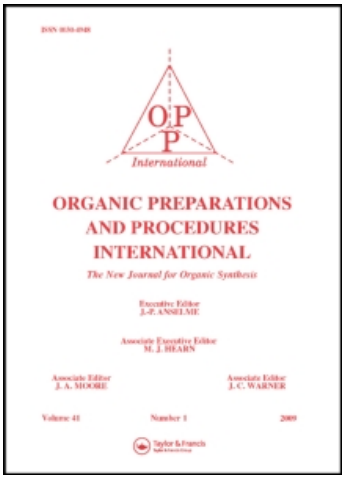

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HYDROXYL GROUP ELIMINATION IN THE MORPHINE SERIES

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HYDROXYL GROUP ELIMINATION IN THE MORPHINE SERIES

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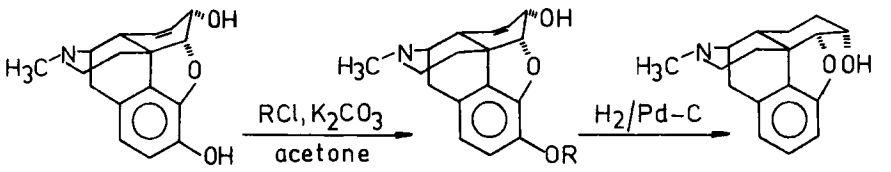
Several methods are known for the elimination of phenolic hydroxyl groups.[1-11] The basis of these methods, in general, is the reductive cleavage of the previously prepared ethers or esters of the phenolic hydroxyl compound. A series of papers[12-13] dealt with the removal of the C_4-OH from alkaloids with morphinane skeleton. Lewis and Readhead[14] reported the elimination of the C_3-hydroxyl group of oripavin derivatives in the course of splitting diethoxy-phosphate esters of the starting materials with metallic sodium in liquid ammonia.

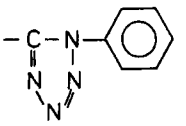
In this paper the removal of the C_3-OH group of morphine is reported. The 1-phenyltetrazolyl-(IIa), and pyrimidyl-(IIb) ethers of morphine (I) were prepared and hydrogenated under pressure. The splitting of the ether linkage took place nearly quantitatively in the expected way. Simultaneously, the saturation of the Δ^7 double bound under reductive conditions resulted in 3-deoxydihydro-morphine (III); the product is difficult to crystallize;

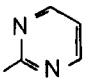
the free base, obtained from its oxalate salt crystallized to constant melting point, was purified from n-hexane.

The structure of the chromatographically homogeneous product is supported by elemental analysis, IR and PMR spectra.



I III

IIa R= 

IIb R= 

EXPERIMENTAL[15]

Morphine-3-(1-phenyl-tetrazolyl)-ether (IIa). - A mixture of 5.7 g (2o mmoles) of morphine, 3.6 g (2o mmoles) of 1-phenyl-5-chlorotetrazole and 6.0 g of anhydrous potassium carbonate in 25o ml of abs. acetone was heated under reflux for 24 hrs. The reaction mixture was then poured into 250 ml of water, basified with 10% potassium hydroxide to pH 10 and extracted with three 50 ml portions of chloroform. The combined chloroform extracts were washed with saturated sodium chloride, dried over magnesium sulfate and evaporated The crude product was recrystallized from 50% ethanol (65 ml to give 6.85 g (76.5%), mp. 121-123° $[\alpha]_D^{26}$ = -212° (0.5 chloroform).

Anal. Calcd. for $C_{24}H_{23}N_5O_3.H_2O$:
C, 64.41; H, 5.63; N, 15.65.
Found: C, 64.40; H, 5.73; N, 15.59.

Morphine-3-(2-pyrimidyl)-ether (IIb). - A mixture of 7.15 g (25 mmoles) of morphine, 2.9 g (25 mmoles) 2-chloro-pyrimidine and 7.5 g anhydrous potassium carbonate in 250 ml of abs. acetone was refluxed for 50 hrs. The reaction mixture was then poured into an equal volume of water, basified with 10% potassium hydroxide to pH 10 and extracted with chloroform (3 x 100 ml). The combined chloroform extracts were washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to give an oil which was crystallized from 20% hot methanol (75 ml) to give 6,4 g, mp. 222-224°. Recrystallization from 25% aqueous methanol (280 ml) yielded 5.76 g (63.5%), mp. 224-226°.
$[\alpha]_D^{26} = -257^\circ$ (0.5 chloroform).

Anal. Calcd. for $C_{21}H_{21}N_3O_3$: C, 69.40; H, 5.83; N, 11.56.
Found: C, 69.67; H, 5.87; N, 11.85.

3-Deoxydihydromorphine (III). -

Method a. Cleavage of morphine-3-(1-phenyl-tetrazolyl)-ether. - A mixture of 4.3 g (10 mmoles) of IIa, 0.8 g of 10% Pd-C and 100 ml of abs. ethanol was shaken in hydrogen atmosphere at 50-60° at an initial pressure of 3 atm. After the hydrogenation was complete, the catalyst was removed and the ethanol was evaporated. The residue was extracted with 10% sodium hydroxide (3 x 50 ml) and the alkaline

phase was extracted with 50 ml of chloroform. The combined chloroform extracts were washed with saturated sodium chloride solution (2 x 50 ml), dried over magnesium sulfate and evaporated. The residue was an almost colourless oil (2.2 g, 81.2 %), homogeneous by thin layer chromatography.

The product was dissolved in 10 ml of abs. ethanol and treated with 1.1 g of oxalic acid in 10 ml of abs. ethanol. After the addition of a small amount of abs. ether the oxalate began to crystallize (2.0 g) mp. 213-214°.

Recrystallization of the oxalate salt from a mixture of 40 ml of abs. ethanol, 4 ml of water and 4 ml of abs. ether yielded 1.7 g (47%), mp. 216-217°.

$[\alpha]_D^{26} = -147^\circ$ (0.5 water).

Method b. Cleavage of morphine-3-(2-pyrimidyl)-ether. - A mixture of 3.63 g (10 mmoles) of morphine-3-(2-pyrimidyl)-ether, 0.75 g of 10% Pd-C and 200 ml of abs. ethanol was agitated in hydrogen atmosphere at 40-50° at 3 atm. until the calculated amount of hydrogen had been absorbed.

The reaction mixture was worked up as in method a. The residue obtained after the evaporation of the mixture (2.63 g; 97%) was a yellow resin, homogeneous by thin layer chromatography.

The product was dissolved in 10 ml of abs. ethanol, and a solution of 1.3 g of oxalic acid in 10 ml of abs. ethanol was added and treated with 5 ml of abs. ether. On stirring, crystallization of the oxalate salt began (2.75 g; mp. 212-213°). Recrystallization of the oxalate from a

mixture of abs. ethanol (50 ml), water (5 ml) and abs. ether (5 ml), yielded 2.25 g (62.3%), mp. 216-217°.

A solution of 0.4 g of 3-deoxydihydromorphine-oxalate in 10 ml of water was basified with 10% sodium hydroxide solution. The mixture was then extracted with three 50 ml portions of chloroform, dried over magnesium sulfate and evaporated. A colourless oil was obtained which was boiled with n-hexane (15 ml), filtered and a part of the solvent was evaporated to give 0.11 g of white solid, mp. 102-104°.

$[\alpha]_D^{24.5}$ = -188° (0.5 chloroform).

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.80; N, 5.16.
Found : C, 75.25; H, 7.81; N, 5.19.

NMR (100 MHz, $CDCl_3$):

aromatic	δ	6.5-7.15	(3H multiplet)
C_5-H	δ	4.55	(1H doublet J = 6 Hz)
N-CH_3	δ	2.38	(3H singlet)

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15. The melting points are uncorrected. For thin layer chromatography Silicagel-G layer and a benzene-methanol (8 : 2) solvent system, developed with Dragendorff reagent were used.

The IR spectra were obtained as KBr pellets on a UNICAM SP 200 G spectrophotometer. The PMR spectra were determined on a Jeol Minimar 100 MHz spectrometer in $CDCl_3$ using TMS as internal standard. The data of optical rotation were measured with a Bendix NPL 143 D automatic polarimeter.

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