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Perchloric acid induced epimerisation of the thevinones: an improved synthesis of 7β-dihydrothevinones

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Abstract

The region above and away from C7 in the orvinols is known to be of particular importance in determining the μ-opioid receptor profile of this important class of opioids. However it has been difficult to explore this site due to the relative inaccessibility of 7β-substituted compounds. Here we report that perchloric acid induced epimerisation of the 7α-ketones (dihydrothevinones) allows considerably improved access to a series of β-ketones (β-dihydrothevinones). The extent of epimerisation of the 7α-ketone is determined by the degree of steric bulk in both the 6,14-bridge and in the ketone side chain.

Keywords: opioids; thevinones; 7β-dihydrothevinones; epimerisation.

1. Introduction

Derivatives of the opioid thevinone (**1a**), obtained from the Diels–Alder reaction of thebaine with methyl vinyl ketone, have been extensively studied. Further elaboration of thevinone leads to a series of compounds termed the orvinols, which include etorphine (Immobilon®, **9**), diprenorphine (Revivon®, **10a**) and buprenorphine (Temgesic®, **10b**), the latter being an analgesic of clinical utility more recently developed as a pharmacotherapy for opioid abuse.[1] The orvinols contain a tertiary alcohol unit attached to the 7α-position of the ring system. It has become clear that the region above and away from C_7 has in particular, a significant impact on the μ-opioid receptor profile of orvinols and related compounds. However the relative inaccessibility of the epimeric ketones (**5**–**8**) has hindered direct exploration into the role and nature of this site. The Diels–Alder reaction gave almost exclusively the 7α-adduct (thevinone, **1a**), although 0.5% of the β-epimer (**7a**) was isolated by fractional crystallisation of the product of a large scale reaction.[2] Following large scale hydrogenation of the Diels–Alder adduct, 1.3% of

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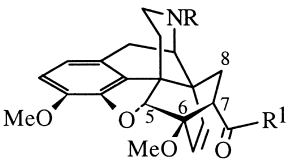
the dihydroepimer (**5a**) was obtained by fractional crystallisation of the bitartrates.[3] The only reported studies of 7α↔7β epimerisation in the thevinone series have used basic conditions. Bentley et al.[2,4] attempted to establish 7α/7β-equilibrium mixtures by reversible enolisation of the 7α-ketones using sodium hydroxide in methanol, but instead of conversion to the 7β-epimer found that rearrangement occurred with the formation of ketals of 5,14-bridged thebainone derivatives (**11**). Marton et al.[5] achieved some success in converting the 7α-ketones (**1a**, **1b**, **3a**, **3c**) to the 7β-epimers (**7a**, **7b**, **5a**, **5c**) using bases with weak nucleophilic character (e.g. DBU), but in most cases rearrangement to **11** could not be prevented and often predominated. In every case the conversion to the 7β-ketone was less than 20%. These basic conditions appeared not to have achieved epimeric equilibrium since when they were applied to the epimeric 7β-ketones (**7b**, **5a**) only about 50% of the 7α-epimer was formed, interestingly without any rearrangement.[5] Here we report more effective acidic conditions for the epimeric conversion of the dihydrothevinones (**3**, **4**) and compare this with the effects of similar conditions on the equivalent thevinones.



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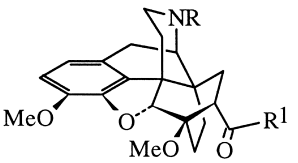

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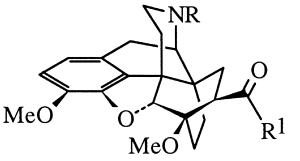

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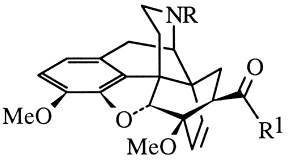


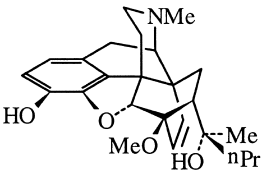
7: R = Me, **8**: R = CPM

(a):R^1 = Me, (b):R^1 = Et,
(c):R^1 = Ph, (d):R^1 = ^{t}Bu

2. Results and discussion

As part of our investigation into the effects of substituents at C7, we wished to prepare the 7α-acetylamino derivative (**12a**) using the Schmidt reaction with *N*-cyclopropylmethylnordihydrothevinone (**4a**).[11] This procedure had been successfully used to give the etheno analogue (**14d**) from thevinone (**1a**).[6,7] When **4a**[10] was treated with 35% aqueous $HClO_4$ and NaN_3 at 70°C, a 2:1 mixture of 7α- and 7β-acetylamino derivatives (**12a**, **13a**) was formed. It was deduced that acid-catalysed epimerisation via the enol (**18**) leading to a mixture of ketones (**4a**, **6a**) was competing with Schmidt rearrangement (Scheme 1). This was confirmed by carrying out the reaction under identical conditions but without NaN_3. The proportions of 7α- and 7β-ketones (**4a**, **6a**) in the product were very similar to those of the acetylamino products (**12a**, **13a**) of the Schmidt reaction. The results are shown in Table 1, entries 1 and 2. The product ratios were determined on the unseparated reaction mixtures using NMR analysis.[8,9] The product ratio was determined by the magnitude of the H-5β signal, which for the ketones show at higher field for the 7α-epimer than for the 7β-epimer. Unusually, with the acetylamino derivatives the relative positions of the H-5β signals were reversed. In Table 2, the chemical shift of the H-5β signal is

recorded for those compounds whose ^{1}H NMR data have not previously been reported. **3d** is included for comparison with **5d**.



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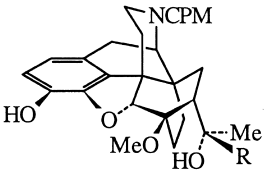

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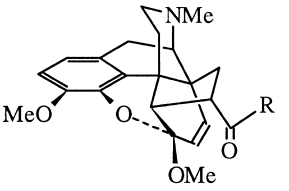
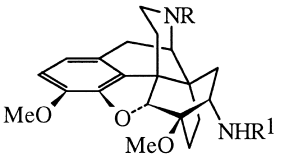


11 (a) R = Me, (b) R = Ph



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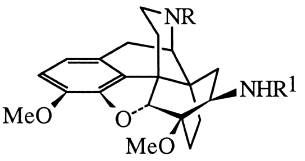

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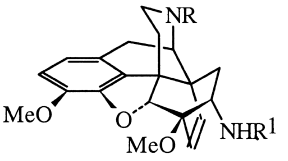

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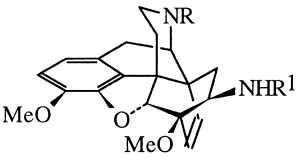
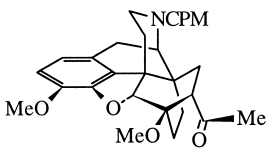
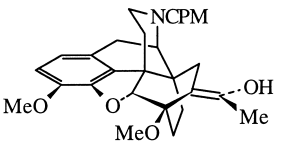
(a) R = CPM, R^1 = $COCH_3$ (b) R = Me, R^1 = $COCH_3$ (c) R = CPM, R^1 = H
(d) R = Me, R^1 = H



CPM = cyclopropylmethyl



4a



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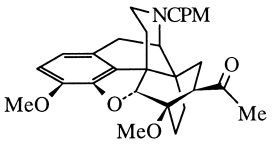
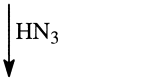
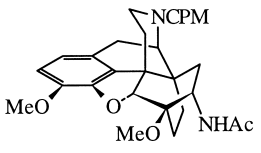
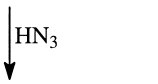


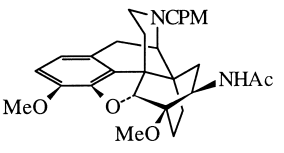
6a





12a





13a

Scheme 1. Competing Schmidt and epimerisation reactions

Table 1
Product ratios for epimerisation in the presence and absence of sodium azide

Entry	Starting material	Sodium azide	Temp. (°C)	Time (h)	Product ratio	
					7α	7β
1	**4a**	Yes	70	16	**12a** (~67)	**13a** (~33)
2	**4a**	No	70	16	**4a** (~67)	**6a** (~33)
3	**3a**	Yes	70	2	**12b** (~75)	**13b** (~25)
4	**3a**	No	70	1	**3a** (58)	**5a** (42)
5	**3a**	No	70	16	**3a** (58)	**5a** (42)
6	**3a**	No	90	16	**3a** (58)	**5a** (42)
7	**5a**	Yes	70	4.5	**3a** (~50)	**5a** (~50)
8	**3d**	No	90	18	**3d** (~50)	**5d** (~50)
9	**3c**	No	70	1	**3c** (~70)	**5c** (~30)
10	**3c**	No	70	4	**3c** (56)	**5c** (44)
11	**1a**	Yes	70	5	**14b** (100)	–
12	**2a**	Yes	70	5	**12b** (100)	–
13	**7a**	Yes	70	4	**14b** (70)	**15b** (25)
14	**1a**	No	70	4.5	**1a** (~67)	**7a** (~17)[a]
15	**7a**	No	70	4	**1a** (~83)	**7a** (~17)
16	**1d**	No	90	5	**16d** (42)	**17d** (37)[b]

[a] ~17% of 6-demethylthevinone (**16a**) also formed.
[b] Product is not a thevinone.

The epimerisation of dihydrothevinone derivatives in perchloric acid with and without Schmidt reaction was further investigated in some detail (Table 1, entries 3–7). Although dihydrothevinone (**3a**) gave less β-epimer than its *N*-CPM analogue (**4a**) in the Schmidt reaction, the proportion of its epimer from perchloric acid treatment alone was higher than for the *N*-CPM analogue. Equilibrium was attained within 1 h with about 40% of the β-epimer (**5a**) being formed. When epidihydrothevinone (**5a**) was subjected to the Schmidt reaction, approximately equal amounts of the 7α- and 7β-acetylamino derivatives (**12b**, **13b**) were formed. This result was very similar to that obtained when **5a** was epimerised under weakly nucleophilic basic conditions.[5]

Table 2
Chemical shift of H-5β proton

Starting material	7α (ppm)	7β (ppm)
4a	**12a** (4.60)	**13a** (4.55)
3a	**12b** (4.70)	**13b** (4.64)
7a	**14b** (4.80)[7]	**15b** (4.77)
3d	**3d** (4.35)[10]	**5d** (5.58)

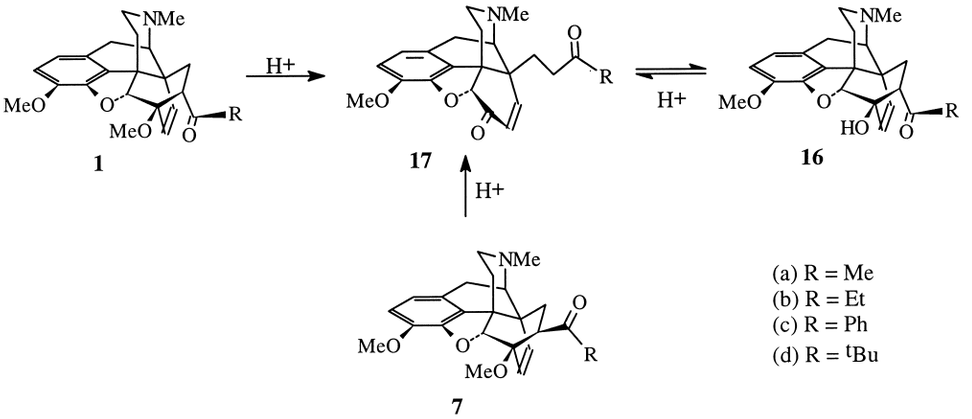
Further examples of the epimerisation of thevinone-related ketones were investigated (Table 1, entries 8–10). The *t*-butyl ketone (**3d**)[8,10] with perchloric acid gave a 1:1 ratio of **3d** with the 7β-epimer (**5d**), and dihydronepenthone (**3c**) similarly was 44% converted to its epimer (**5c**). The higher proportion of epimerisation in these cases is most likely due to the greater steric bulk of the *t*-butyl and phenyl groups thus causing more unfavourable interaction with the 6,14-ethano bridge in the 7α-epimers. Separation of epithevinone and dihydroepithevinone was achieved by literature methods.[3,5] The epi-*t*-butyl ketone could be isolated by silica gel chromatography, whereas the other examples reported were not separable by this method.

We confirmed the lack of epimerisation of the etheno-ketone, thevinone (**1a**) and the *N*-CPM analogue (**2a**) in the Schmidt reaction and showed that epithevinone (**7a**)[5] was converted into a 3:1 mixture of 7α- and 7β-acetylamino derivatives (**14b**, **15b**) (Table 1, entries 11–13). When thevinone was treated with perchloric acid alone at 70°C, a small amount of conversion to epithevinone (**7a**) was detected together with a second product identified as 6-*O*-demethylthevinone (**16a**). Under these conditions epithevinone was converted largely to thevinone, confirming the substantially greater stability of the 7α- over 7β-ketone (entries 14 and 15).

The mechanism of the Schmidt reaction involves initial protonation of the ketone, followed by attack of hydrazoic acid. In the ethano series it appears that deprotonation of the 7α-protonated ketone to give the enol and epimerisation can occur in competition with the hydrazoic acid attack. In the etheno series the greater accessibility of the 7α-protonated ketone to hydrazoic acid allows the Schmidt reaction to predominate and no epimerisation is observed. That in the etheno series Schmidt reaction is faster than epimerisation was confirmed when the hydrazoic acid was omitted from the reaction of thevinone (**1a**) and epithevinone (**7a**). In both cases more epimerisation was observed than in the equivalent Schmidt reactions. In the ethano series, the 7α-ketone was epimerised to the same extent in the Schmidt and non-hydrazoic acid conditions showing that the Schmidt reaction was slower than epimerisation.[†]

When the temperature of the perchloric acid conditions alone was raised to 90°C, both thevinone (**1a**) and epithevinone (**7a**) were converted largely to 6-deoxythevinone (**16a**). The reaction involves the opening of the bridged ring to give the 14-(3-oxoalkyl)codeinone (**17a**), which can ring close again to give the 6-deoxy ketone (**16a**) in the more stable 7α-acyl configuration (Scheme 2). It was difficult to isolate the codeinone intermediate (**17a**) since the ring closure to **16a** occurs so readily. In the expectation of increased stability of the codeinone relative to the 6-*O*-demethylthevinone derivative, the action of perchloric acid on the *t*-butyl ketone (**1d**) was investigated. The codeinone (**17d**) was isolated in 37% yield, as well as the 6-deoxy ketone (**16d**) (42%). The equilibrium between the two products was demonstrated by subjecting the isolated deoxy ketone (**16d**) to the perchloric acid conditions to give a 1:1 mixture of starting material and codeinone (**17d**), effectively increasing the yield of the latter.

[†] General procedure for Schmidt reaction. Perchloric acid (70%: 10 ml/g of ketone) was added dropwise to a vigorously stirred suspension of ketone in water (10 ml/g of ketone). After dissolution, sodium azide (2.7 equiv.) was added and the solution warmed to 70 or 90°C. After the required time the solution was cooled to rt, basified with ammonia (pH 10) and the products were extracted with EtOAc (3×50 ml). The combined organics were dried (Na_2SO_4), the solvent removed in vacuo and the ^1H NMR spectrum recorded for the crude mixture.



Scheme 2. Epimerisation via a 14-arylethylcodeinone (**17**)

3. Conclusions

The use of perchloric acid has led to a considerably improved method for generating 7β-thevinones. The extent of epimerisation has been shown to be controlled by the nature of the 6,14-bridge with the more bulky ethano bridge leading to greater amounts of β-epimer. Similarly, the ketone side chain also influences the outcome, with the bulky *t*-butyl ketone providing a greater proportion of 7β-epimer at equilibrium.

Acknowledgements

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