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SYNTHESIS OF SECOISOQUINOLINE ALKALOIDS. TOTAL SYNTHESIS OF (±)-CORYDALISOL, (±)-AOBAMINE AND (±)-HYPECORININE

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Abstract - The total synthesis of three 7,8-secoberbines: (±)-corydalisol (1), (±)-aobamine (2) and (±)-hypecorinine (3) was carried out using hydrastinine chloride (4) and propylenedithioacetal of methoxycarbonylpiperonal (5) as the main building blocks. Compound 6, condensation product, was the key intermediate in the synthesis and was transformed either into corydalisol (1) and aobamine (2) (Scheme 1) or into hypecorinine (3) (Scheme 2).

Secoberbines form a relatively large group of secoisoquinoline alkaloids[1]. These minor bases are assumed to be formed in plants from protoberberine alkaloids as a result of various degradation processes causing oxidative cleavage of some bonds. The variety of structures of secoberbines shows that the quinolizidine ring in the parent base can be opened in many places leading either to 6,7--seco or 7,8-seco or 8,8a-seco derivatives.

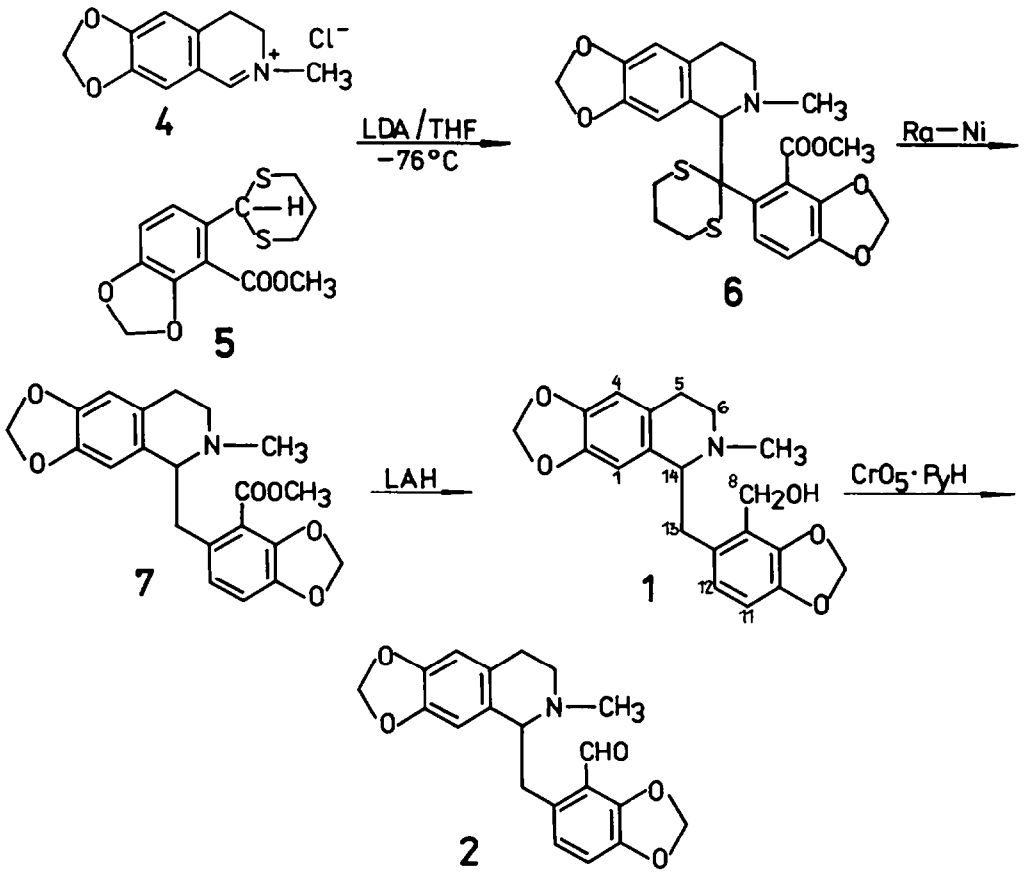
In this work we would like to present a total synthesis of three alkaloids of 7,8-secoberbine group: (±)-corydalisol (1), (±)-aobamine (2) and (±)-hypecorinine (3), also called corydalispirone.

The first two cyclic bases, 1 and 2, incorporate the N-methyltetrahydroisoquinoline unit with benzyl substituent at C-14, which posesses the "berbine bridge" carbon C-8. Both enantiomeric forms of corydalisol (1) have been found in nature. The dextrarotatory isomer was isolated from *Corydalis incisa* Pers. by Nonaka et al.[2], while the levorotatory one from *Hypecoum procumbens* L. by Gözler et al.[3]. Aobamine (2), for which no optical activity was reported, was extracted from *Corydalis ochotensis* var. *raddeana* by Kametani et al.[4]. Racemic hypecorinine 3, a tetracyclic alkaloid containing additional ring between C-14 and C-8 atoms, seems to be the most spread representative of the 7,8-seco group. It was found in four species: *Hypecoum erectum* L. by Yakhontova et al.[5], *Pteridophyllum racemosum* Sieb. et Zucc. by Ikuta and Itokawa[6] and along with corydalisol (1) in *Hypecoum procumbens* L.[3] and *Corydalis incisa* Pers.[2].

Up till now a number of syntheses of the 7,8-secoberbine alkaloids have been carried out. In many of the syntheses other isoquinoline alkaloids have been used as substrates. In the biogenetically patterned approach both quaternary protoberberinium salts and tetrahydroprotoberberine bases have been applied. The N-7 to C-8 bond was cleaved by regioselective Hofmann degradation[7] or by means of chloroformates[8,9]. Pyrolytic Meisenheimer rearrangement of protopine N-oxide was also used to produce the 7,8-secoberbines[10,11]. Other isoquinoline

alkaloids such as: phtalideisoquinoline[12], spirobenzylisoquinoline[13] or benzylisoquinoline[14] were converted into 7,8-seco bases as well. Thus, the racemic corydalisol (1) and aobamine (2) were obtained by Shamma et al.[7] from coptisine chloride. Shamma et al.[10] as well as Iwasa et al.[11] converted protopine N-oxide into (±)-corydalisol (1), while Yakhontova et al.[15] prepared it from hypecorine. Nalliah and MacLean[12] carried out the synthesis of hypecorinine (3) from dehydrobicuculline.

In order to continue our studies on the synthesis of secoisoquinoline alkaloids with the use of lithiated 1,3-dithians as the masked equivalents of acyl anions[16-18] we carried out the total synthesis of the alkaloids 1, 2, 3 belonging to the 7,8-secoberbine group. We used the same substrates for the synthesis of these three bases, i.e. hydrastinine chloride (4) and propylenedithioacetal of methoxycarbonylpiperonal (5). The latter one was successfully applied for the synthesis of peshawarine[17], a bissecoberbine alkaloid.

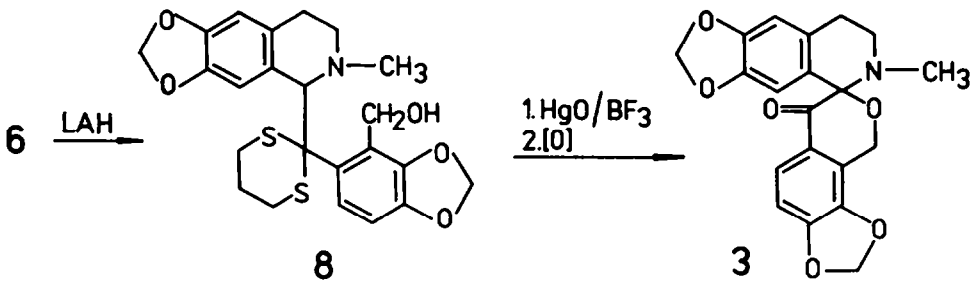


SCHEME 1

Compound 6 was the key intermediate in the synthesis of these three alkaloids. It was obtained with 85% of yield as a result of condensation of lithium derivative of dithian 5 with immonium salt 4.

The course of the synthesis of corydalisol (1) and aobamine (2) is presented in Scheme (1) and of hypecorinine (3) - in Scheme 2.

Compound 6, m.p. 173 - 175°C, was characterised by the presence of ester carbonyl absorption band at 1720 cm^{-1} in the IR spectrum and by PMR and MS spectra. The former showed signals coming from $COOCH_3$ group (3.90 δ), C_{14}-H methine proton (4.50 δ) and two methylenedioxy substituents (5.86 δ and ABq, 6.06 δ,



SCHEME 2

6.11 δ, J=1.5Hz). The protons of five methylene groups originating from both dithian and nitrogen-containing rings as well as from the N-CH_3 group formed two multipletes around 1.85 δ and between 2.38 - 2.95 δ, respectively. One of the four aromatic protons was shifted upfield to 5.73 δ. It was probably the C_1-H atom which in the most stable conformation was forced into the shielding zone of the "lower" aromatic ring. Such a conformation of the molecule seemed to be caused by the presence of the spirocyclic dithian ring at carbon C-13. In the mass spectrum peaks at m/z 298 and m/z 190, corresponding to benzyl and isoquinolinium ions, respectively, might represent two "halves" of the molecule.

In the next step of the synthesis desulfuration of the addition product 6 by means of Raney nickiel W-2 in the presence of 1% sodium hydroxide was performed. As the result the amino-ester 7, m.p. 133 - 135°C, was obtained with 80% yield. Ester carbonyl absorption appeared in the IR spectrum at 1705 cm^{-1}, and in the PMR spectrum the $COOCH_3$ group protons were demonstrated by a singlet at 3.89 δ. In the same spectrum the N-CH_3 group singlet (2.35 δ) dominated over a multiplet derived from three methylene groups (2.35 - 3.70 δ), on the edge of which a triplet (3.60 δ, J=5Hz) due to methine C_{14}-H proton could be noticed. In the aromatic region two doublets (6.50 δ and 6,75 δ, J=8Hz) and two singlets (6.35 δ and 6.49 δ) represented the four aromatic protons. In the mass spectrum the base peak at m/z 190 and the peak at m/z 193 characterized the isoquinoline part and the benzyl substituent, respectively. Instead of the molecular ion a peak at m/z 352 representing the M-OCH_3 ion could be found.

The reduction of compound 7 with lithium aluminum hydride led to the formation of racemic corydalisol (1), yield 80%, m.p. 145.5 - 147°C. In the literature the following values of m.p. were recorded for the racemic form: 127 - - 128°C [7], 146 - 147°C [15], 147 - 148°C [11] and 160 - 161°C [2]. The synthetic corydalisol (1) we obtained was identical (TLC) with the sample of this alkaloid sent to us by Prof. M. Shamma. Moreover, the IR, PMR and ^{13}CNMR spectra corresponded to those reported in the literature [2,7,10,11]. In the PMR spectrum we found the C_{14}-H proton assumed a form of triplet (3.59 δ, J=6Hz) [2,7]. Protons from the hydroxymethyl group appeared as an AB quartet (4.48 δ and 4.62 δ, J=12Hz). The EI MS disclosed the M-1 ion peak at m/z 354, the base peak at m/z 190 along with a peak at m/z 165, the latter two indicating the fisson of the molecule between C-13 and C-14 atoms.

Corydalisol (1) oxidized by chromium peroxide-pyridine complex[19] or triethylammonium chlorochromate[20] led to the formation of aobamine (2), yield 50%, and 71%, respectively, m.p. 166 - 167°C. This alkaloid also turned out to be identical with a sample of 2 obtained from Prof. M. Shamma in terms of TLC R_f value, IR and PMR spectra. Mass spectrum of aobamine (2), similarily as those of the remaining substances described here, involved the central dibenzyl bond cleavage with the formation of fragment ions of the "upper" base peak at m/z 190 and "lower" weak peak at m/z 163 parts of the molecule.

The addition product 6 was used as well for the synthesis of the third alkaloid, hypecorinine (3). This product was reduced with lithium aluminum hydride to give alcohol 8, m.p. 156 - 158°C, yield 78%. The presence of the hydroxy group was shown in the IR spectrum by a broad absorption band at 3170 cm^{-1}. The PMR data included broad multiplet between 1.37 - 2.80 δ containing ten methylene group protons and protons from the $N-CH_3$ group. Three singlets at 3.47 δ, 5.89 δ and 6.05 δ represented the C_{14}-H and two methylenedioxy groups, respectively. A distinct AB quartet for the hydroxymethyl substituent (4.82 δ and 5.08 δ, J=12Hz) could be seen in the spectrum only after the addition of heavy water. The aromatic region consisted of two broad signals around 6.49 δ and 7.38 δ. The major fragmentation under electron impact resulted in two peaks at m/z 190 and m/z 270, indicating again the cleavage of the bond between two benzylic positions.

During the hydrolysis of alcohol 8 performed under the influence of HgO/BF_3 a product was formed, whose IR spectrum did not show absorption in the carbonyl region, but a sharp band at 3150 cm^{-1}. This compound, probably having the character of cyclic semiacetal or acetal, was slowly changed into hypecorinine (3) when kept in methylene chloride solution, while under the action of mercuric acetate it oxidized quickly to hypecorinine (3) with high yield (88%). This alkaloid crystallized from methanol in pure state and exhibited m.p. 197 - - 199°C (literature data: 196 - 198°C [2,12], 197 - 198°C [5], 200 - 201°C [6]). IR, PMR and MS spectral data were identical with those reported in the literature[2,5,6,12].

Our dithian approach to the synthesis of secoisoquinoline alkaloids turned out to be the method of choice for the synthesis of 7,8-secoberbine alkaloids as well. The synthetized alkaloids: corydalisol (1), aobamine (2) and hypecorinine (3) were obtained with relatively good over-all yields amounting to 54.4%, 38.6% and 58.3%, respectively.

EXPERIMENTAL

Melting points were determined on a Köfler block. IR spectra were taken in KBr pellets on a Perkin-Elmer 180. PMR spectra were recorded on Jeol FX-90 (90Hz) in chloroform-d soln with TMS as internal standard. Mass spectra were taken on a Jeol JMS-D-100 at 75 eV. Purity of all compounds prepared was checked by TLC on precoated plates (Merck, silica gel 60 F-254). MN silica gel 60 200-300 mesh was used for column chromatography.

The condensation product 6.

n-BuLi (2.2 mmol) was added dropwise to a soln of diisopropylamine (0.22 g, 2.2 mmol) in dry THF (4 ml) at -10°C under argon and kept at this temp for 10 min. Then the soln was cooled to -76°C and dithian 5 (0.298 g, 1 mmol) in THF (4 ml) was introduced dropwise yielding a violet soln. The carboanion was generated at this temp for 0.5h and then the temp was allowed to rise to -40°C. Suspension of hydrastinine chloride (4) (0.226 g, 1 mmol) in THF (4 ml) was added dropwise. The mixture was kept at -40°C for 1h, then brought to room temp and stirred under argon overnight. It was then poured on 20% ammonium chloride, phases were separated and the aqueous one was extracted with ether. The combined organic extracts were treated with 5% HCl and next the acidic aqueous phase was rendered alkaline with 20% NaOH. It was extracted with ether till Dragendorff test was negative. The organic extracts were combined, dried and evaporated giving 6, amorphous solid (0.414 g, 85%), which crystallized from methanol, m.p. 173 - 175°C. IR cm^{-1}: 1720. PMR δ: 1.85 (m,2H,dithian-CH_2), 2.38-2.95 (m,11H,NCH_3,$ArCH_2CH_2N$,dithian-CH_3), 3.90 (s,3H,OCH_3), 4.50 (s,1H,C_{14}-H), 5.73 (s,1H,C_1-H), 5.86 (s,2H,OCH_2O), 6.06 and 6.11 (ABq,J=1.5Hz,2H,OCH_2O), 6.58 (s,1H,C_4-H), 6.80 and 7.31 (2d,J=8Hz,1H each,ArH). MS m/z (%): 298 (32), 267(7), 238(4), 223 (24), 209 (35), 190 (95), 188 (100), 172 (32). Found: C 59.06, H 5.12, N 2.82 Calc. for $C_{24}H_{25}NO_6S_2$: C 59.12, H 5.17, N 2.87.

The amino-ester 7

Compound 6 (0.243 g, 0.5 mmol) was dissolved in THF (15 ml) containing 1% NaOH (7 ml) and then treated with Raney nickel W-2 (ca. 4 g). The mixture was stirred vigorously under reflux for 1.5 h. The catalyst was filtered off (celite) and washed with THF and chloroform. Solvents were evaporated in vacuo to dryness. The resulting oil (0.153 g, 80%) was crystallized from methanol to give pure crystalline 7, m.p. 133 - 135°C. IR cm^{-1}: 1705. PMR δ: 2.35 (s,3H,N-CH_3), 2.35--3.70 (m,6H,ArCH_2CH_2N,ArCH_2CHN), 3.60 (t,1H,J=5Hz,C_{14}-H), 3.89 (s,3H,OCH_3), 5.84 and 5.86 (ABq,J=1.5Hz,2H,OCH_2O), 5.99 (s,2H,OCH_2O), 6.35 (s,1H,ArH), 6.49 (s,1H,ArH), 6.50 and 6.75 (2d,J=8Hz,1H each,ArH). MS m/z (%): 353 (M-30, <1), 352 (M-31, <1), 193 (<1), 192 (4), 191 (32), 190 (100), 162 (4), 148 (50), 147 (17). Found: C 65.51, H 5.39, N 3.45. Calc. for $C_{21}H_{21}NO_6$: C 65.79, H 5.52, N 3.65%.

(±)-Corydalisol (1)

Compound 7 (0.191 g, 0.5 mmol) was dissolved in THF (20 ml) and $LiAlH_4$ (0.38 g) was added in portions. The mixture was stirred for 1 h at room temp and the excess of $LiAlH_4$ was decomposed with 20% ammonium chloride. The organic layer was decanted and the inorganic residue was extracted with ether till Dragendorff test was negative. The organic extracts were combined, dried and the solvent removed to give 0.142 g (80%) of oil. It was crystallized from methanol to deposit pure, crystalline (±)-corydalisol (1), m.p. 145.5 - 147°C (lit. 127 - - 128°C [7], 145 - 146°C [15], 147 - 148°C [11], 160 - 161°C [2]). IR cm^{-1}: 3150. PMR δ: 2.23 (s,3H,N-CH_3), 2.46-3.14 (m,6H,ArCH_2CH_2N,ArCH_2CHN), 3.59 (t,J=6Hz,1H,C_{14}-H), 4.48 and 4.62 (ABq,J=12Hz,2H,CH_2OH), 5.93 (s,2H,OCH_2O), 5.97 and 5.99 (ABq, J=1.5Hz,2H,OCH_2O), 6.54 (s,1H,ArH), 6.64-6.76 (m,3H,ArH). MS m/z (%): 354 (M-1, <1), 190 (100), 175 (3), 165 (1), 160 (3), 149 (2), 148 (2), 132 (4), 131 (4). Found: C 67.47, H 5.83, N 3.79. Calc. for $C_{20}H_{21}NO_5$: C 67.59, H 5.96, N 3.94%.

(±)-Aobamine (2)

1. Oxidation of (1) with chromium peroxide-pyridine complex[19].
Corydalisol (1) (0.08 g, 0.23 mmol) was dissolved in methylene chloride (7 ml) and then Py·CrO_5 (0.1 g, 0.47 mmol) was added. The mixture was stirred vigorously at room temp for 2.5 h. After this time methylene chloride (5 ml) was added and inorganic solid was filtered off, then washed with methylene chloride, chloroform and triethylamine. Solvents were evaporated in vacuo to give 0.075 g of brown oil which was chromatographied on silica gel (1:10) with chloroform - - methanol (100:1) to give 0.04 g (50%) of (±)-aobamine (2), m.p. 166 - 167°C (methanol), (lit. 168 - 168.5°C [7]). IR cm^{-1}: 1680. PMR δ: 2.35 (s,3H,N-CH_3), 2.35-3.27 (m,6H,ArCH_2CH_2N,ArCH_2CHN), 3.58 (m,1H,C_{14}-H), 5.87 and 5.89 (ABq,J= =1.5Hz,2H,OCH_2O), 6.09 (s,2H,OCH_2O), 6.49 (s,2H,ArH), 6.50 and 6.83 (2d,J=8Hz, 1H each,ArH), 10.07 (s,1H,CHO). MS m/z (%): 352 (M-1, <1), 191 (78), 190 (100), 188 (15), 175 (9), 163 (7), 160 (12), 148 (12), 132 (20). Found: C 67.72, H 5.72, N 3.80. Calc. for $C_{20}H_{19}NO_5$: C 67.98, H 5.42, N. 3.96%. UV λ_{max} (lg ε): 212 (4.24), 234 (4.06), 291 (3.80), 348 (3.31).

2. Oxidation of (1) with triethylamine chlorochromate[20].
Soln of (±)-corydalisol (1) (0.048 g, 0.14 mmol) in methylene chloride (1 ml) was added to a soln of $Et_3NHClCrO_3$ (0.24 g) in methylene chloride (0.5 ml). The reaction mixture was stirred vigorously for 4 days and then filtered through "Florisil". Solvents were evaporated in vacuo to dryness and the residue was dissolved in methylene chloride then washed with 1% NaOH and the organic solution was worked up in the usual manner to give a dark brown oil (0.046 g). It was chromatographied on silica gel (1:10) with chloroform - methanol (100:1) and pure (±)-aobamine (2) (0.034 g, 71%) was obtained, m.p. 166-167°C (MeOH).

The reduction product 8

Compound 6 (0.24 g, 0.49 mmol) was dissolved in dry ethyl ether (35 ml) and $LiAlH_4$ (0.48 g)was added. The mixture was stirred under reflux for 4 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 ether till Dragendorff test was negative. The organic extracts were combined, dried and the solvent removed to give 0.176 g (78%) of pure oil 8, which crystallized from methanol, m.p. 156 - 158°C. IR cm^{-1}: 3170. PMR δ: 1.37-2.80 (m,13H, dithian-CH_2, CH_2CH_2N-CH_3), 3.47 (s,1H,C_{14}-H), 4.82 and 5.08 (ABq,J=12Hz,2H,

CH_2OH), 5.89 (s,2H,OCH_2O), 6.05 (s,2H,OCH_2O), 6.49 (s,broad,3H,ArH), 7.38 (s, broad,1H,ArH). MS m/z (%): 270 (17), 252 (4), 205 (19), 195 (12), 190 (30), 189 (42), 188 (100), 164 (22), 163 (22), 130 (20). Found: C 59.90, H 5.52, N 2.99. Calc. for $C_{23}H_{25}NO_5S_2$: C 60.11, H 5.48, N 3.05%.

(±)-Hypecorinine (3)

BF_3·etherate (0.25 ml) followed by soln of 8 (0.23 g, 0.5 mmol) in THF (4 ml) were added to a well stirred suspension of HgO (0.435 g, 2 mmol) in 15% aq THF (6 ml). After 1 h, water (4 ml) and THF (4 ml) were added to the reaction mixture and the phases were separated. The aqueous layer was extracted with methylene chloride till Dragendorff test was negative. The combined organic extracts were washed with 1% NaOH, then dried and evaporated to give oil (0.18 g, IR 3150 cm^{-1}). It was then dissolved in methylene chloride and treated with mercuric acetate (0.2 g) at room temp for 2 h. After this time the reaction mixture was filtered off (celite) and solvent was evaporated in vacuo to give hypecorinine (3) (0.162 g, 88%), which crystallized from methanol in pure state, m.p. 197 - 199°C (lit. 196 - 198°C [2,12], 197 - 198°C [5], 200 - 201°C [6]). IR cm^{-1}: 1625, 1685. PMR δ: 2.37 (s,3H,N-CH_3), 2.66-3.46 (m,4H,ArCH_2-CH_2N), 4.79 and 5.14 (ABq,J= =16Hz,2H,ArCH_2O), 5.88 (s,2H,OCH_2O), 6.09 (s,2H,OCH_2O) 6.52 and 6.61 (2s,1H each,ArH), 6.88 and 7.79 (2d,J=8Hz,1H each,ArH). MS m/z (%): 367 (M^+,4), 205 (2), 190 (7), 177 (2), 162 (100), 149 (22). Found: C 65.34, H 4.95, N 3.63. Calc. for $C_{20}H_{17}NO_6$: C 65.39, H 4.67, N 3.81%.
In another experiment the crude hydrolysis product was stirred in methylene chloride solution for two days to deposit hypecorinine (3).

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