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Photooxidation of Thebaine. A Route to 14-Hydroxymorphinones and Hydrodibenzofuran Analogs of Methadone.

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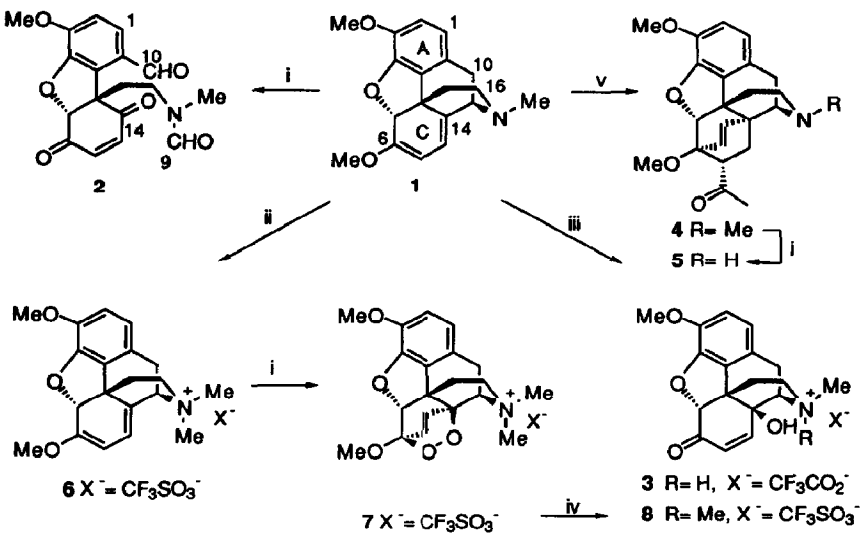
Abstract: The photooxidation of thebaine (1) produces a highly functionalized hydrodibenzofuran 2 *via* formation of the endoperoxide and a tert-amine radical cation. Photooxidation of the quaternary ammonium salt of thebaine 6, allows the isolation of the endoperoxide 7. Photooxidation of thebaine 1 in acidic medium (TFA), yields 14-hydroxycodeinone salt 3 *via* the corresponding endoperoxide.

One route to modified morphine and other opioids (reference 1 lists some of the extensive literature in this field and a recent paper regarding pharmacological activity), is Diels-Alder cycloaddition to the C ring of thebaine (1) and its analogs.[2] Because of the high analgesic activity of some of these derivatives, (e.g. etorphine and buprenorphine), this approach has been used with a wide variety of dienophiles.[2] However, although photooxidation has been employed for N-demethylation of other opioid, e.g. codeine,[3] the [4+2] cycloaddition of singlet oxygen to the diene of thebaine (1) or analogs has not been reported. This transformation should be of great interest as an easy route to compounds with oxygen-containing groups at C(6) and C(14) of the alkaloid. Several examples are known, (e.g. oxycodone, oxymorphone, naloxone, all in clinical use), in which groups at those positions play a part in the analgesic activity.[4]

In this paper, we report that the photooxidation of thebaine[5] (1) is a viable route to the hydrodibenzofuran 2 or, when carried out under acidic conditions, to the 14-hydroxycodeinone salt 3 (Scheme 1).[6]

The pale yellow hydrodibenzofuran 2[7] was formed in 62% yield when a solution of thebaine (1) and tetraphenylporphyrin (TPP) as photosensitizer, was irradiated (UV-Vis) in oxygenated dichloromethane. The molecular ion of the product had *m/z* 343.1055 (HRMS), corresponding to the molecular formula $C_{18}H_{17}NO_6$ (calcd 343.1051) with 11 DBEs, as in the proposed structure. The ^1H and ^{13}C NMR spectra of this compound both showed two sets of signals, suggesting that in solution it exists in two forms in equilibrium. In $CDCl_3$ and benzene-d_6 the ratio of the two species was 2:1, while in DMSO-d_6 it was 1:1; each set of peaks corresponds to one rotational isomer of the formamide 2. Characteristic signals in the NMR spectra in $CDCl_3$ are: those of an aromatic aldehyde, at chemical shifts δ 10.21/10.06 (^1H) and 189.5/189.4 ppm (^{13}C); those of a formamide, at δ 7.89/7.87 (^1H) and 162.8/162.6 ppm (^{13}C); and those of an enedione, at 194.3/193.8 and 191.0/191.0 ppm (^{13}C). In keeping with the proposed structure, high temperature ^1H NMR showed coalescence of the signals due to both rotamers at 393 K. In addition, the presence of those functional groups in 2 was confirmed by catalytic hydrogenation producing saturated triol alcohols at C-6, C-9 and C-10, and by refluxing 2 with MeOH/pTSA that gave a dimethyl ketal at C-6.

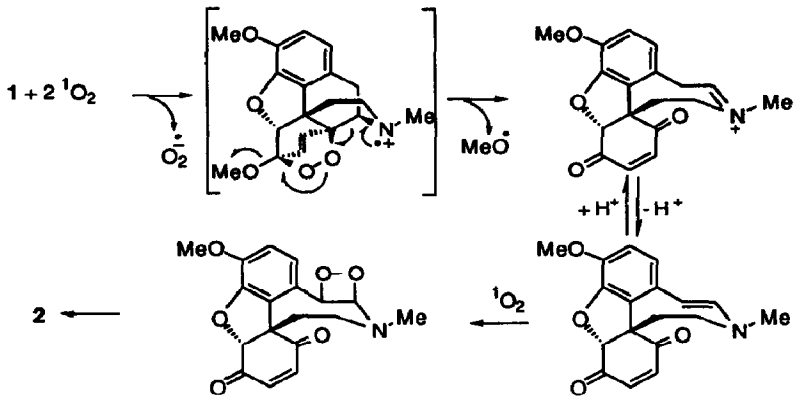


Scheme 1. i) O_2, TPP, hv, CH_2Cl_2; ii) $MeOSO_2CF_3$, $MeNO_2$; iii) O_2, TFA, TPP, CH_2Cl_2, hv; iv) TFA, 75°C, CH_2Cl_2; v) MVK, 80°C.

From a mechanistic point of view, this conversion of **1** to **2** involves reaction at two sites in the thebaine molecule: the electron-rich 1,3-diene, and the tertiary amine group. The reaction should proceed *via* the endoperoxide, however, even when the reaction was carried out at low temperature (-30 °C) the endoperoxide of **1** was not isolated or detected by NMR spectroscopy. An explanation for the instability of this intermediate is its rapid decomposition assisted by either the ketal at C(6) or the amino group. To establish which of these two functions were involved, derivatives of **1** in which one group was unable to participate in the photooxidation reaction were synthesized. Thus, photooxidation of the methyl vinyl ketone adduct thevinone **4**,[8] in identical experimental conditions, occurred exclusively at the nitrogen atom giving the N-demethylated derivative **5** formed through the corresponding amine radical-cation. For its part, the N-protected crystalline salt **6**, obtained by quaternization of **1** with methyltriflate, gave by photooxidation the isolable endoperoxide **7**.[9] These observations, and the fact that **7** was stable in dilute TFA at r.t. suggest that it is the nitrogen that induces the lability of the endoperoxide of **1**, and that the ketal plays no part. A retro Mannich-like mechanism from the endoperoxide can be formulated to justify the obtention of **2**, but the easy photoxidation of **4** to the radical-cation under the same experimental conditions seems to favour a mechanism in which the Diels-Alder addition of $^1O_2$ to **1** occurs with concomitant oxidation of the nitrogen to an amino radical-cation, which then assists in the opening of the endoperoxide ring in a concerted process. The iminium cation is then transformed to an enamine which reacts with another equivalent of $^1O_2$ to give the formyl groups found in **2**, *via* a 1,2-dioxetane[10] (Scheme 2).

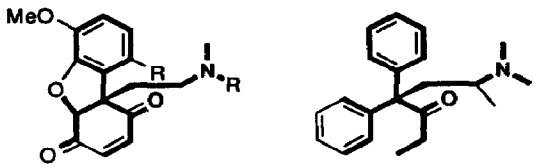
In view of these results, we attempted to prevent oxidation of the nitrogen in **1** by photooxidation of the ammonium salt. Photooxidation of an acidic solution of **1** in CH_2Cl_2 /TFA proceeded *via* the corresponding endoperoxide, which broke down in the acidic medium to give the 14-hydroxycodeinone[11] salt **3** in 61% yield,

and is therefore an excellent one-pot method for functionalization at C(6) and C(14) in thebaine. Heating the endoperoxide **7** at 75 °C in methanolic TFA for 7 h confirmed the result of this reaction by smoothly transforming **7** into the keto alcohol **8**, which is analogous to **3**.



Scheme 2

Partially reduced dibenzofurans[12] and structurally related compounds are of interest owing to their analgesic activity. Several procedures for preparation of this class of compounds have been described,[13] all of which involve multi-stage synthesis and are non-stereoselective. This reaction, involving the photooxidation of thebaine, is by far the simplest preparation of functionalized hydrodibenzofurans yet reported. It is noteworthy to point out the close resemblance between the frame of hydrodibenzofuran **2** and that of the widely used agonist methadone (**9**) as is shown in Fig. 1. This similarity strongly appoints **2** as a new entry to modified rigid methadones of potential use as analgesics devoid of addiction potential.



2 **9**

Figure 1

These results constitute the first report on the isolation and synthetic use of the endoperoxide of the diene system present in several morphine alkaloids. An interesting variant is the bridged C(5)-C(10) epidioxide described by Kirby et al. and its efficient conversion to 10-oxothebaine.[14]

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5. ***General Procedure for the Photooxygenation of Thebaine.*** Oxygen was bubbled through a solution of thebaine (**1**) (200 mg, 0.64 mmol) and TPP (20 mg, 0.03 mmol) in 150 mL of CH_2Cl_2 in a flask fitted with a cooling-water-jacket. This was irradiated 90 min by a sun lamp (300W) 45 cm away, the solvent evaporated in vacuo and **2** isolated by flash chromatography on silica-gel.
6. All compounds gave satisfactory analysis and spectroscopic data.
7. ***Compound 2:*** Major rotamer: ^{13}C NMR ($CDCl_3$) [atom number] δ: [1] 112.8, [2] 128.1, [3] 150.0, [4] 147.9, [5] 85.7, [6] 194.3, [7] 140.5, [8] 142.6, [9] 162.8, [10] 189.5, [11] 127.0, [12] 128.1, [13] 61.6, [14] 191.0, [15] 35.4, [16] 40.5, [3-OMe] 56.3, [NMe] 34.4. ^1H NMR ($CDCl_3$) [atom number] δ: [1] 7.59 (d, J=8.5 Hz), [2] 6.94 (d, J=8.5 Hz), [5] 5.29 (s), [7] 6.96 (d, J=10.4 Hz), [8] 6.87 (d, J=10.4 Hz), [9] 7.87 (s), [10] 10.21 (s), [15] 2.30-2.38 (m), 2.64-2.72 (m), [16] 3.02-3.18 (m), 3.45-3.75 (m), [3-OMe] 3.97 (s), [NMe] 2.93 (s). Minor rotamer: ^{13}C NMR ($CDCl_3$) [atom number] δ: [1] 112.8, [2] 126.0, [3] 150.3, [4] 148.0, [5] 86.8, [6] 193.8, [7] 140.0, [8] 142.9, [9] 162.6, [10] 189.4, [11] 127.3, [12] 128.5, [13] 61.4, [14] 191.0, [15] 34.6, [16] 45.3, [3-OMe] 56.2, [NMe] 29.5. ^1H NMR ($CDCl_3$) [atom number] δ: [1] 7.57 (d, J=8.5 Hz), [2] 6.94 (d, J=8.5 Hz), [5] 4.98 (s), [7] 6.92 (d J=11.1 Hz), [8] 6.88 (d, J=11.0 Hz), [9] 7.89 (s), [10] 10.06 (s), [15] 2.39-2.50 (m), 2.52-2.60 (m), [16] 3.18-3.32 (m), 3.45-3.75 (m), [3-OMe] 3.91 (s), [NMe] 2.80 (s). EI *m/z* (% relative intensity): 343(15), 315(8), 284(32), 271(50), 256(45), 243(27), 203(43), 202(100).
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9. ***Endoperoxide 7***: ^{13}C NMR ($CDCl_3/CD_3OD$) [atom number] δ: [1] 120.2, [2] 117.1, [3] 144.4, [4] 145.7, [5] 90.8, [6] 96.0, [7] 130.8, [8] 136.7, [9] 69.3, [10] 26.3, [11] 121.9, [12] 129.6, [13] 46.8, [14] 80.4, [15] 28.0, [16] 58.5, [3-OMe] 55.8, [6-OMe] 55.8, [NMe] 49.4 and 51.9. ^1H NMR ($CDCl_3/CD_3OD$) δ [1] 6.67 (d, J=8.1 Hz), [2] 6.59 (d, J=8.1 Hz), [5] 4.58 (s), [7] 6.23 (d, J=9.1 Hz), [8] 6.06 (d, J=9.1 Hz), [9] 4.33 (d, J=6.9 Hz), [10]/[16] 3.10-3.94 (4H), [15] 2.14-2.22 (m), 2.50-2.65 (m), [3-OMe] 3.48 (s), [6-OMe] 3.47 (s), [NMe] 3.23 (s) and 3.32 (s). EI m/z (% relative intensity): 357(2), 343(1), 256(1), 254(1), 240(2), 230(3), 228(2), 199(2), 185 (3), 58 (100).
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