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Acid Catalysed Rearrangements of the Thevinols: The Mechanism of Furanocodide Formation.

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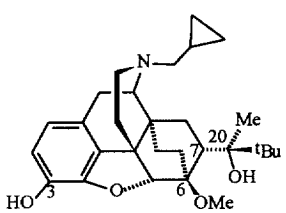
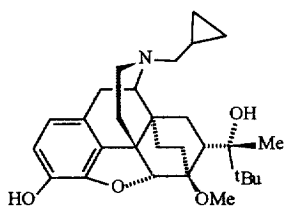
Abstract: The acid catalysed rearrangement of thevinols has been shown to proceed with retention of configuration at C-7 and therefore not via a sp2 hybridised centre at C-7 as had been proposed previously. Additionally a single diastereomer possessing the 20[*R*] configuration is formed in the rearrangements of the two diastereomeric *i*-propyl alcohols.

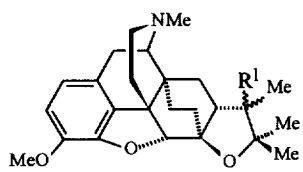
One of the major aims of our research has been to gain a better understanding of the significance of the lipophilic group attached to C-20 of the orvinols[#]. In particular the importance of the *t*-butyl group in buprenorphine (**1**), a potent opioid analgesic possessing a pharmacological profile that is useful in the treatment of drug abuse.[1]



1: Buprenorphine



1a: Buprenorphine
(less favoured conformation)



2: R1=H
3: R1=Me

We have previously reported on our work towards 7,8- and 7,7- spiro ring constrained analogues of buprenorphine and 5,7-cyclic imines and pyrrolidines.[2,3,4] We were therefore greatly interested in the work of

[#]Bentley *et al*[7] had the given the methyl ketone **17** the trivial name thevinone and hence alcohols derived from this ketone are called thevinols. A 3-O demethylated thevinol is termed an orvinol.

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Bentley *et al*[5] who synthesised a limited range of furanocodides such as **2**, **3** by acidic rearrangement of a tertiary thevinol (**4**) possessing a branched chain at C-20 (e.g ^{i}Pr or ^{t}Bu). We envisaged that the related furanomorphides, formed by the 3-O demethylation of the furanocodides, could be compared with the conformation of buprenorphine (**1a**) in which the *t*-butyl group is in the less favoured position.[11] In order to be able to interpret the pharmacological data on **2** it was important to know the stereochemical outcome of the rearrangement, *i.e.* whether the product from **4** was **2a** or **2b**. Although Bentley *et al*[5] did not assign stereochemistry to the furanocodide (**2**) a mechanism was proposed for the rearrangement (Figure 1). This involved initial ring opening with dehydration and hydrolysis to give the 14-alkenyldihydrocodeinone **5**, followed by ring closure to give the carbocation intermediate (**6**). Hydride shift followed by cyclisation from the C-6 oxygen would result in the observed product (**2**). We found interesting the suggestion that the 14-alkenyldihydrocodeinone (**5**) was formed during the reaction. Previously it has been reported that the acid catalysed rearrangement of equivalent straight chain alcohols (eg. ^{n}Pr) also proceeds via this intermediate.[6] However, in these cases rearrangement then proceeds via oxide bridge fission and Markovnikov addition of C5 to the double bond, thus resulting in a 4-phenol. Clearly with the branched chain alcohols this process does not occur and yet an equivalent intermediate was invoked by Bentley.[5] It was therefore decided to reinvestigate this reaction in order to shed further light on the mechanism of the rearrangement.

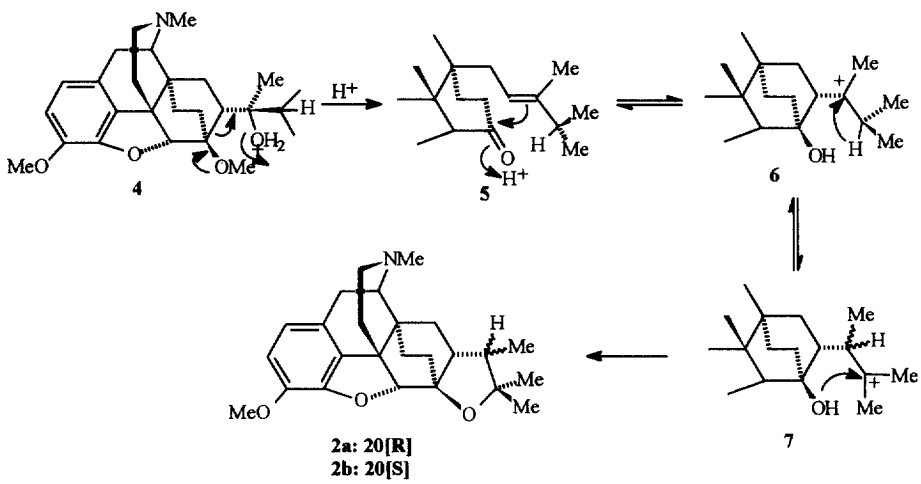
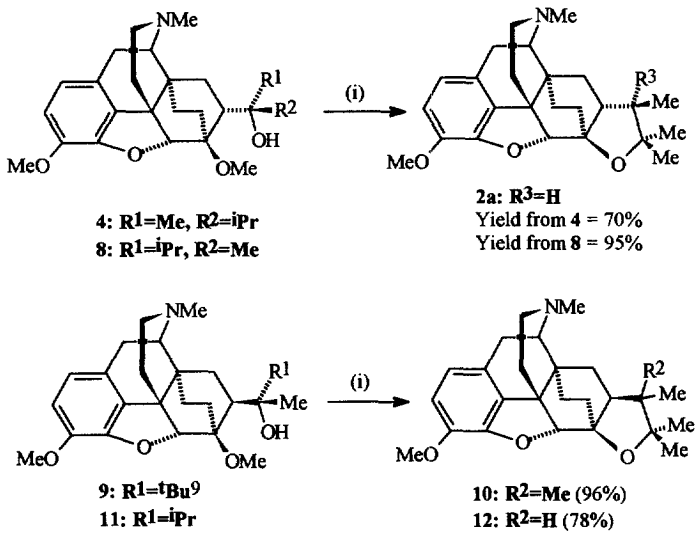


Figure 1: Previously proposed mechanism for the acid catalysed rearrangement to a furanocodide with undetermined stereochemistry at C-20.

Four thevinols were synthesised in order to carry out this investigation. Each was prepared from the appropriate, known ketone with addition of alkyl Grignard reagent. Thus **8** was prepared from the isopropyl ketone[8] by addition of methyl magnesium iodide in 67% yield, while its diastereomer (**4**) was synthesised from the methyl ketone as reported previously.[7] Addition of *t*-butyl- or *i*-propylmagnesium bromide to the β-methyl ketone[9] afforded the 7β-analogues (**9** and **11**) in yields of 45% (^{t}Bu) and 87% (^{i}Pr). If Bentley's proposed mechanism for the rearrangement was correct, then **9** would be expected to yield the same product (**3**) as that

reported for the 7α-epimer, arising from the formation of an sp2 hybridised centre at C-7. Similarly, **8** and **11** would yield identical cyclised products. However it was found that treatment of each of these tertiary alcohols with acid yielded the furanocodide with retention of configuration at C-7 (Figure 2). This was clearly demonstrated by ^{1}Hnmr spectroscopy in which the C5 proton in the 7β analogues is shifted approximately 0.5 ppm downfield compared to the equivalent proton in the 7α series. Clearly these results preclude the formation of the sp2 hybridised centre at C-7. Additionally when either **4** or **8** was treated with formic acid at reflux for 2 hours, a single furanocodide to which structure (**2a**) has been assigned by X-ray crystallography,[10] was the only observable product.



(i): formic acid, 2 h, reflux or 1N HCl, 4 h, steam bath.

Figure 2: Synthesis and acid catalysed rearrangement of the thevinols.

To account for these observations a mechanism can be proposed that involves formation of the carbocation (**13**) followed by, for examples with a *t*-butyl side chain, methyl shift and attack by the C-6 oxygen (Figure 3, but Me in place of H). The equivalent mechanism could also account for both diastereomeric *i*-propyl thevinols giving the same, single furanocodide. Thus formation of the carbocation would be followed by hydride shift and ring closure. In these cases the transition state for ring closure would favour the formation of the 20[*R*] epimer due to less unfavourable steric interactions between the 20-methyl group and the ethano bridge. Alternatively, a deprotonation-reprotonation process could take place to give the alkene (**16**) and carbocation (**14**) respectively, followed by ring closure. A concerted mechanism appears to suffer from unfavourable steric interactions between the ethano bridge and one of the methyl groups on the side chain and therefore appears the less likely mechanism.

Thus we have demonstrated that the rearrangement proceeds with retention of configuration at C-7 and therefore cannot proceed via an alkenyldihydrocodeinone (**5**) intermediate. Additionally a single diastereomer

possessing the 20[*R*] configuration is formed in the rearrangements of the diastereomers **4** and **8**. Subsequently these furanocodides have been 3-O demethylated to their furanomorphide counterparts and preliminary evaluation indicates that they are potent, but non-selective opioids. The further pharmacological characterisation of these compounds will be reported elsewhere.

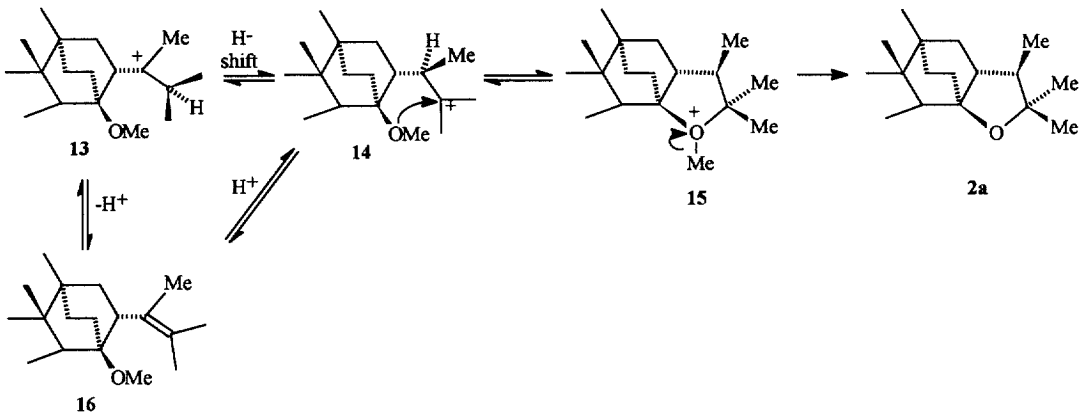


Figure 3: Proposed mechanism for the acid catalysed rearrangement.

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10. Crystal data for 2a: $C_{25}H_{33}NO_3$: colourless plates, 0.85 x 0.85 x 0.35 mm, M_r = 395.5, monoclinic spacegroup $P2_1$, a = 6.967(2), b = 8.978(3), c = 16.984(5) Å, β = 98.74(2)°, V = 1050.0(6) Å^3, Z = 2, D_{calc} = 1.25 gcm^{-3}. Siemens R3m/v diffractometer, Mo-Kα X-radiation, $\bar{\lambda}$ = 0.71073 Å, T = 293(2)K. Total reflections collected 5511 ($2\theta \leq 60.0°$), independent reflections 3229 (R_{int} = 0.026). The structure was refined by full-matrix least-squares against F, final R = 0.0505, [2616 reflections with $F > 3\sigma(F)$], GOF = 1.44.
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