AN IMPROVED HYDROLYSIS OF 7α-CHLORO-7β-CYANO-6,14-ENDO-ETHENOTETRAHYDROTHEBAINE TO ITS 7-OXO DERIVATIVE

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Abstract - An efficient method for the conversion of 7α-chloro-7β-cyano-6,14-endo-ethenotetrahydrothebaine (4) to 6,14-endo-etheno-7-oxotetrahydrothebaine (3) using Na2S•9H2O is described. This method requires no chromatography for purification, and is therefore amenable to large scale preparation of the potentially important opioid intermediate.

Diels-Alder adducts of thebaine have resulted in a number of pharmacologically important opioid ligands, including the orvinols buprenorphine (1) and dihydroetorphine (2), both of which are currently being investigated as potential treatment agents for opiate abuse.2,3 Studies have shown that the nature of the lipophilic group attached to C-20 has an enormous effect of the pharmacology of these ligands, and Lewis has proposed that this is due to the lipophilic group occupying different regions of space when bound to the opioid receptors.2 Indeed, Lewis has shown that the conformational fixing of lipophilic groups at this position has a major effect on the pharmacology of this class of drugs.4,5,6

As part of our own studies in this area, we considered that lipophilic groups attached directly to C-7 would have less conformational freedom due to the lack of the 7,20-bond, without having to tie up the lipophilic group as a ring to another position of the opioid skeleton. Such analogs were briefly investigated in the 1970’s,7 however the inefficient method for the preparation of the key intermediate ketone 3,7 has discouraged this route. To open up this avenue and fully evaluate such compounds using
opioid subtype selective assays not available in the 1970’s, we required an efficient method to prepare significant quantities of the intermediate 6,14-endo-etheno-7-oxotetrahydrothebaine (3).

The preparation of 3 was previously described by Lewis\(^7\) as a two-step synthesis: the cycloaddition of 2-chloroacrylonitrile with thebaine to yield 7α-chloro-7β-cyano-6,14-endo-ethenotetrahydrothebaine (4) as the major product, followed by treatment with aqueous NaOH (1 N, 6.7 equivalents) in refluxing EtOH for 16 h to yield 3. The yield of the hydrolysis of 4 to 3 was reported to be ca. 30%, and the majority of the product isolated was the C-4 phenolic lactone (5). Following their procedure, we obtained similarly low (and inconsistent) yields of 3. The authors speculated that excess hydroxide was responsible for the extensive rearrangement of 3 to 5, thus resulting in such low yields. Such basic rearrangements of the Diels-Alder adducts of thebaine are frequently encountered, but we have had significant success in the development of basic reaction conditions which do not lead to rearrangements.\(^9\) We considered that milder reaction conditions (i.e. less NaOH and shorter reaction times) would enable us to hydrolyze the chlorocyano adduct (3) to the resulting ketone (4) without extensive rearrangement to 5.

The reagent Na\(_2\)S\(\cdot\)9H\(_2\)O\(^{10,11}\) has been employed as a means to accomplish similar hydrolysis reactions quickly and efficiently in simple alkyl ring systems and, as lesser equivalents of NaOH and shorter reaction times were needed for these conversions, we postulated that this method may prove compatible with the sensitive opioid ring system.

The chlorocyano adduct (4) was prepared by the method of Lewis and co-workers.\(^{12,13}\) Compound (4) (0.39 g, 1 mmol) and Na\(_2\)S\(\cdot\)9H\(_2\)O (0.48 g, 2 mmol) was then suspended in EtOH/H\(_2\)O (4:1, 20 mL), followed by the addition of 1N NaOH (2 mL, 2 mmol). The suspension was then heated to vigorous reflux for 6 h, when the reaction was judged complete by TLC. The solvents were removed by rotary evaporation, and the resulting solid was suspended in H\(_2\)O. To prevent any possibility of generating HCN, additional 1 N NaOH was added to ensure pH > 8. The aqueous layer was extracted with EtOAc, and the extract was washed with H\(_2\)O, brine, then dried over Na\(_2\)SO\(_4\). The solvent was removed by rotary evaporation, and the crude material was recrystallized from MeOH to yield 0.22 g (63%) of the final product (3). TLC: R\(_f\) (EtOAc/hexanes, 1:1; silica gel) = 0.18; mp (uncorrected) 189-191 °C (lit.,\(^7\) 190-192 °C); electron spray ionization MS (ESI-MS): [M+H\(^+\)] = 353.9 (calcd 354.1); IR (CH\(_2\)Cl\(_2\), cm\(^{-1}\)) 1733; NMR (CDCl\(_3\), 300 MHz) \(\delta\) = 1.86 (d, 1H, \(J\) = 13.4 Hz), 2.01-2.21 (m, 3H), 2.38 (s, 3H), 2.43-2.52 (m, 4H), 3.02-3.31 (m, 4H), 3.63 (s, 3H), 3.84 (s, 3H), 4.68 (d, 1H, \(J\) = 8.6 Hz), 5.68 (d, 1H, \(J\) = 8.3 Hz), 6.58 (d, 1H, \(J\) = 7.8 Hz), 6.66 (d, 1H, \(J\) = 7.8 Hz).

The ratio of Na\(_2\)S\(\cdot\)9H\(_2\)O to starting material was found to have a profound effect on yield and reaction time. Fewer equivalents of Na\(_2\)S\(\cdot\)9H\(_2\)O (1 and 1.5 equivalents) resulted in extended (>48 h) reaction times and substantial amounts of starting material still present. With 2 equivalents of Na\(_2\)S\(\cdot\)9H\(_2\)O, the reaction proceeded quickly and efficiently, with trace evidence of starting material seen after 6 h.

The amount of H\(_2\)O in the solvent mixture also proved to be quite important. When run under conditions using anhydrous EtOH and solid KOH, a complex mixture of products arose, resulting in low yields (<20%) which necessitated column chromatography for purification. When lower percentages of H\(_2\)O in the reaction solvent (i.e. < 20%) were used, a precipitate was seen in the refluxing reaction mixture, and this led to extended reaction times and incomplete reactions as monitored by TLC.

In conclusion, Na\(_2\)S\(\cdot\)9H\(_2\)O has proven to be an effective reagent for the hydrolysis of 7α-chloro-7β-cyano-6,14-endo-ethenotetrahydrothebaine (4) to the desired 6,14-endo-etheno-7-oxotetrahydrothebaine
This method resulted in increased yields, shorter reaction times and requires no chromatography for purification. The use of Na$_2$S•9H$_2$O will facilitate the future preparation of multi-gram quantities of this important opioid intermediate.

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REFERENCES AND NOTES


13. The yield of this reaction was 67%. The melting point, NMR and MS data were consistent with literature values for cyanochloro adduct (4).