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SYNTHESIS OF 2,3-DIHYDROBENZOFURAN-3-SPIRO-4'-DIHYDROPYRIDINES

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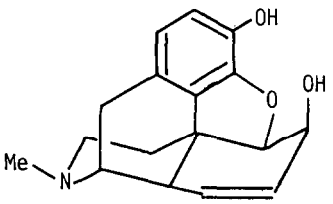
Abstract. 2,3-Dihydrobenzofuran-3-spiro-4'-dihydropyridines are readily available via intramolecular addition of enolates to pyridinium ions.

A corner stone in the structure of morphine (1) and related analgesics is the 4,4-disubstituted piperdine moiety (2). Current methodology for the preparation of compounds containing this fragment utilizes reactions which bring about an irreversible bonding of groups to this quaternary center.[1] Application of these methods to racemic materials results in the subsequent loss of the undesired stereoisomer. One strategy to increase the efficiency of the process is resolution of intermediates prior to 2 with racemization and reuse of the unwanted isomer.[2] With the hope of devising a practical pathway towards the morphine analgesics, we have investigated an alternative sequence which allows the reversible construction of the quaternary center. The reaction chosen for investigation was the intramolecular addition of carbon nucleophiles to 4-arylpyridinium salts 3 to form the 2,3-dihydrobenzofuran-3-spiro-4'-(1-methyldihydropyridine) system 4. Pyridinium salts are excellent acceptors of enolates but few examples are known which lead to the formation of a quaternary center.[3,4] Additionally, the pioneering work of Kröhnke demonstrates that pyridinium enolate adducts are generally reversed by acid treatment.[3] Thus the spirosystem 4 is expected to undergo facile reversal to 3. As described below, both the formation of 4 and its reversion to 3 are easily accomplished.

The required pyridinium salts 3 were synthesized as shown in Scheme I.[5] This procedure is an improvement of the Weiss method for the preparation of 2,4,6-triarylpyridines and utilizes the oxidatively labile 2,6-difuryl groups to prepare the 2,6-unsubstituted pyridine.[6,7] By this method, pyridine 9 is obtained from O-methoxybenzaldehyde in 57% yield.[8] Cleavage of the methyl ether with HBr and methyl iodide treatment give the key methiodide 10, which is easily alkylated in DMF with chloroacetone or ethyl bromoacetate to the desired salts 3a,b, respectively.[9]



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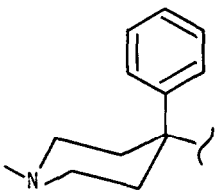

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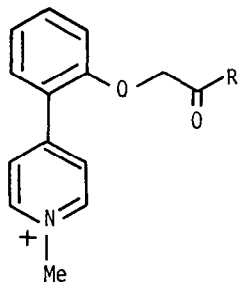
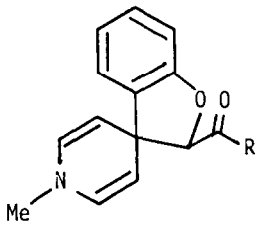
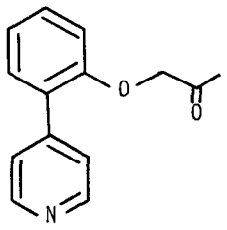


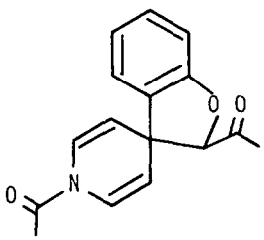
3a R=CH_3
3b R=OC_2H_5



4a,b

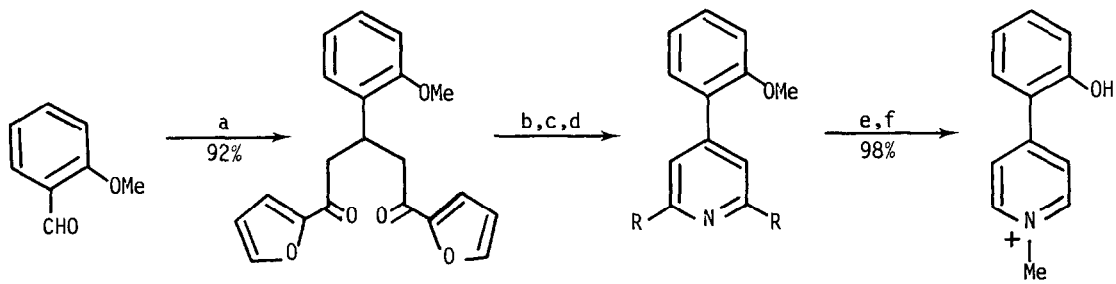


11



12

SCHEME I



5 6 7 R=2-Furyl 71% 8 R=CO_2H 91% 9 R=H 89% 10

a) 2-acetylfuran(XS), KOH, CH_3OH, 25°; b) $H_2NOH \cdot HCl$, n-BuOH, 125°;
c) $KMnO_4$, acetone, 25°; d) $(C_6H_5)_2O$, 220°;
e) conc. HBr, 125°; f) CH_3I, DMF, 25°

Ring closure to the spirodihydropyridines is effected by treatment of salts 3a,b with an appropriate base. Addition of a DMSO solution of 3a to a stirred mixture of 4N NaOH/benzene gives 4a in 92% yield. The assignment of structure to 4a rests on the striking changes in the ^{1}H and ^{13}C NMR spectra upon ring closure. The proton spectrum of 4a shows the dihydropyridine ring protons as four distinct doublets of doublets at chemical shifts expected for enamine protons.[10] The enamine character of the dihydropyridine system is also evident in the carbon NMR spectrum with C-3' and C-5' showing resonances at δ=98.0 and 99.8 ppm.[11] The most outstanding feature of the carbon spectrum is, however, the appearance of a singlet at δ=49.9 ppm due to C-4' of the dihydropyridine. The ester analog 4b is formed in 62% yield upon treatment of 3b with sodium ethoxide in refluxing ethanol, and shows analogous NMR spectra.[10] As expected, when treated with acids the dihydropyridines 4 are converted into the salts 3. Reaction of 4a in ethanol with stoichiometric amounts of conc. HI results in nearly quantitative precipitation of 3a. A similar reaction of 4b with HI leads initially to a protonated species which only slowly yields 3b. More rapid reversal is effected by reaction with a weak acid (phenol, triethylammonium hydrochloride) in refluxing ethanol in the presence of a salt such as LiBr or NaI. Under these conditions, conversion to the pyridinium salt is complete within ten minutes.[12]

Finally, we attempted the formation of spirocylic dihydropyridines via N-acylpyridinium salts. Reaction of pyridine 11 with ethyl chlorocarbonate or benzoyl chloride and a variety of bases has thus far given no evidence of ring closure.[13] However, treatment of 11 with acetic anhydride and triethylamine at 100° gave the N-acyldihydropyridine 12 in 55% yield. In this case, ring closure may be reversed by treatment of 12 with ethanolic HI, but as expected, the reaction is much slower than for the N-methyl analog 4a. In summary, we find that the 2,3-dihydrobenzofuran-3-spiro-4'-dihydropyridine system is readily formed from the appropriate pyridinium enolate precursor and that the ring closure reaction is easily reversed by acid treatment.

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8. Details of this efficient synthesis of 4-arylpyridines will be reported shortly.

9. The yields of the pyridinium salts 3a and 3b are 92% and 99% based upon isolation of the iodide. Presumably the crude precipitated salts contain small amounts of chloride (3a) or bromide (3b) counter ions and inorganic salts. For characterization, authentic methiodide salts were obtained by O-alkylation of the phenol 10 and treatment with CH_3I. The crude salts were used directly in the ring closure reaction.

10. The dihydropyridine protons showed the following resonances. 4a, $\delta(CDCl_3)$ = 6.02(J=8,2); 5.80(7,2); 4.49(7,3); 4.19(8,3); 4b $\delta(CDCl_3)$ = 6.07(J=8,2); 5.87(7,2); 4.51(7,3); 4.33(8,3).

11. These resonances may be interchanged with the C-2 methine resonance at $(CDCl_3)$ = 99.6.

12. Preliminary results indicate that the salts promote an equilibrium reaction between 4b and 3b (ethoxide salt) which is driven to 3b by protonation of the ethoxide co-product. A detailed examination of this process will appear in the full paper.

13. Bases which have been utilized include triethylamine, diisopropylethylamine, potassium carbonate, disodium hydrogen phosphate, and 2,4,6-collidine.

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