

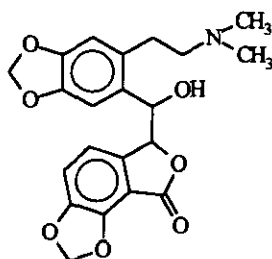
TOTAL SYNTHESIS OF (\pm)-NARLUMICINE, A SECOPHTHALIDEISOQUINOLINE ALKALOID¹

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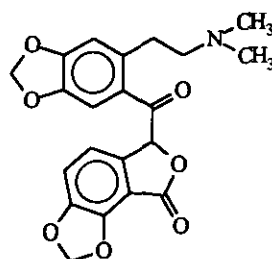
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Abstract - The first total synthesis of (\pm)-narlumicine (1), a *secophthalideisoquinoline* alkaloid, has been performed by addition of 6,7-methylenedioxyphthalide (4) lithium salt to 2-(*N,N*-dimethylaminoethyl)piperonal (3).

Narlumicine (1), a new *secophthalideisoquinoline* alkaloid, has been isolated as a minor component from the stems of *Fumaria indica* by Tripathi and Pandey in 1992.¹ It has been accompanied by a structurally related narlumidine (2), previously isolated from the same plant by Pandey *et al.*² These two bases differ from the other known *secophthalideisoquinoline* alkaloids³ in the oxidation state of the central ethylenic linkage. In the latter ones this linkage exists either in the *keto* form (or combined with the carboxylic group as the corresponding enol lactone or ene lactam) or as diketone (benzil), while in compounds (1) and (2) it is a part of dihydrobenzoin and benzoin moieties, respectively. Other characteristic structural features of *secophthalideisoquinolines*, e.g. the *N,N*-dimethylaminoethyl side chain and carboxyl group could be found in molecules of compounds (1) and (2) as well. As with other *secoisoquinolines* the problem of their genesis is an intriguing question. A hypothetical biosynthetic pathway could be put forward assuming an enol lactone, the first degradation product of the classic isoquinoline alkaloids metho salts, as the plausible precursor. Hydration, followed by oxidation would then produce 1 and/or 2, respectively. It is worth noting that the parent phthalideisoquinolines, adlumidine and bicuculline, have also been found in this plant along with bicucullinine, the final degradation product.^{2,4,5}



1



2

The structure of narlumicine (1) has been established by Tripathi and Pandey¹ on the basis of spectroscopic methods and by chemical correlation with narlumidine (2). Sodium borohydride reduction

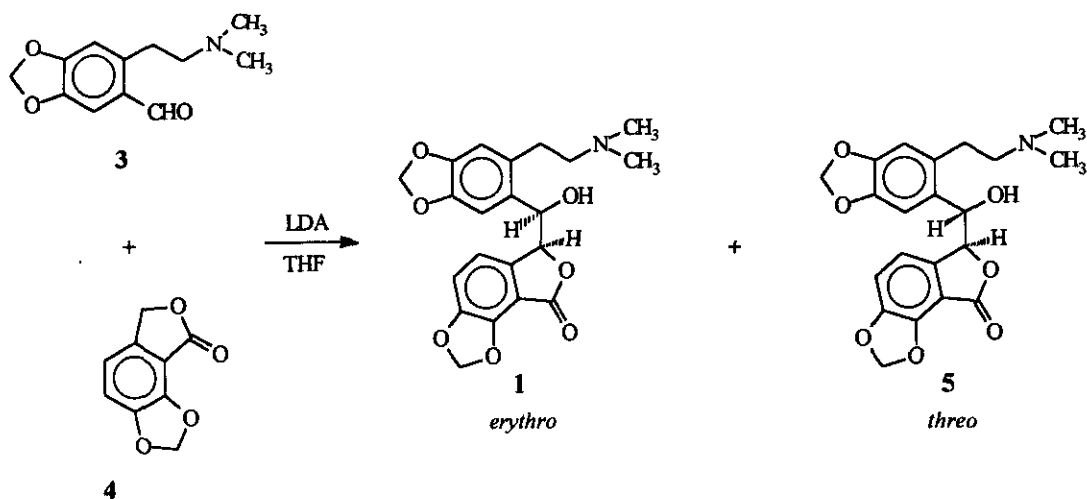
¹This paper is dedicated to Dr. Koji Nakanishi on the occasion of his 75th birthday.

of **2** resulted in a mixture of compounds, from which one showing spectral characteristics and mp similar to those of narlumicine (**1**) was isolated.

In this paper we wish to report on total synthesis of narlumicine (**1**), performed by combination of two building blocks: amino aldehyde (**3**) and phthalide (**4**) (Scheme 1). Both compounds (**3**) and (**4**), have been prepared from a common starting material, piperonal, according to the known procedures.^{6,7}

Construction of the alkaloid's carbon framework involved the addition of anion, generated from phthalide (**4**) under the action of LDA in THF at -70°C ,⁸ to amino aldehyde (**3**). As a result a mixture of diastereomeric addition products was obtained with yields varying from 18% to 56% and diastereomer ratio from 6:1 to 3:1, depending on reaction conditions applied (see Table). The optimum results were obtained when two molar equivalents of phthalide anion (**4**) and one molar equivalent of amino aldehyde (**3**) were used and the reaction mixture was quenched after one hour at -40°C (Entry 5).

Scheme 1



(\pm)-Narlumicine (**1**) in pure form was obtained from the mixture of products by column chromatography separation (silica gel, CH_2Cl_2 -methanol). After crystallization from methanol its mp $200 - 202^{\circ}\text{C}$ differed significantly from that reported for the natural product (mp $163 - 165^{\circ}\text{C}$).¹ There were also differences observed in the IR (KBr) absorption, whereas the ^1H NMR spectra of both compounds were superimposable, except for the OH group proton absorption. In the spectrum of the alkaloid it was found as a multiplet centered at δ 4.15 ppm, while in the spectrum of our sample it appeared as a singlet at δ 3.48 ppm.

In order to explain this discrepancies we have assumed the existence of two different types of hydrogen bonding in molecules of the two substances, an intramolecular one in the natural product and intermolecular in our synthetic material. In order to clarify this problem an X-Ray crystallographic analysis was performed on a single crystal of our synthetic product (**1**).⁹ Indeed, an intermolecular hydrogen bond O-H...N (2.716(5)Å) linking the molecules into chains was found in it. The *erythro* relative stereochemistry around the stereogenic centers was also established.

All attempts to isolate the diastereomer (5) in pure form failed, even after several chromatographic separations.

Table. Yields and the ratio of narlumicine (1) to its diastereomer (5) as depending on the reaction conditions.

| Entry | Molar ratio of LDA:4:3 | Temperature °C | Time h | Yield ^a % | Unreacted 3 to diastereomeric mixture (1) and (5) ^b 3:(1+5) | Diastereomers ratio ^b 1:5 |
|-------|------------------------|----------------|---------|----------------------|--|--------------------------------------|
| 1 | 1.1:1.1:1 | -70 r.t. | 2 18 | 18 | 5:1 | 6:1 |
| 2 | 1.1:1.1:1 | -70±-40 | 3 | 30 | 1:1 | 3:1 |
| 3 | 2.2:1.1:1 | -70±-40 | 2.5 | 13 ^c | 1.3:1 | 3:1 |
| 4 | 2.1:2:1 | -70±-40 | 2.5 | 20 ^c | 1:1 | 3:1 |
| 5 | 2.2:2:1 | -70±-40 | 1 | 56 | 0:1 | 4:1 |

^a after purification by column chromatography or/and recrystallisation

^b evaluated on the basis of the ¹H NMR spectral data analysis

^c crude reaction mixture decomposed on standing

EXPERIMENTAL

Mps were determined on a Kofler block and are uncorrected. IR spectra were taken in KBr pellets on FT-IR BRUKER IFS113v. EI and HRMS measurements were performed on JEOL JMS-D-100 by peak matching (resolution = 5000) using perfluorokerosene as the reference standard. ¹H NMR spectra were recorded in CDCl₃ solution on Varian Gemini 300, using TMS as internal standard. The purity of all compounds prepared was checked by TLC on precoated plates (Merck, Si gel 60 F₂₅₄). Merck silica gel 60 (200-300 mesh) was used for column chromatography.

2-[(*N,N*-Dimethyl)aminoethyl]-4,5-methylenedioxyphenylaldehyde (**3**) and 6,7-methylenedioxyphthalide (**4**) were prepared from piperonal according to the previously described procedures.^{6,7}

(±)-**Narlumicine (1)**. *n*-Buthyllithium (2 mmol) was added to a solution of diisopropylamine (0.20 g, 2 mmol) in dry THF (4 mL) at 0 °C under an Ar atmosphere and kept at this temperature for 10 min. The solution was cooled to -70 °C and suspension of phthalide (**4**)⁷ (0.32 g, 1.8 mmol) in THF (14 mL) was introduced dropwise yielding an orange solution. The carbanion was generated for 30 min at -70 °C and then aldehyde (**3**)⁶ (0.20 g, 0.9 mmol) in THF (4 mL) was added in one portion. The cooling bath temperature was allowed to reach -40 °C during about 1 h, then the reaction mixture was poured onto 20% NH₄Cl (ca. 10 mL). Phases were separated and the aqueous one was extracted with Et₂O and then with CHCl₃. The combined organic extracts were dried over Na₂SO₄ and evaporated to give 0.48 g of an yellow foam (solid). On the basis of ¹H NMR spectrum the crude products mixture consisted of unreacted phthalide (**4**) and diastereomeric addition products (**1**) and (**5**) in ratio 4:1. Diastereomers (**1**) and (**5**) were separated by column chromatography on silica gel (1 : 10) using CH₂Cl₂ - methanol (gradient 50:1 to 30:1); 0.20 g (56%) of narlumicine (**1**) was eluted. Crystallization from methanol gave pure, cream colour crystals of mp 200-202 °C (lit.,¹ 163 - 165 °C). IR (KBr) cm⁻¹: 2900-3060 (OH), 1770 (C=O γ-lactone); ¹H NMR (CDCl₃) δ: 2.16 (s, 6H, CH₃), 2.49-2.55 (m, 2H, ArCH₂CH₂N), 2.74-2.80 (m, 2H, ArCH₂CH₂N), 3.48 (s, 1H, OH, exchanges with D₂O), 4.63 (d, J=8.1 Hz, 1H, H-8 or H-9), 5.67 (d, J=8.1 Hz, 1H, H-8 or H-9), 5.95 (s, 2H, OCH₂O), 6.18 (s, 2H, OCH₂O), 6.64 (s, 1H, ArH), 6.95 (s, 1H, ArH), 7.08 (d, J=8.0 Hz, 1H, *ortho* ArH), 7.19 (d, J=8.0 Hz, 1H, *ortho* ArH); EI MS *m/z* (%): 399 (M⁺, 30), 222 (14), 177 (12), 60 (11), 59 (100). HR MS *m/z* (%): 399.1316 ; For C₂₁H₂₁NO₇ calcd: 399.1318.

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