# Asymmetric Synthesis *via* Heterocyclic Intermediates. I. Synthesis of 3,4-Dihydro-11a-(*S*)-methyl-4-(*R*)-phenyl-1,4-oxazino[4,3-*b*]isoquinolin-1(6*H*,11*H*)-one



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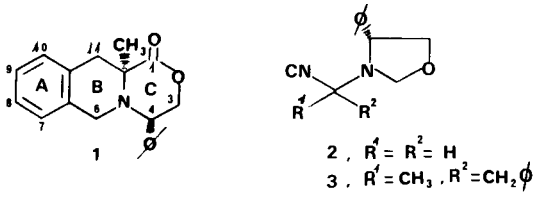
Received April 1, 1987

The synthesis of 3,4-dihydro-11a-(*S*)-methyl-4-(*R*)-phenyl-1,4-oxazino[4,3-*b*]isoquinoline-1(6*H*,11*H*)-one **1** is described.

*J. Heterocyclic Chem.*, **24**, 1235 (1987).

The heterocyclic ring system [1,4]oxazino[4,3-*b*]isoquinoline, despite its simplicity, seems not to have received great attention in synthetic heterocyclic chemistry [1a-d]. In this communication we describe the synthesis of the title compound, a new member of this group, in enantiomerically pure form.

In connection with our work in asymmetric synthesis using chiral heterocyclic α-aminonitriles [2], we were recently confronted with the determination of the absolute configuration of the major epimer of compound **3**, obtained as a diastereomeric mixture (crude d.e.: 52%), that we could not separate, by sequential dialkylation of **2** with methyl iodide and benzyl bromide [2a].




1

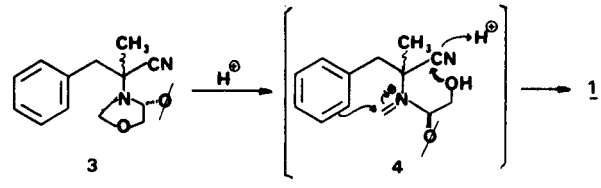
Formulae

The absolute configuration, in the new stereocenter, of the major diastereomer **3**, was tentatively assigned as (*S*) by spectroscopic data and comparation with the ones described for analogous compounds of known stereochemistry [3]. To confirm this hypothesis a chemical correlation with α-methylphenylalanine was desired.

When the mixture **3** was treated with concentrated sulfuric acid, in methylene chloride, at -20°, after standard work-up and flash-chromatography, a mixture of diastereomers was obtained from which, by repeated recrystallization, the major one was obtained in pure form. To our great surprise, the spectroscopic data of this compound did not agree with the anticipated amide derivative of **3**. The structure of the new compound was established as **1** based on the following grounds.

Combustion analysis and mass spectrometry gave a $C_{19}H_{19}NO_2$ molecular formula. The ir spectrum showed no N-H absorption, but a strong band centered at 1725 $cm^{-1}$, suggesting a carbonyl type group, also confirmed by a singlet at 173.19 ppm in the $^{13}C$-nmr spectrum; in addition, three triplets at 73.24, 48.64 and 39.62 ppm were observed assigned to C-3, C-6 and C-10 (these two last may be interchanged), respectively; a singlet at 59.79 ppm (C-11a), a doublet at 58.76 (C-4) and finally a quartet ($CH_3$) at 14.22 ppm. In full agreement with the structure advanced, the $^1H$-nmr spectrum showed a singlet at 1.41 ppm ($CH_3$), two AB systems at 3.20 and 3.65 ppm ($J_{AB}$ = 16 Hz) and at 3.35 and 3.46 ppm ($J_{AB}$ = 16 Hz) corresponding to the two methylene protons of ring B.

Obviously, compound **1** [4] came from an acid catalyzed Pictet-Spengler cyclization [5], where the latent formaldehyde equivalent present in the α-aminoether moiety of **3** provided the highly reactive electrophilic species; final attack to the nitrile function accounts for the ring C formation.




3 4

Scheme

Recently, Singh [6] and Pandit [7] have described related intermediates to **4** in reactions of one carbon transfer from oxazolidines, thiazolidines and imidazolidines, in their bimolecular reactions with amines. The example reported here fits in this group, being the first case, to our knowledge, of an exclusive uni- and intramolecular transfer of one carbon atom from an optically pure 1,3-oxazolidine to give the basic nucleus of tetrahydroisoquinoline present in compound **1**.

## EXPERIMENTAL

The melting points were determined in a Kofler apparatus and are uncorrected. The ir spectra were recorded in a Perkin-Elmer 297 Spectrophotometer. The nmr spectra were obtained with a Brucker WP 400 Spectrometer, using tetramethylsilane as internal standard. Mass spectra were scanned with an AEI MS 50 at 70 eV.

Synthesis of **1**.

Compound **3** (2.4 g, 8.2 mmoles) in 20 ml of dry methylene chloride, cooled at -20° (bath temperature) was treated, under argon and stirring, with 6 ml of concentrated sulfuric acid, added dropwise in 5 minutes. After 3 hours at this temperature, the mixture was left in the freezer at 5° (18 hours). After careful treatment, at 0°, with 20% ammonium hydroxide up to *p*H = 10, the crude mass was extracted several times with methylene chloride. The combined organic extracts were washed with brine, dried with sodium sulfate and evaporated to yield a solid that was dissolved in warm ethyl acetate, filtered and evaporated. The residue was recrystallized from *n*-hexane/ethyl acetate to give 378 mg of **1**; a recrystallization gave 278 mg of **1** (26% overall yield). The mother liquors (650 mg, 26%) were formed ($^1$H-nmr inspection) by **1** and its epimer in C-11a, that could not be obtained in pure form.

Compound **1a** had mp 197-199°; $[\alpha]_D^{25}$ -180.69° (chloroform, c 1.44): ir (potassium bromide): 1725 cm$^{-1}$; $^1$H-nmr (deuteriochloroform): $\delta$ 1.41 (3 H, s), 3.20 (1 H, d, J = 16 Hz), 3.35 (1 H, d, J = 16 Hz), 3.46 (1 H, d, J = 16 Hz), 3.65 (1 H, d, J = 16 Hz), 3.90 (1 H, dd, J = 3 and 12 Hz), 4.23-4.38 (2 H, m) and 6.80-7.40 (9 H, m); $^{13}$C-nmr (deuteriochloroform): $\delta$ 173.19 (s), 136.33 (s), 132.54 (s), 130.08-125.99 (aromatic and phenyl ring), 73.24 (t), 59.79 (s), 58.76 (d), 48.64 (t), 39.62 (t), 14.22 (q); ms: m/z 293 (M$^+$, 13), 278 (40), 249 (90), 235 (17), 178 (20), 144 (47), 130 (53), 111 (100).

*Anal.* Calcd. for $C_{19}H_{19}NO_2$: C, 77.79; H, 6.53; N, 4.77. Found: C, 77.65; H, 6.45; N, 4.76.

## REFERENCES AND NOTES

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[3] K. Weinges, K. Gries, B. Stemmle and W. Schrank, *Chem. Ber.*, **110**, 2098 (1977).

[4] The absolute configuration of **1** has not been independently established. It is assumed to have the same absolute configuration in C-11a as the major epimer in **3**, whose absolute configuration had been previously assigned by $^1$H-nmr analysis [2a].

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