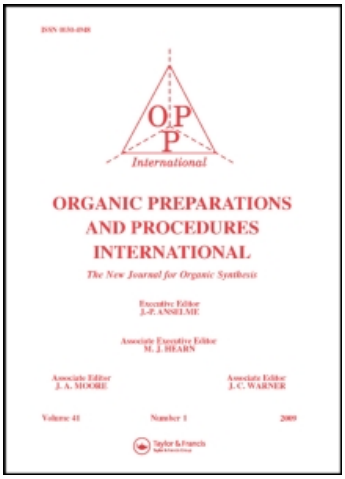


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# A SIMPLIFIED PROCEDURE FOR THE SYNTHESIS OF THE 6,7-BENZOMORPHAN NUCLEUS

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Anal. Calcd. for $C_8Cl_2N_2O_2$: C, 12.34; N, 42.40
Found: C, 12.44; N, 42.29

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## A SIMPLIFIED PROCEDURE FOR THE SYNTHESIS OF THE 6,7-BENZOMORPHAN NUCLEUS

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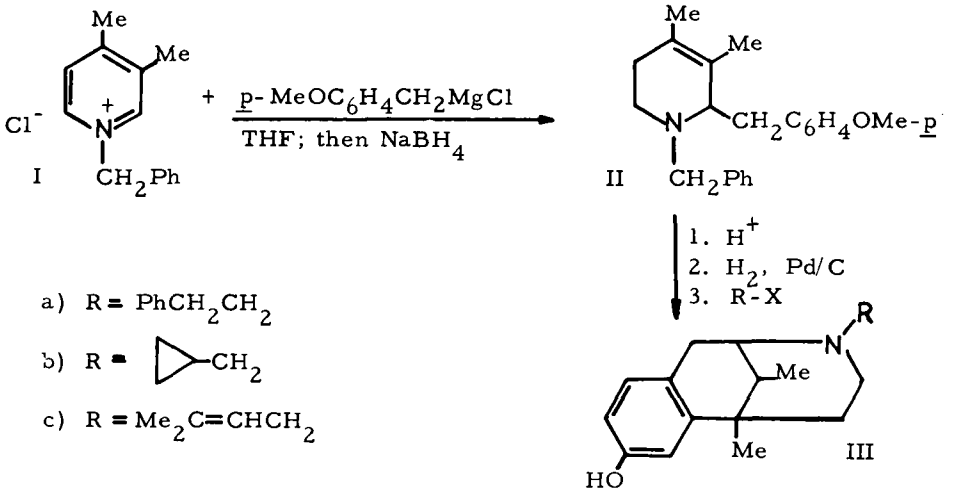
Benzomorphan derivatives such as phenazocine (IIIa),[1] cyclazocine (IIIb),[2] and pentazocine (IIIc)[3] have proved to be potent analgesics. The latter compound in particular which is commercially available, has been found to be an effective, non-addictive analgesic. The synthesis of the basic nucleus according to the Grewe method,[4,5] although modified by several authors,[6,7] still suffers from serious disadvantages.[8,9]






In view of the pharmacological utility of substituted benzomorphans, a simple and reproducible modification of the standard synthetic method which alleviates these difficulties, was devised. Our procedure utilizes tetrahydrofuran as solvent in the Grignard step. This allows the facile formation and manipulation of the Grignard reagent and eliminates the need for large excesses of magnesium and solvent and for the tedious operations involved in the subsequent treatments.

## EXPERIMENTAL

To a refluxing mixture of 24.32 g (1 g. atom) of magnesium turnings, a small amount of iodine and 720 ml of dry tetrahydrofuran, was added dropwise a solution of 130.5 g (0.833 mole) of p-methoxybenzyl chloride in 720 ml of tetrahydrofuran over a period of 2 hrs. The mixture was refluxed for an additional hour, cooled to 35°, and 1-benzyl-3,4-dimethylpyridinium chloride[6] (I) (136.33 g, 0.5833 mole) was added, portionwise. The suspension was refluxed for 20 min.,

cooled to room temperature and poured into excess 20% ammonium chloride solution. The oil was separated and the aqueous solution was extracted with ether. The oil was combined with the ethereal solution and washed with saturated NaCl solution then with water. The organic solution was dried over anhydrous magnesium sulfate and evaporated to dryness to give 230 g of 1-benzyl-1,2-dihydro-2-(4-methoxybenzyl)-3,4-dimethylpyridine (II) as a reddish oil. This oil was dissolved in 1200 ml of ethanol and treated with 15.62 g (0.418 mole) of sodium borohydride. The mixture was stirred overnight and evaporated to dryness. The residue was taken up in ether, washed with water, then extracted in four portions with a total of 70 g of 85% $H_3PO_4$ in 1600 ml of water. The acidic extract was made basic with 30% sodium hydroxide solution and the oil which separated was extracted with ether. The ethereal layer was washed with water, dried (magnesium sulfate) and evaporated to dryness. The oily base was dissolved in 300 ml of acetone and added to 36.64 g of oxalic acid in 394 ml of acetone to precipitate 135.4 g (56% yield) of II, oxalate, mp. 154-156°. The product was identical (ir, 60 MHz nmr, tlc, glpc) with a sample obtained as described by Albertson and Wetterau.[6]

Cyclization of compound II to phenazocine with 48% hydrobromic acid and subsequent catalytic debenzylation has been described.[6,7]

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## SYNTHESIS OF NEW PHENYLQUINOXALINES

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The unusual solubility characteristics of phenylated quinoxaline polymers,[1-3] has prompted the synthesis of several model compounds.