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SYNTHESIS OF 3-METHYL-2,3,4,4a,5,6-HEXAHYDRO-1H-BENZOFURO[3,2-e]ISOQUINOLINE-7(7aH)-ONES

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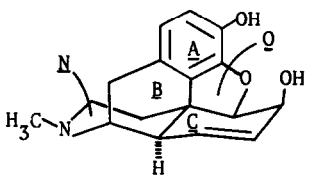
Abstract. The 2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinoline-7(7aH)-one ring system is prepared from a 4-arylpyridine precursor by sequential intramolecular enolate addition to a pyridinium ion, Dieckmann cyclization, and catalytic hydrogenation.

In the study of the morphine alkaloids, compounds possessing the ACNO ring fragment of morphine (1) have recently been the target of several synthetic approaches.[1,2,3] Interest in these compounds has been further stimulated in that some have been found to exhibit potent analgesic properties.[4] We now report the successful preparation of members of this group, the 3-methyl-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinoline-7(7aH)-ones 11, from 4-aryl-pyridine precursors. Of particular note, we are able to prepare the isomer 11a possessing the trans CN ring junction characteristic of the morphine series, almost exclusively. The synthesis of 11 was accomplished by an extension of our earlier studies,[5] wherein treatment of the N-methylpyridinium salt 2a with base generates an enolate which adds intramolecularly to the 4-position of the pyridinium ring to yield the spirobenzofuranopyridine 3a, the tricyclic skeleton of which corresponds to the ANO ring system of morphine. With a side chain incorporated onto the β-position of the N-methylpyridinium salt, as in 2b, this methodology was extended to the preparation of the tetracyclic ACNO system by enolate addition to give 3b and subsequent Dieckmann reaction.



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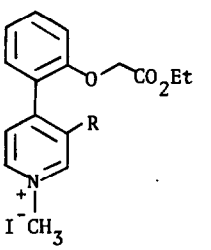
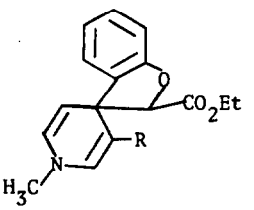




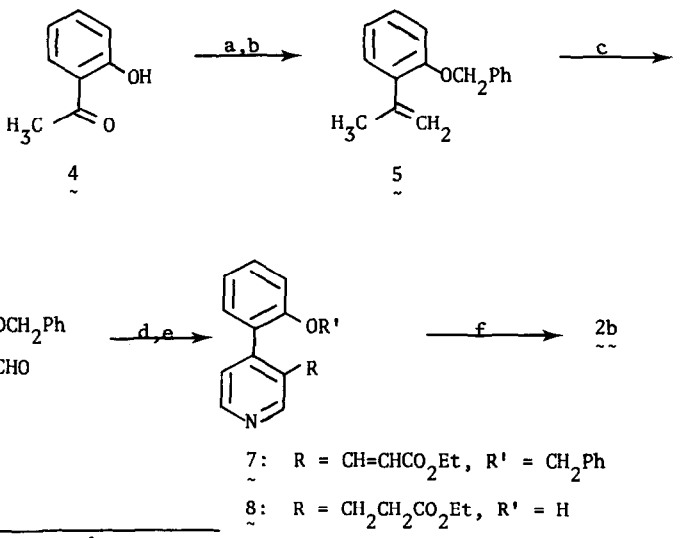
2a: R=H

2b: R=$CH_2CH_2CO_2Et$

3a: R=H

3b: R=$CH_2CH_2CO_2Et$

Scheme 1



4 5

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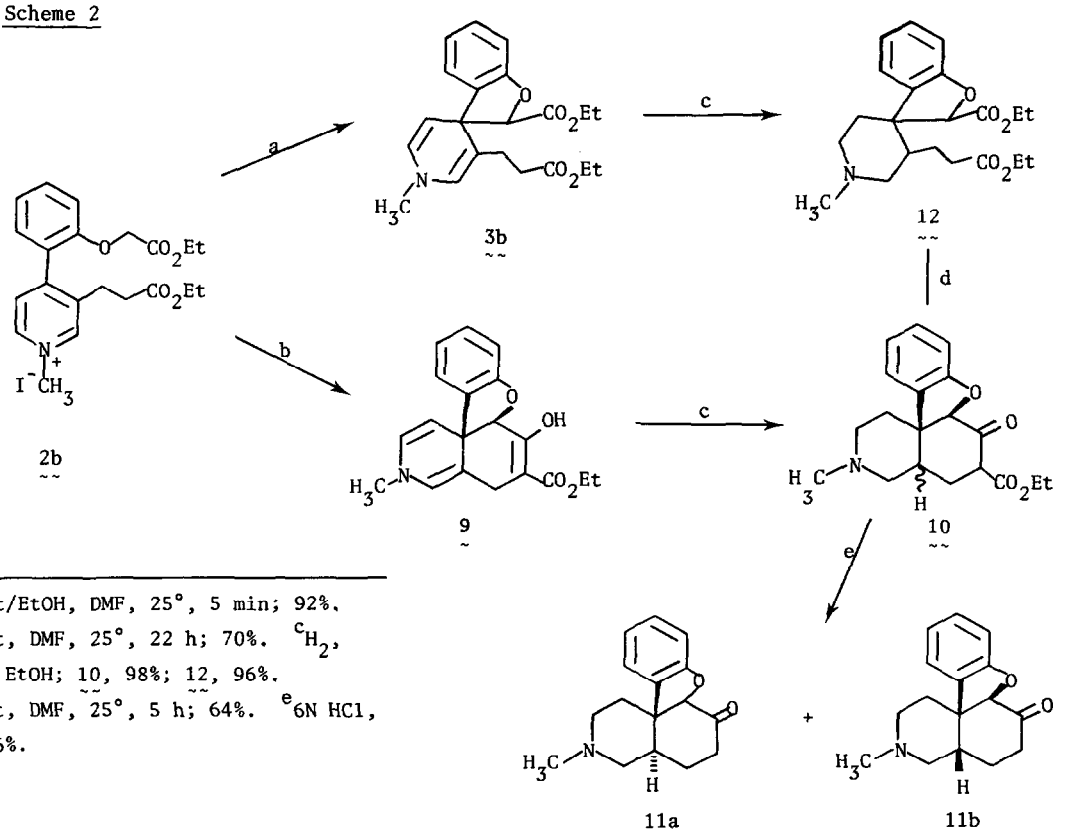
7: R = $CH{=}CHCO_2Et$, R' = CH_2Ph

8: R = $CH_2CH_2CO_2Et$, R' = H

[a] $PhCH_2I$, K_2CO_3, acetone; 93%. [b] CH_3MgI, Et_2O; H_2O, NH_4Cl; Δ; 94%. [c] $(COCl)_2$, DMF, $ClCH_2CH_2Cl$; NH_4OAc, HOAc, H_2O; 76%. [d] $HO_2CCH_2CO_2Et$, C_5H_5N, $C_5H_{11}N$(cat); 85%. [e] H_2, Pd/C, EtOH; H_2, Pd/C, HCl/EtOH; 95%. [f] CH_3I, DMF; $BrCH_2CO_2Et$, K_2CO_3, DMF; 98%.

Scheme 2



2b

3b

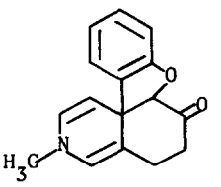
[a] NaOEt/EtOH, DMF, 25°, 5 min; 92%. [b] NaOEt, DMF, 25°, 22 h; 70%. [c] H_2, PtO_2, EtOH; 10, 98%; 12, 96%. [d] NaOEt, DMF, 25°, 5 h; 64%. [e] 6N HCl, Δ_x; 76%.

The preparation of 2b is depicted in Scheme 1.[6] 2-Hydroxyacetophenone 4 is treated with benzyl iodide and K_2CO_3 to give the corresponding benzyl ether in 93% yield. This then undergoes Grignard reaction with methyl magnesium iodide, followed by thermal dehydration of the intermediate carbinol, to give 94% of the α-methylstyrene 5. In a modification of Jutz's procedure,[7] 5 is treated with excess Vilsmeier reagent and the intermediate iminium salt refluxed with $NH_4OAc/HOAc/H_2O$ to give the pyridinecarboxaldehyde 6 in 76% yield. Condensation of 6 with ethyl hydrogen malonate in the presence of pyridine and piperidine gives 85% of the α,β-unsaturated ester 7. Catalytic hydrogenation of the double bond over Pd/C, followed by hydrogenolysis of the benzyl ether, gives 95% yield of 4-arylpyridine 8. Successive alkylations of 8, first N-alkylation with CH_3I, then O-alkylation with ethyl bromoacetate in the presence of K_2CO_3, give 98% of the pyridinium salt 2b which bears the appropriate β-side chain on the pyridine ring for construction of the C-ring.

As in Scheme 2, upon treatment with NaOEt/EtOH in DMF, 2b yields 92% of the spirobenzofuropyridine 3b as a mixture of syn and anti epimers (40/60) after only 5 min at 25°. Under these conditions, in the presence of added ethanol, the Dieckmann cyclization is very slow. However, treatment of 2b with ethanol-free NaOEt in DMF gives 70% yield of ethyl 3-methyl-7-hydroxy-5,7a-dihydro-3H-benzofuro[3,2-e]isoquinoline-6-carboxylate 9 as the sole product after 22 h at 25°. Monitoring the reaction by NMR shows the immediate formation of the spirocyclic dihydropyridine 3b and, subsequently, the slower Dieckmann condensation over the course of the reaction time.

Catalytic hydrogenation of 9 has the possibility of yielding both the cis and trans CN ring junction stereoisomers. When 9 is hydrogenated over PtO_2, 10 is obtained in 98% yield, and by NMR, one isomer appears to predominate. Indeed, upon decarboethoxylation with refluxing 6N HCl, 11a and 11b are isolated in 76% yield in a ratio of 88:12, respectively.[8] Thus, the catalytic hydrogenation is highly selective for the trans ring junction stereochemistry. Cis isomer 11b can also be prepared as the predominate species by a variation of this route, which involves catalytic hydrogenation at the spirocyclic dihydropyridine stage prior to C-ring closure. Thus, hydrogenation of 3b over PtO_2 gives 96% yield of the spirobenzofuranopiperidine derivative 12 as an isomeric mixture. Dieckmann condensation of 12 with NaOEt in DMF yields 64% of 10. Again, by NMR one isomer appears to predominate, but the major isomer in this case is the minor isomer obtained upon hydrogenation of 9. Decarboethoxylation of 10, as before, gives 11a and 11b in a ratio of 29:71, respectively.

Finally, treatment of 9 with refluxing 6N HCl followed by aqueous NaOH forms the important 3-methyl-5,6-dihydro-3H-benzofuro[3,2-e]isoquinoline-7(7aH)-one 13 in 71% yield. As predicted from our earlier work,[5] treatment of 13 with HI/EtOH gives the interesting 3-oxacyclononanone derivative 14 in high yield, which is readily reconverted to 13 with NaOH in aqueous DMSO. Studies on the conversion of this system into the morphine system are in progress.



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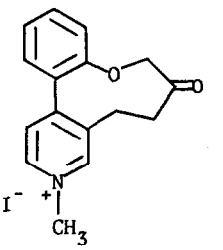

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6. NMR, IR, low resolution mass spectra and either high resolution mass spectra or combustion analyses have been obtained for all new compounds. The following compounds were obtained as solids: 2b, 135.0-135.5°C; 8, 155-156°C; 11a, 187.5-188.3°C.

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8. Assignment of structures 11a and 11b is based on spectral and chromatographic considerations, and is supported by comparison to the 9-methoxy analogs prepared by Rapoport, et al. (Reference 3). Thus, the trans isomer 11a shows a methine proton at δ = 4.37 and an N-methyl at δ = 2.43 in its ^{1}H NMR. In accord with Rapoport's findings the cis isomer 11b shows a methine proton downfield of that of 11a at δ = 4.59, and an upfield N-methyl at δ = 2.35. Also consistent with Rapoport's results, the trans isomer 11a is chromatographically less mobile on silica gel than the cis isomer 11b. Compound 11a can be isolated from the product mixture of 11a/11b by crystallization from benzene/hexane. Alternatively, 11a and 11b may be separated chromatographically on silica gel, ($CH_3OH/Et_3N/CHCl_3$ 5/1/94).

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