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SYNTHESIS OF SECOISOQUINOLINE ALKALOIDS TOTAL SYNTHESIS OF PESHAWARINE

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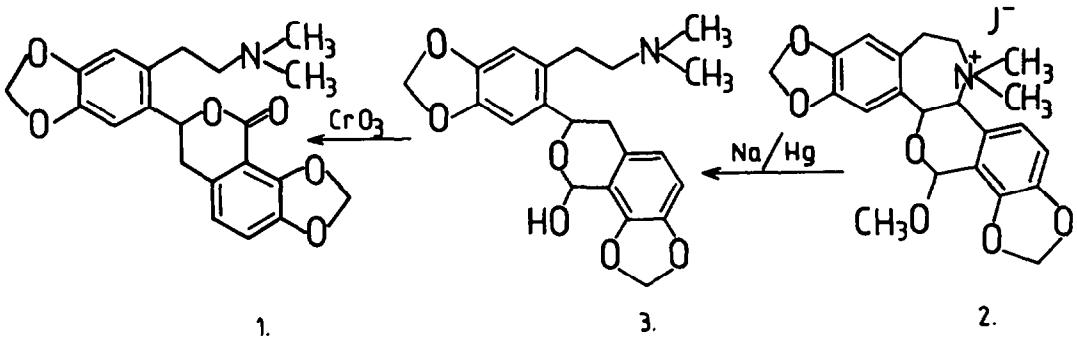
Abstract - In the total synthesis of (±)-peshawarine (1) hydrastinine derivative 6 was acylated with 1,3-dithian 7 applied as an acyl anion equivalent. The dithian masking group in addition product 8 was reductively removed using Raney nickel.

Upon examining the alkaloid extract of the plant Hypecoum parviflorum Kar.and Kir. (Papaveraceae) growing in the area of Peshawar in Pakistan, Shamma and coworkers[1,2] isolated an alkaloid: (-)-peshawarine (1). On the basis of spectral data and chemical transformations, they determined its structure as (S)-(-)-3-(2'-[(N,N-dimethyl)aminoethyl]-4',5'-methylenedioxyphenyl)-7,8-methylenedioxyisochroman-1-one (1) and classified it to the secoisoquinoline alkaloids as secoberbine.

So far two independent syntheses of (±)-peshawarine (1) have been carried out, each time with different isoquinoline alkaloid used as substrate. Simanek et al.[3] obtained (±)-peshawarine (1) from rhoeadine (Scheme 1). Emde degradation of rhoeadine methiodide (2) followed by hydrolysis in acidic medium yielded hemiacetal 3, from which after oxidation with chromic acid racemic peshawarine (1) was obtained with the total yield 17 %.

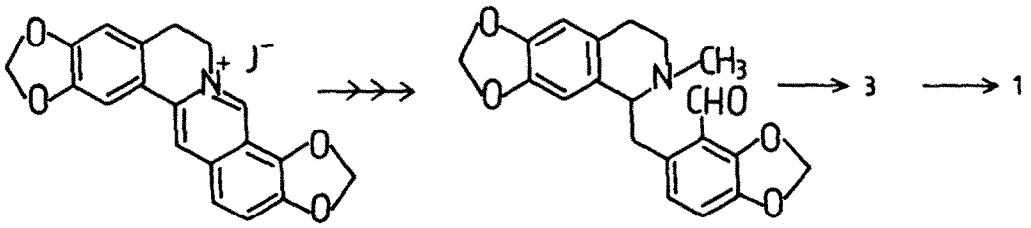


1. 3. 2.

Scheme 1

Shamma's group[2,4] synthesized (±)-peshawarine (1) by multistep transformation of coptisine iodide (4) (Scheme 2). In this process another secoberbine, namely

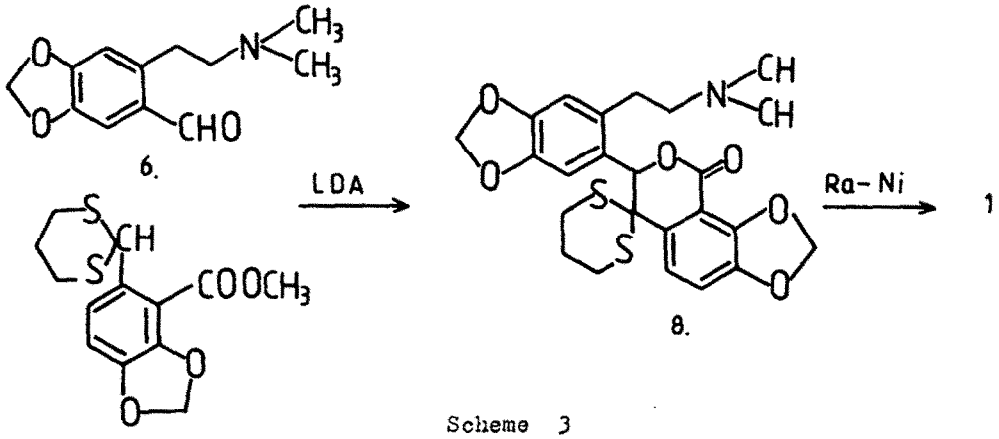
aobamine (5) was one of the intermediate products. In a series of reactions involving i.a. treatment with ethyl chloroformate and lithium aluminum hydride reduction, it was subsequently transformed into hemiacetal 3 which upon oxidation with Jone's reagent gave (±)-peshawarine (1) with over-all yield amounting to 28 %.



4. 5.

Scheme 2

In our total synthesis of (±)-peshawarine (1) (Scheme 3) we followed our previous model study[5], using as substrates aldehyde 6 and 1,3-dithian 7, forming synthons of the "upper" and "lower" part of the molecule, respectively. The dithian method[5] seemed to be the method of choice for the synthesis of peshawarine (1) since it enabled a direct transformation of the thioacetal masking group into benzylic methylene group.



6. 7. 8.

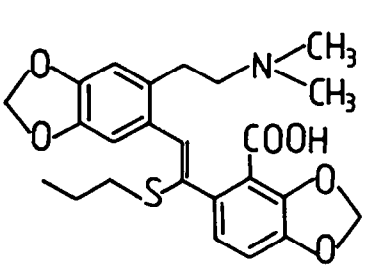
Scheme 3

Compound 6 was prepared from hydrastinine according to the previously described procedure[6,7]. Thioacetal 7 was obtained from piperonal by introducing a methoxycarbonyl group into position C-2 by Ziegler method[8] followed by treatment of the intermediate aldehyde ester with 1,3-propanedithiol in glacial acetic acid. Dithian 7, m.p. 115-116° C, obtained with high yield exhibited a strong absorption band in the infrared spectrum at 1710 cm^{-1}. In the PMR-spectrum methylene protons of dithian ring occured as two multiplets at 1.17-2.24δ and 2.73-3.22δ . The three-proton singlet at 3.94δ came from the ester methoxy group, whereas one-proton singlet at 5.94δ from a proton attached to dithian C-2 carbon atom. The singlet at 6.03δ originated from the methylenedioxy group, while the two doublets in the aromatic region at 6.89δ and 7.27δ with J=8 Hz were characteristic of two protons in the ortho position of the aromatic ring. In the rich mass spectrum of thioacetal 7 a molecular ion peak of high intensity at m/z=298 along with the M+2 peak contributing 10 % to the intensity of the molecular ion were observed.

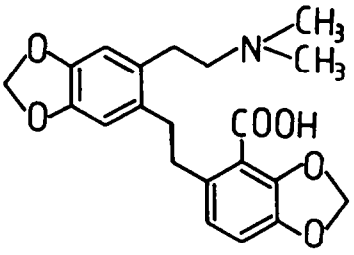
The carbon skeleton of the alkaloid was formed as a result of deprotoration of dithian 7 with LDA and a reaction of so generated anion with aldehyde 6. The product 8, m.p. 209-212° C, showed a strong absorption band in the infrared spectrum at 1720 cm^{-1}, characteristic of conjugated δ-lactone. The PMR spectrum indicated a presence of the $N(CH_3)_2$ substituent (singlet at 2.27δ), two methylenedioxy groups (two-proton singlet at 5.94 δ and two one-proton singlets at 6.12 δ and 6.22 δ), and two aromatic protons in ortho position (two doublets at 7.04 δ and 7.64 δ with J=8 Hz). Methylene groups of the dithian ring and the aminoethyl side chain signals superimposed on each other, producing a wide multiplet within the range 1.90-3.48 δ. The only proton of the lactone ring was perceived as a singlet at 5.30 δ. The mass spectrum exhibited a base peak at m/z=58 for the ion $CH_2=\overset{+}{N}(CH_3)_2$ and peaks at m/z=190 and m/z=208 owing to the cleavage of the molecule into two fragments by fission of the central dibenzylic bond. The above data confirm the proposed structure 8 for the product of the reaction between dithian 7 with aldehyde 6 as well as indicate that the addition process was accompanied by the cyclization yielding spontaneously the lactone system present in the peshawarine (1) molecule.

As it was anticipated, in the final stage of the planned synthesis a reductive removal of the dithian masking group in lactone 8 was to occur. For this purpose Raney nickel was chosen[9,10]. As a result of many attemps undertaken to desulfurize lactone 8, using different solvents (e.g. THF, DME, ethanol, dioxan, benzene) and catalysts with or without deactivation (ethyl acetate, acetone) compound 9 was always formed as the major product. After chromatographic separation and/or crystallization from methanol it showed m.p. 200-202.5° C. This compound differed from peshawarine not only by TLC R_f value but also in spectral features. Instead of the expected absorption of δ-lactone at 1725 cm^{-1}, its IR spectrum indicated the presence of a broad band at 1600 cm^{-1} coming from carboxylate anion as well as a band within the range 2550-2150 cm^{-1} typical of ammonium cation. The last observation was confirmed by the PMR spectrum in which the absorption signal of the N,N-dimethylamino group was shifted downfield to 2.81 δ. A characteristic feature of PMR spectrum was the presence of a clear-cut $A_3M_2X_2$ system in the form of a triplet (0.85 δ, J=7 Hz), multiplet (1.51 δ) and triplet (2.58 δ, J=7 Hz), which may originate from a n-propylthio substituent. Moreover, two methylenedioxy groups (two two-proton singlets at 5.95 δ and 6.04 δ) and five protons in the aromatic region were observed. Two of the latter formed doublets at 6.74 δ and 7.05 δ with J=8 Hz characteristic of protons in the ortho position whereas the remaining three assumed the form of singlets at 6.59 δ, 6.67 δ and 6.93 δ, respectively, originating from two protons from the "upper" ring and one vinyl hydrogen. The mass spectrum of compound 9 was very simple. The molecular ion peak appeared at m/z=457, the base peak for the ion $CH_2=\overset{+}{N}(CH_3)_2$ at m/z=58 and the third peak of significance at m/z=382 could be formed by removing the n-proplythio chain from the molecular ion. On the basis of these data as well as the results of elemental analysis and measurement of molecular mass by HRMS we could assign to the product of desulfurization of lactone 8 the structure presented by formula 9 or its regio- and/or stereoisomer.

Having analysed the reasons of only partial desulfurization of lactone 8 we concluded that such a reaction course might be caused by the presence of the susceptible to hydrogenolysis lactone system in the molecule. In order to avoid the undesirable effect we decided to perform the desulfurization step on a hydrolyzed lactone. Under the action of 0.1N sodium hydroxide, lactone 8 was easily hydrolyzed, however, attempts at isolating the δ-hydroxy acid failed because of the recyclization which occured readily even under very mild conditions. Because of that the desulfurization step had to be carried out in a one-



9.



10.

pot experiment. Compound 8 in THF or DME was refluxed with 0.1N sodium hydroxide at pH maintained around 13 until no more starting material was observed on TLC plate and then treated with Raney nickel W-2[11] at reflux for 1 hr. After the reaction products were separated by column chromatography, we obtained racemic peshawarine (1), melting at 196-198° C with 26 % yield (15 % over-all yield). According to Shamma et al. the m.p. of natural(-)-peshawarine(1) was 190-191° C[1] and of the synthetic one 182-183° C[2,4], while Simanek et al.[3] reported 201-203°C. The synthetic material we obtained was identical in terms of TLC R_f value PMR and mass spectra with the sample of peshawarine obtained from Professor Shamma. In addition to peshawarine (1) we also isolated amino acid 10 from the products mixture of desulfurization of lactone 8, which was formed with 19-25 % yield. Its spectral characteristics agreed with the literature data[1-3], despite the discrepancy in the m.p. which was 236-238° C, whereas the reported ones were: 238-240° C[1,2] and 248-253° C[3], respectively. The HRMS measurement of the molecular mass confirmed the structure indicated by formula 10.

The synthesis of peshawarine (1) described in this paper is the third synthesis of this alkaloid in general, and the first one in which simple derivatives of commercially available compounds were used as substrates. This synthesis may serve as an example of practical application of our model study[5] to total synthesis of secoisoquinoline alkaloids in which 1,3-dithians were used as reagents for nucleophilic acylation.

EXPERIMENTAL

Melting points were determined on a Kofler block. IR spectra were taken in KBr pellets on a Perkin-Elmer 180. PMR spectra were recorded on 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. High-resolution measurements were performed by peak matching (resolution=8000) using perfluorokerosene as the reference standard. Purity of all compounds prepared was checked by TLC on precoated plates (Merck, silicagel 60 F-254). MN silica gel 60 200-300 mesh was used for column chromatography.

2-(2'-Methoxycarbonyl-3',4'-methylenedioxyphenyl)-1,3-dithian (7)

To a well stirred soln of 2-methoxycarbonylpiperonal[8] (4.16g, 20 mmol) in glacial acetic acid (25 ml) 1,3-propanedithiol (3.24 g, 30 mmol) and BF_3 etherate (0.85 g, 6 mmol) were added at ice-bath temp. After 1h a crystalline solid was filtered off and washed with cold water (ca.2 l). Recrystallization from ethyl ether yielded 5.4 g (91 %) of 7 as colorless crystals, m.p. 115-116° C. IR cm^{-1} 1710 (C=O). PMR δ: 1.64-2.20 (m,2H,dithian-CH_2), 2.73-3.22 (m,4H,dithian-CH_2), 3,94 (s,3H,$COOCH_3$), 5.97 (s,1H,dithian-C_2-H), 6.03 (s,2H,OCH_2O), 6.89 (d,J=8Hz, 1H,ArH), 7.27 (d,J=8Hz,1H,ArH). MS m/z (%): 298 (M^+,67), 283 (2), 267 (15), 209 (100), 117 (85), 149 (12), 106 (23). Found: C 52.24, H 4.72. Calc. for $C_{13}H_{14}O_4S_2$: C 52.33, H 4.73 %.

3-(2'-[(N,N-Dimethyl)aminoethyl]-4',5'-methylenedioxyphenyl)-7,8-methylenedioxyisochroman-1,4-dione 4-1,3-propylenedithioacetal (8)

n-BuLi (2.6 mmol) was added dropwise to a soln of diisopropylamine (0.26 g, 2.6 mmol) in dry THF (5 ml) at 0° C under argon and kept at this temp. for 10 min. Then the soln was cooled to -76° C and dithian 7 (0.71 g, 2,4 mmol) in THF (5 ml) was introduced dropwise yielding a violet soln. The temp was allowed to rise to -65° C and compound 6[6,7] (0.53 g, 2.4 mmol) in THF (2 ml) was added dropwise. The mixture was kept at -40° C for 1h then brought to room temp and poured on 20 % ammonium chloride. Phases were separated and the aqueous one was extracted with methylene chloride. The combined organic extracts were dried, evaporated and the resulting oil (1.2 g) was chromatographied on silica gel (1:10) with chloroform-methanol (100:1) to give 1 g (86 %) of amorphous solid, which crystallized from anhyd ethanol; m.p. 209-212 °C. IR cm^{-1}: 3420 (water of crystallization), 1720 (C=O). PMR : 2.27 (s,6H,NCH_3), 1.90-3.48 (m,10H,dithian-CH_2 and $ArCH_2CH_2N$), 5.30 (s,1H,ArCHO-), 5.94 (s,2H,OCH_2O), 6.18 and 6.22 (2s,2H,OCH_2O), 6.72 (s,1H,ArH), 7.04 (d,J=8Hz,1H,ArH), 7.22 (s,1H,ArH), 7.64 (d,J=8Hz,1H,ArH). MS m/z(%): 487 (M^+,4), 422 (2), 380 (3), 190 (1), 106 (1), 58 (100). Found: C 57.98, H 5.18, N, 2.88.Calc. for $C_{24}H_{25}NO_6S_2 \cdot 1/2\ H_2O$: C 58.05, H 5.28, N, 2.82%

2-(2'-[(N,N-Dimethyl)aminoethyl]-4',5'-methylenedioxyphenyl)-1-(2''-carboxy-3'',4''-methylenedioxyphenyl)-1-propylthioethene (9)

Lactone 8 (0.41 g, 0.85 mmol) was dissolved in DMF (15 ml) and Raney nickel W-2[11] (ca. 4.5 g) was added. The mixture was stirred at room temp for 1.5h and then filtered through celite. The catalyst was washed with chloroform and the organic filtrates were combined and evaporated in vacuo to dryness. The resulting oil (0.2 g, 51 %) was crystallized two times from methanol to give crystalline 9; m.p. 200-202.5°C, IR cm^{-1}: 2550-2150 ($R_3\overset{+}{N}H$), 1600 (COO^-). PMRδ : 0.85 (t,J=7Hz, 3H,$SCH_2CH_2\underline{CH_3}$), 1.51(m,2H,$SCH_2\underline{CH_2}CH_3$), 2.58 (t,J=7Hz,2H,$SC\underline{H_2}CH_2CH_3$), 2.81 (s,6H, $\overset{+}{N}CH_3$), 2.96 (s,4H,$ArCH_2CH_2N$), 5.95 (s,2H,OCH_2O), 6.04 (s,2H,OCH_2O), 6.59, 6.67, 6.93 (3s,3H,ArH and -C$\underline{H}$=C), 6.74 (d,J=8Hz,1H,ArH), 7.05 (d,J=8Hz,1H,ArH). MS m/z(%): 457 (M^+,2), 382 (15) 204 (13), 58 (100). HRMS: M^+=457.1562. Calc. for $C_{24}H_{27}NO_6S$: 457.1557. Found: C 61.52, H 6.17, N 2.90, S 6.54. Calc. for $C_{24}H_{27}NO_6S \cdot 1/2\ H_2O$: C 61.79, H 6.05, N 3.00, S 6.87 %

(±)-Peshawarine (1)

Lactone 8 (0.25 g, 0.5 mmol) was dissolved in THF (20 ml) and 0.1N NaOH (ca. 15 ml) was added to maintain pH at ca. 13. The mixture was refluxed until TLC indicated the disappearance of starting lactone and formation of a slower moving compound (ca. 3.5h). Raney nickel W-2[11] (ca. 4.5 g) was then added and the mixture was stirred under reflux for 1h. The catalyst was filtered off (celite) and washed with THF and chloroform. Solvents were evaporated in vacuo, the resulting oil was dissolved in THF (10 ml) containing 5 % HCl (0.5 ml) and left in refrigerator for 3 days. Solvent was then removed and the residue after being made basic with 1 % NaOH (pH ca. 13) was extracted with chloroform. Organic extracts were dried and evaporated to give 0.13 g of oil, which was chromatographied on silica gel (1:10) with chloroform-methanol (100:1) to give 0.05 g (26 %) of (±)-peshawarine(1); m.p. 196-198°C (lit. 182-183[1,2]; 201-203° C[3]). IR KBr cm^{-1}: 1705(C=O). PMRδ : 2.27 (s,6H,NCH_3), 2.30-3.40 (m,6H,$ArCH_2CH_2N$, $ArCHC\underline{H_2}Ar$), 5.66 (dd,J_{AX+BX}= 16Hz,1H,ArCHOCO), 5.95 (s,2H,OCH_2O), 6.15 and 6.21 (2d,J=1Hz,2H,OCH_2O), 6.68 (d, J=8Hz,1H,ArH), 6.69 (s,1H,ArH), 6.97 (d,J=8Hz,1H,ArH), 7.05 (s,1H,ArH). MS m/z (%): 383 (M^+,3), 190(1), 163 (1), 134 (1), 58 (100). HRMS: M^+=383.1373. Calc. for $C_{21}H_{21}NO_6$: 383.1368.

The aqueous residue, which was left after extraction with chloroform, was acidified with 10 % HCl and then neutralized with dil. ammonia and extracted with chloroform again. Organic phase was dried and evaporated to give 0.024 g (15 %) of amino acid 10; m.p. 236-238° C (decomp.) from methanol (Lit. 238-240°C[1,2]; 248-253° C[3]). IR cm^{-1}: 2550-2050 ($R_3\overset{+}{N}H$), 1560 (COO^-). PMRδ : 2.86 (s,6H,NCH_3), 2.60-3.46 (m,4H,$ArCH_2CH_2N$), 3.06 (s,4H,$ArCH_2CH_2Ar$), 5.91 (s,2H,OCH_2O), 5.98 (s, 2H,OCH_2O), 6.54 (s,1H,ArH), 6.66 (s,2H,ArH), 6.75 (s,1H,ArH). MS m/z (%) : 385 (M^+,4), 340 (2), 179 (1), 148 (8), 59 (17), 58 (100). HRMS: M^+=385.1530. Calc. for $C_{21}H_{23}NO_6$: 385.1524.

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