Heteroatom Directed Photoarylation: Synthesis of a Tetracyclic Morphine Structural Analogue

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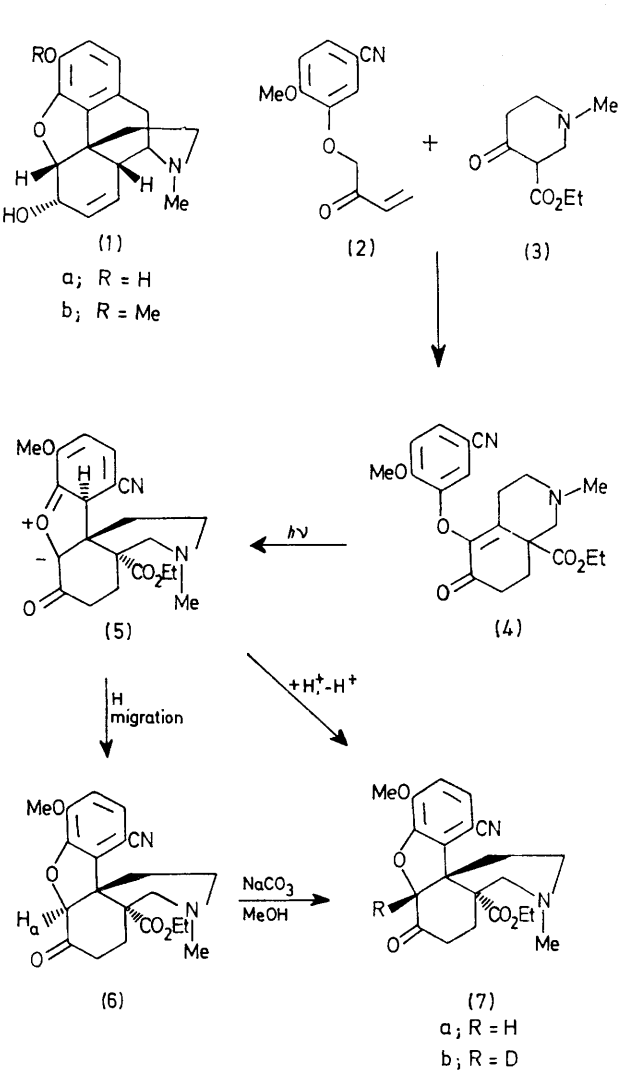
Summary The tetracyclic structural analogue (**7**) of morphine is prepared in high yield by photocyclization–rearrangement of the aryloxyenone (**4**).

WE describe our approach towards a total synthesis of morphine (**1a**) and codeine (**1b**). The key step involves photocyclization–rearrangement of the aryloxyenone (**4**) (heteroatom directed photoarylation) to give a tetracyclic intermediate (**7**) with functionality necessary for formation of the remaining carbon–carbon bond in the morphine alkaloids.

An annelation approach was used to construct the required aryloxyenone (**4**) from the piperidone (**3**).[1] Reaction of chloroacetic acid with 3-hydroxy-4-methoxybenzonitrile[2] in aqueous NaOH solution gave an aryloxyacetic acid; sequential treatment of the acid with Li_2CO_3 (1 equiv.) in H_2O (isolated salt dried at 60 °C *in vacuo*), and vinylmagnesium bromide (1·5 equiv.) in dimethoxyethane–tetrahydrofuran solution at room temperature gave the annelation reagent (**2**). Addition of (**2**) to a solution of the piperidone (**3**) (1 equiv.) and KOH in methanol–benzene gave the expected aldol. Without further purification, the annelation was completed by treating the aldol with pyrrolidine in refluxing benzene solution[3] followed by warming with aqueous sodium acetate in acetic acid to give (**4**) [m.p. 171—172 °C, 40% isolated yield from (**3**)].†

Pyrex-filtered irradiation of (**4**) in degassed benzene solution (0·05 M) gave the *trans*-fused dihydrofuran (**6**) (m.p. 145—147 °C) in > 90% yield.[4] On the other hand, irradiation of (**4**) in benzene–methanol solution (1 : 1) gave (**6**) and the *cis*-fused dihydrofuran (**7a**) (m.p. 163—165 °C; isomer distribution 1·3 : 1, respectively). That these two photoproducts are epimers was established by conversion of (**6**) in methanolic solution saturated with Na_2CO_3 into (**7a**) in 90% isolated yield. Furthermore, irradiation of (**4**) in benzene–methanol saturated with Na_2CO_3 gave exclusively (**7a**) in 88% isolated yield.

We believe that (**6**) and (**7**) are formed by a unique conrotatory photocyclization of (**4**) to the carbonyl ylide (**5**);[4] suprafacial 1,4-hydrogen migration gives the strained *trans*-fused dihydrofuran (**6**), while competitive protonation[5] gives (**7a**). We considered investigating the reactivity of the hypothetical (**5**) in protic solvents; however, while (**6**) is completely stable to the photolysis conditions, (**7a**) exchanges H_a with MeOD to give (**7b**).



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† Compounds (**4**), (**6**), and (**7a**) gave satisfactory elemental analyses.

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[2] J. H. Hunt, *Chem. and Ind.*, 1961, 1873.
[3] S. Ramachandran and M. S. Newman, *Org. Syntheses*, 1961, **41**, 38.
[4] For assignment of the stereochemistry of the perhydroisoquinoline ring junction in (**6**) and (**7**) see: A. G. Schultz and W. Y. Fu, *J. Org. Chem.*, 1976, **41**, 1483.
[5] A. G. Schultz and M. B. DeTar, *J. Amer. Chem. Soc.*, 1976, **98**, 3564, and references cited therein.