower (lit. 188-190°C[1]), our sample was throughly examined. The molecular ion $M^+$ = 371.1369 recorded by HRMS was in good agreement with the value calculated theoretically for $C_{20}H_{21}NO_6$ (371.1368). Also the elemental analysis fully corresponded to this molecular formula. We also prepared and characterized hydrochloride salt of cryptopleurospermine (1), which formed yellow crystalls melting at 225-226°C. In its PMR spectrum the expected down field shift (to 3.09δ and 3.48δ) of absorption of protons from $N{-}CH_3$ and $-CH_2{-}N$ groupings was observed.

Our synthesis of cryptopleurospermine (1) is not the only synthesis of this alkaloid. The first to synthesize it was Dunmore et al.[5] who applied O-trimethylsilyl cyanohydrin of 2-dimethylaminoethyl-4,5-methylenedioxybenzaldehyde as the equivalent of nucleophilic acyl group and methoxymethy ether of isovanillin as the electrophilic partner. Upon condensation of these two substrates, produced benzoin was oxidized and hydrolysed resulting in cryptopleurospermine (1). The synthesis[5] has been reported in a form of a short communication which did not disclose any experimental data neither the characteristics of obtained compounds.

In the present synthesis of cryptopleurospermine (1) no blocking of the phenolic hydroxy group was needed making the synthesis clearly shorter.

## EXPERIMENTAL

M.ps.were determined on a Köfler block. IR spectra were taken in KBr pellets on a Perkin-Elmer 180. PMR spectra were recorded on a Tesla BS 467 (60 MHz) and on Jeol FX-90 (90 MHz) in chloroform-d soln with TMS as internal standard. Mass spectra were taken on a Jeol JMS-D-100 at 75 eV. HRMS measurements were performed by peak matching (resolution = 8000) using perfluorokerosene as the reference standard. Purity of all prepared compounds was checked by TLC on precoated plates (Merck, silicagel 60 F-254). MN silicagel 60 200-300 mesh was used for column chromatography.

### 2-(3-Hydroxy-4-methoxyphenyl)-1,3-dithian (3)

To a well stirred soln of isovanillin (3.04 g, 20 mmol) in glacial acetic acid (20 ml), 1,3-propanedithiol (3.24 g, 30 mmol) and $BF_3$ etherate (0.9 g, 6 mmol) were added at ice-bath temp. and left in the refrigerator overnight. The crystalline solid was filtered off and washed with water. Recrystallisation from acetic acid yielded dithian 3 with 89 % yield. M.p. 95-96°C. IR $cm^{-1}$: 3500 (OH). PMR $\delta$ : 2.12 (m,2H,dithian-$CH_2$), 2.93-3.20 (m,4H,dithian-$CH_2$), 3.92 (s,3H,$OCH_3$), 5.17 (s,1H,dithian-$C_2$-H), 5.75 ( s,1H,disappears on treatment with $D_2O$,OH), 6.77--7.20 (m,3H,ArH). MS m/z (%): 242 ($M^+$,50), 168 (100), 137 (14), 106 (6). Found: C 54.51, H 5.87. Calc. for $C_{11}H_{14}O_2S_2$:C 54.52, H 5.82 %.

### 2-Hydroxy-2(2-[β-(N-ethoxycarbonyl-N-methyl)aminoethyl]-4,5-methylenedioxyphenyl) -1-(3-hydroxy-4-methoxyphenyl)ethanone 1,3-propylenedithioacetal (4)

n-Butyl lithium (2 mmol) was added to a soln of dithian 3 (0.48 g, 2 mmol) in THF (8 ml) at -76°C under argon and kept at this temp for 40 min, then at -20°C for 30 min yielding a yellow soln. It was cooled to -76°C again and hydrastinine derivative 2[6] (0.56 g, 2 mmol) in THF (8 ml) was introduced dropwise. The mixture was kept at -60°C for 30 min and at -20°C for another 30 min. When it reached the room temp it was poured on 20 % ammonium chloride, then phases were separated and the aqueous one was extracted with benzene. The combined organic extracts were dried, evaporated and the resulting oil (1.05 g) was twice crystallized from methanol to give 0.70 g (67 %) of crystalline 4. M.p. 197-199°C. IR $cm^{-1}$: 3480, 3250 (OH), 1665 (C=O). PMR $\delta$ : 1.23 (t,J=7Hz,3H,$NCOOCH_2C\underline{H}_3$), 1.93(m, 2H,dithian-$CH_2$), 2.30-3.50 (m,9H,1H disappears on treatment with $D_2O$,OH,$ArCH_2CH_2N$, dithian-$CH_2$), 2.87 (s,3H,$NCH_3$), 4.00 (s,3H,$OCH_3$), 4.18 (q,J=7Hz,3H,1H dissapears on treatment with $D_2O$,OH,$NCOOC\underline{H}_2CH_3$), 5.27 (s,1H,$ArC\underline{H}OH$), 6.00 (s,2H,$OCH_2O$), 6.62 (s,1H,ArH), 6.85 (s,1H,ArH), 6.98 (s,1H,ArH), 7.43 (s,1H,ArH), 7.58 (m,1H, ArH). MS m/z (%): 503 (M-$H_2O$,1), 415 (2), 280 (44), 241 (100), 206 (43), 177(19), 167 (21), 116 (28), 72 (9), 44 (73). Found: C 57.23, H 5.91, N 2.61. Calc. for $C_{25}H_{31}NO_7S_2$: C 57.56, H 5.99, N 2.69 %.

### 2-Hydroxy-2-(2-[β-(N,N-dimethyl)aminoethyl]-4,5-methylenedioxyphenyl)-1-(3-hydroxy-4-methoxyphenyl)-ethanone 1,3-propylenedithioacetal (5)

Compound 4 (0.66 g, 1.26 mmol) was dissolved in THF (150 ml) and $LiAlH_4$ (0.66 g) was added. The mixture was stirred under reflux for 3 h, cooled and the excess of $LiAlH_4$ was decomposed with 20 % ammonium chloride. The organic layer was decanted and the inorganic residue was extracted with THF till Dragendorff test was negative. The organic extracts were combined, dried and the solvent removed to give 0.65 g of oil. It was crystallised from methanol to deposit 0.42 g (72 %) of pure, crystalline 5. M.p. 205-206°C. IR $cm^{-1}$: 3460 (OH). PMR $\delta$ : 2.20 (s,6H,$NCH_3$),1.72-2.82 (m,10H,$ArCH_2CH_2N$ and dithian-$CH_2$), 3.95 (s,3H,$OCH_3$), 5.16 (s,broad,3H,2H disappear on treatment with $D_2O$, ArOH and $ArC\underline{H}O\underline{H}$), 5.98 (s, 2H,$OCH_2O$), 6.55 (s,1H,ArH), 6.95 (m,2H,ArH), 7.38 (m,1H,ArH), 7.58 (s,1H,ArH). MS m/z (%): 463 ($M^+$,1), 357 (<1), 241 (1), 222 (10), 177 (3), 167 (2), 58 (100). Found: C 58.72, H 6.70, N 2.97. Calc. for $C_{23}H_{29}NO_5S_2 \cdot 1/2\ H_2O$: C 58.45, H 6.40, N 2.96 %.

### Cryptopleurospermine (1)

1. Deblocking of the 1,3-dithian masking group in compound 5 using $CF_3COOH/NaNO_2$[3]

To a soln of compound 5 (0.23 g, 0.5 mmol) in $CF_3COOH$ (0.7 ml) and water (0.15 ml) $NaNO_2$ (1.2 mg, 0.02 mmol) was added. The mixture was stirred at room temp for 2 h then the solvents were evaporated under reduced pressure, the residue neutralised with 2.5 % ammonia and extracted with chloroform. The organic extracts were dried, evaporated and the residue was crystallized from acetone to give 30 mg crystalline cryptopleurospermine (1), m.p. 183-184°C,decomp. Additional 46 mg of the alkaloid (yield 42 %) was obtained from mother liquors after chromatography on silicagel with chloroform-methanol (50:1). M.p. 183-184°C, decomp.(lit.[1] 188-190°C) could not be increased by several recrystallisations from acetone or methylene chloride. IR $cm^{-1}$: 3450 (OH), 1665, 1650 (benzil C=O), PMR $\delta$ : 2.34 (s,6H,$NCH_3$), 2.50-3.30 (2m,4H,$ArCH_2CH_2N$), 3.97 (s,3H, $OCH_3$), 5.98 (s,2H,$OCH_2O$), 6.81-7.56 (2m,5H,ArH). MS m/z (%): 371 ($M^+$,1), 326 (1)

220 (2), 175 (1), 162 (1), 151 (4), 58 (100). HRMS: $M^+$=371.1367, calc. for $C_{20}H_{21}NO_6$ = 371.1368. Found: C 64.44, H 5.94, N 3.74. Calc. for $C_{20}H_{21}NO_6$: C 64.68, H 5.70, N 3.77 %.

2. Deblocking of the 1,3-dithian masking group in compound 5 using $CF_3COOH/CH_2O$[4]

To a soln of compound 5 (0.23 g, 0.5 mmol) in chloroform (0.5 ml) and $CF_3COOH$ (0.25 ml) 36 % formalin (0.05 ml) was added and the mixture was stirred under argon for 4 h. Then chloroform (0.5 ml) and $CF_3COOH$ (0.25 ml) and 36 % formalin (0.05 ml) were added and the mixture was left for 3 days. Solvents were evaporated under reduced pressure and the residue was neutralised with 2,5 % ammonia and extracted with chloroform. Work up of the organic extracts deposited oil which after crystallisation from acetone gave yellow crystalls of cryptopleurospermine (1), 50 mg, m.p. 183-184°C, decomp. Additional 67 mg (total yield 63 %) of the alkaloid was obtained from mother liqueours after column chromatography.

Cryptopleurospermine hydrochloride: m.p. 225-226°C, decomp. (from methanol). IR $cm^{-1}$: 1665, 1540 (benzil C=O). PMR ($D_2O$) $\delta$ : 3.09 (s,6H,$NCH_3$), 3.45 (s,4H, $ArCH_2$-$CH_2N$), 3.99 (s,3H,$OCH_3$), 6.10 (s,2H,$OCH_2O$), 6.96-7.39 (m,5H,ArH). Found: C 58.29, H 5.59, N 3.28. Calc. for $C_{20}H_{21}NO_6 \cdot HCl \cdot 1/4\ H_2O$: C 58.25, H 5.44, N 3.40 %.

Aknowledgement: This research was supported by Polish Academy of Sciences (M.R. I.12).

## REFERENCES

1. S.R. Jones, J.A. Lamberton, A.A. Sioumis, R.J. Willing, Aust.J.Chem., 23, 353 (1970)
2. M.D. Rozwadowska, M. Chrzanowska, Tetrahedron, 41, 2885 (1985)
3. G.A. Olah, S.C. Narang, G.F. Salem, B.G.B. Gupta, Synthesis, 273 (1979)
4. T. Yamamori, J. Adachi, Tetrahedron Lett., 21, 1747 (1980)
5. G.C. Dunmore, R.H. Manske, R. Rodrigo, Heterocycles, 8, 391 (1977)
6. M.D. Rozwadowska, Bull.Acad.Polon.Sci., Ser.Sci.Chim., 19, 673 (1971)