Short Synthesis of 14β-Acylaminocodeinones from the Cycloadducts of Thebaine and Acylnitroso Compounds

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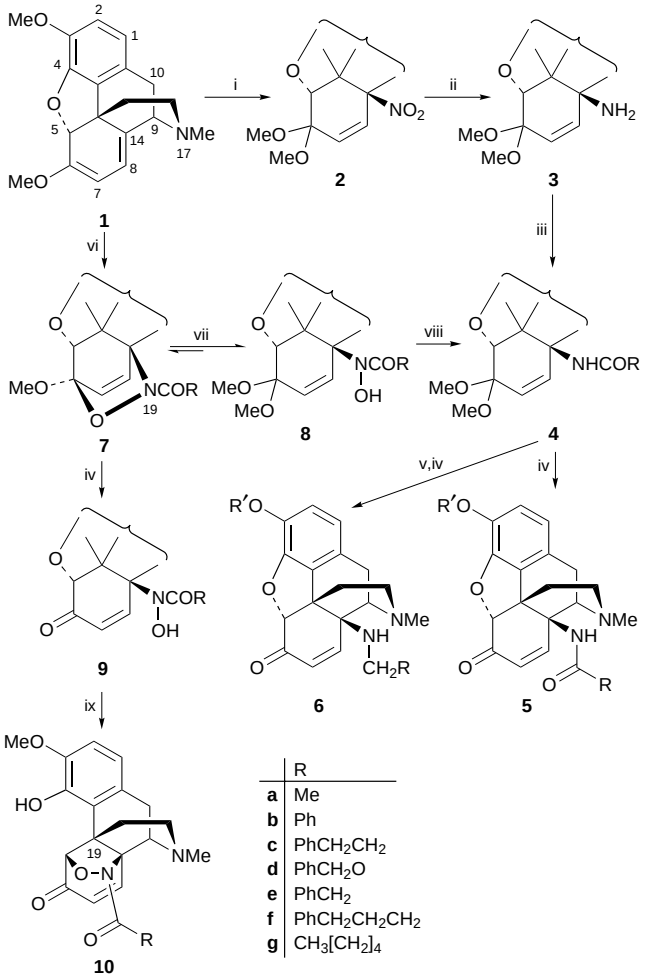
Thebaine **1** has been converted in four steps, *via* its cycloadducts **7** with acylnitroso compounds and the derived dimethyl ketals **8** or ethylene ketals **13**, into 14β-acylaminocodeinones **5** (R′ = Me), analgesics formerly prepared from 14β-aminocodeinone dimethyl ketal **3**.

14β-Aminocodeinone dimethyl ketal **3**, originally prepared[2] from thebaine **1** *via* the nitro ketal **2**, was a key intermediate in the synthesis of the acylamino- **5** (R′ = Me) and alkylamino-codeinones **6** (R′ = Me) (Scheme 1).[1] These codeinones and the corresponding morphinones (R′ = H) have shown promise as clinically useful analgesics. For example, 14β-pentylaminomorphinone, pentamorphone **6** (R = Bu, R′ = H), has been evaluated[3] in man and identified as an effective analgesic with clinically tolerable side-effects in the dose range 0.12–0.24 μg kg^{-1}. In the mouse hot-plate test, pentamorphone showed[4] 1872 times the potency of morphine and 4 times that of fentanyl.

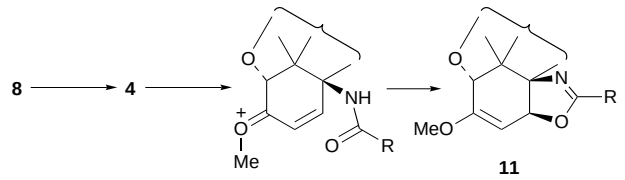
Since the compounds having substantial analgesic potency are all *N*-acyl (**5**) or *N*-alkyl (**6**) derivatives of the parent aminocodeinone, we have now devised a synthetic route from thebaine **1** in which the required acyl groups are introduced directly in the first step and which avoids nitration with tetranitromethane and the consequent formation of potentially hazardous salts of trinitromethane. Thebaine **1** reacts with transient acylnitroso compounds, RCONO, generated *in situ* by oxidation of hydroxamic acids, RCONHOH, with periodate, to give the cycloadducts **7** in high yield.[7] In principle, a general synthesis of the acylamino ketals **4** might then be completed in two, unremarkable steps, *viz*. methanolysis of the cyclic ketals **7** and deoxygenation of the resulting hydroxamic acids **8**. The 3-phenylpropanoyl cycloadduct **7c** was selected initially for detailed study since the corresponding codeinones **5c** (R′ = Me) and **6c** (R′ = Me) and morphinones (R′ = H) were especially potent analgesics.



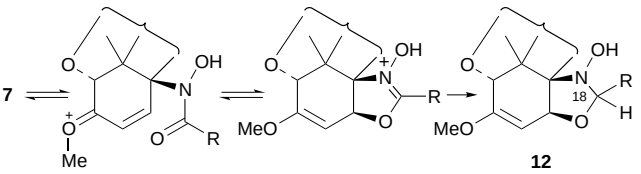
Scheme 1 *Reagents and conditions:* i, $C(NO_2)_4$ in MeOH–NH_3; ii, Zn–NH_4Cl in MeOH; iii, RCOCl–pyridine; iv, HCl–H_2O; v, B_2H_6–THF or $LiAlH_4$; vi, RCONHOH–$NaIO_4$; vii, dry MeOH–HCl; viii, PCl_3–pyridine at 10 °C; ix, NaOEt–EtOH at 20 °C

Brief treatment of the cycloadduct **7c** with dry, methanolic hydrogen chloride at 0 °C gave the dimethyl ketal **8c** in good yield. However, attempted deoxygenation of the hydroxamic acid **8c** with standard reagents was uniformally unsatisfactory. For example, zinc in acetic acid, or acetic acid alone, simply regenerated the cycloadduct **7c**, while zinc and ammonium acetate caused no significant change. Other, more powerful reducing agents caused reductive removal of the entire 14-acylamino group. However, phosphorus trichloride in pyridine[10] at 10 °C rapidly gave, in high yield, the required amide **4c**, which was hydrolysed with methanolic hydrochloric acid to afford the codeinone **5c** (R′ = Me). Other transformations of the cycloadduct **7c** gave successively the hydroxamic acid **9c** and the bridged phenol **10c** (Scheme 1)[7] and the oxazolidine **12c** (Scheme 3).

Unexpectedly, a serious limitation of this route to the dimethyl ketals **4** became apparent when other cycloadducts



Scheme 2 *Reagents and conditions:* SO_2 in pyridine at 115 °C



Scheme 3 *Reagent:* $NaBH_3CN$–HCl in dry THF

7 were investigated. Although methanolysis of the 3-phenylpropanoyl derivative **7c** was essentially quantitative, incomplete conversion was observed for all the other cycloadducts tested. The approximate positions of the equilibria **7**⇌**8**, determined from the ^{1}H NMR spectra of the reaction mixtures, are expressed, as follows, as % conversions into the ketals **8**: **8a**, 85%; **8b**, 63; **8c**, >95; **8d**, 50; **8e**, 90; **8f**, 60; **8g**, 70. Since methanol was already employed in a large excess as the solvent, there was no means of displacing the ketal equilibria substantially in the forward direction. Attention was there-

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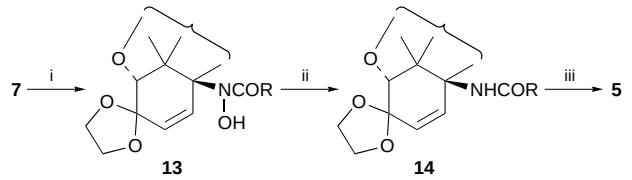
fore turned to the thermodynamically more stable, cyclic, ethylene ketals **13** (Scheme 4).[6]

Treatment of the cycloadduct **7c** in dichloromethane with an excess of anhydrous, glycolic hydrogen chloride at room



Scheme 4 *Reagents and conditions:* i, dry $(CH_2OH)_2$–HCl at 20 °C; ii, SO_2 in pyridine at 115 °C; iii, HCl–H_2O–MeOH

temperature effected essentially quantitative formation of the ethylene ketal **13c**. Significantly, the benzoyl cycloadduct **7b**, which gave only *ca*. 63% of the dimethyl ketal **8b**, also underwent essentially complete conversion into the ethylene ketal **13b**. Although the ketals **13** were deoxygenated effectively with phosphorus trichloride in pyridine, an alternative method,[13] which gave cleaner products, was devised. Thus, solutions of the ethylene ketals **13** in pyridine were saturated at room temperature with sulfur dioxide then heated under reflux, to afford the amides **14** in good yield. When this method was applied to the dimethyl ketal **8c**, concomitant deoxygenation and cyclisation gave the oxazoline **11c** (Scheme 2). Finally, hydrolysis of the ethylene ketals **14** with hydrochloric acid gave the acylaminocodeinones **5** (R′ = Me).

In conclusion, the route (Scheme 4) involving deoxygenation of the ethylene ketals **13** with sulfur dioxide in pyridine is recommended generally for the conversion of thebaine, in four steps, into 14β-acylaminocodeinones. No chromatographic purifications are necessary and yields of 70–80% per step are usual. The route (Scheme 1) employing deoxygenation of the dimethyl ketals **8** with phosphorus trichloride in pyridine was satisfactory only for the cycloadducts **7a**, **c** and **e**; with the other derivatives the equilibration **7**⇌**8** reduced the overall yield.

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Techniques used: IR, ^{1}H NMR, mass spectrometry

References: 14

Schemes: 4

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