Tetrahedron Letters,Vol.27,No.40,pp 4829-4832,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SYNTHETIC STUDIES ON MORPHINE: RACEMIZATION OF BIARYL INTERMEDIATES

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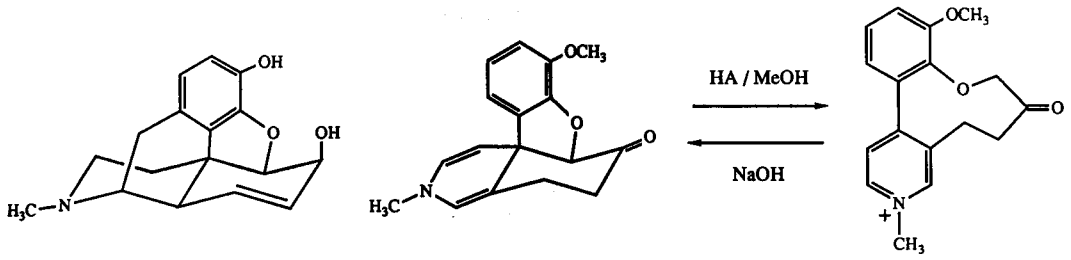
Abstract. Benzofuroisoquinolines, projected intermediates for the synthesis of morphine, are racemized by ring opening to 8,9-dibenzo-4,5-dihydro-6,7-pyrido[4,3-d]oxanin-3(2H)-ones.

The total synthesis of morphine continues to be a prime objective, and several new approaches have appeared within the last ten years[1]. One key feature missing from most of the approaches is the ability to efficiently control the absolute stereochemistry during the synthesis[2]. During our synthetic studies in the morphine field we have developed the use of the intramolecular addition of enolates to pyridinium ions as a way of constructing advanced morphine precursors such as 2[3]. An important feature of this reaction is that it may be reversed by the proper application of acidic conditions. This raises the possiblity that intermediates in this process could be used to control the absolute stereochemistry during morphine synthesis. For example, acid treatment of 2 will induce ring opening to the oxaninone 3 which will exist as a pair of interconverting enantiomers by virtue of rotation about the biaryl axis. Base treatment will reclose the ring, providing a means of interconverting the antipodes of 2. Since several schemes could be envisioned to take advantage of this interesting relationship of 2 and 3 we decided to confirm this sequence and investigate the rate of rotation about the biaryl bond in 3.



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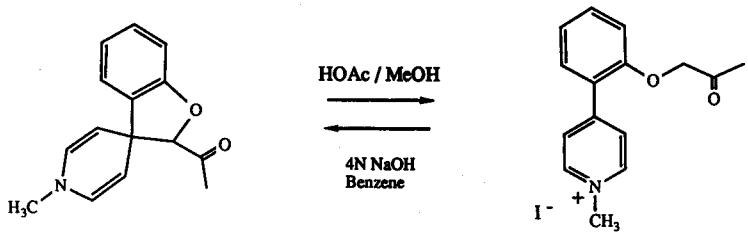
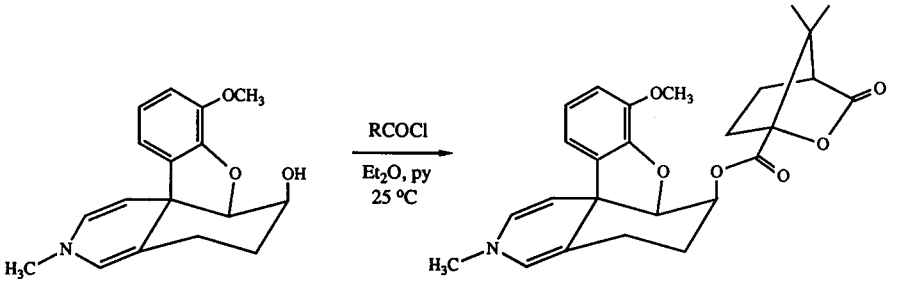


4 5

Ketone 2 was prepared as previously described[3c]. The ring opening of 2 was not as facile as for the simpler dihydropyridine 4. In that case ring opening to 5 occured simply upon dissolution in a solvent of proper polarity, eg., aqueous ethanol, or by treatment with one equivalent of acetic acid in methanol[3b]. Ketone 2 existed exclusively in the ring closed form under these conditions. When 2 was treated with an equimolar amount of trifluoroacetic acid in deuteriomethanol an equilibrium was established containing 66% of the ring opened form as judged by proton NMR. Additional trifluoroacetic acid shifted the equilibrium but did not result in complete conversion to 3. However, one equivalent of p-toluenesulfonic acid in this solvent converted 2 completely into 3.

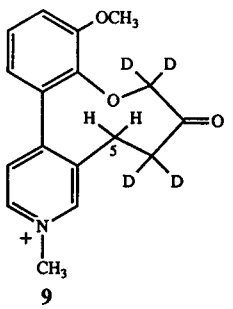
Our initial experiments to ascertain the rate of rotation about the biaryl axis in 3 employed optically active material. This was obtained by resolution of the alcohol 6[4], which was readily available by reduction of 2 with L-Selectride (95% yield, 100% de). The diastereomeric camphanate esters 7 were purified to homogeneity by preparative TLC on alumina. After hydrolysis and oxidation, the resolved ketones were judged to be optically pure by the application of chiral shift reagents in the 400 MHz NMR spectrum. The methoxy groups of the diastereomeric ketone-Eu(tfc)$_3$ complexes are widely separated and easily integratable.



6 7

+ 7 71% $[\alpha]_D$ +44.0°
- 7 82% $[\alpha]_D$ -50.4°
KOH/EtOH, 25 °C
+ 6 96% $[\alpha]_D$ + 66.4°
- 6 96% $[\alpha]_D$ - 66.4°
SO_3· py, Et_3N, DMSO/CH_2Cl_2, 0 °C
+ 2 80% $[\alpha]_D$ + 48.3°
- 2 79% $[\alpha]_D$ - 48.3°

To test the racemization scheme, optically active 2 was treated with one equivalent of p-toluenesulfonic acid in methanol. After one minute the solution was added to a rapidly stirred mixture of 4N NaOH and benzene. The isolated ketone (90%) possessed no optical activity and was found to be racemic by the NMR chiral shift method. For comparison, the dibenzocyclononane carboxylic acid 8 racemizes with a half life of 24 hours at 25°C[5]. The more rapid racemization of 3 is consistent with the effects reported in unbridged biaryl systems upon substitution of a methylene group by an oxygen at one of the ortho positions[6]. The extremely rapid rotation in 3 made possible a more detailed analysis of the racemization by dynamic proton NMR. At 10°C in d_4-acetic acid, the protons at C-5 of the tetradeuterated oxaninone 9[7] are a sharp doublet of doublets (δ=2.81, 3.14, J=15.2 Hz). These signals collapse to a singlet at 90°C, with a coalescence temperature of 60°C, from which ΔG is calculated to be 15.8 Kcal/mol[8].



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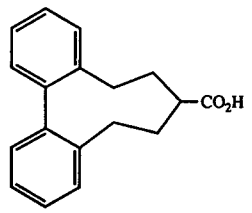

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Although the present scheme for the resolution of 2 is not appropriate for an efficient synthesis of the morphine alkaloids, several alternatives are possible, including the resolution of 2 or related dihydropyridines on a chiral chromatographic phase such as triacetylcellulose[9]. The fact that this may be done on a relatively advanced intermediate should render it practical. We are presently studying methods for the resolution of 2 as well as the racemization of morphine precursors containing additional substituents at the biaryl ortho positions.

Acknowledgement. We thank the National Institute of Drug Abuse for support. NMR spectra were obtained on a Bruker AM 400 purchased in part through grants from the National Science Foundation (CHE-8216190) and from the M.J. Murdock Charitable Trust to Oregon State University.

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4. All new compounds have been characterized by 400 Mz NMR, IR, and HRMS.

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7. The tetradeuterated oxaninone was prepared by deuterium exchange at the positions α to the carbonyl in 2 (NaOD in D_2O/benzene (5/1), 40°C). The deuterated solvent provides the final deuterium during the ring opening of 2 to 9.

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(Received in USA 23 June 1986)