Synthesis and Characterization of a Novel *Diels–Alder* Adduct of Codeine[1])

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The *Diels–Alder* reaction was applied to 4,5-epoxymorphinan opioids to generate a novel aromatic cycloadduct at C(7)–C(8): Thermolytic cleavage of sultine **8** produced the reactive diene *o*-quinodimethane **7** which condensed favorably with codeine (**11**), but not with codeinone (**9**) or 14-hydroxycodeinone (**10**), producing the desired tetrahydronaphtho adduct **12** with (7*R*,8*R*) geometry (*Scheme*). The configuration of the cycloadduct was determined by 1D- and 2D-NMR experiments. The unanticipated reactivity of these codeine derivatives was investigated by quantum-mechanical calculations, and it was determined that steric effects of the 6-keto and 14-hydroxy group likely precluded condensation by raising the molecular energy of their respective transition states.

Introduction. – *Diels–Alder* [4+2] cylcoadditions of 4,5-epoxydehydromorphinans have been heavily investigated, resulting most significantly in the development of orvinols such as etorphine (**1**) and buprenorphine (**2**) [1] (*Fig.*). The electron-rich diene system of thebaine (**3**) undergoes catalyst-free cycloaddition with electron-poor vinyl ketones in high yields under mild conditions [2]. Despite the wealth of information regarding *Diels–Alder* reactions of thebaine analogs, few studies have reported the use of 4,5-epoxydehydromorphinan opioids as dienophiles. *Kshirsagar* and *Portoghese* [3] have described the cycloaddition of the highly reactive, electron-poor cyano-*o*-quinodimethane (=(2*E*)-2-(6-methylenecyclohexa-2,4-dien-1-ylidene)acetonitrile) across the less-hindered β-face of the C(8)=C(14) bond of **3** to give **5**, and across the C(6)=C(7) bond of the 6-demethoxy derivative **4** to give **6**. To date, however, there have been no reports of *Diels–Alder* cycloadditions across C(7)=C(8) of 4,5-epoxy-7,8-didehydromorphinan dienophiles.

It was envisioned that aromatic *Diels–Alder* cycloadducts at C(7)=C(8) could be produced by combining the reactive diene *o*-quinodimethane (=5,6-bis(methylene)-cyclohexa-2,4-diene; **7**) [4] with 7,8-etheno opioids to give the appropriate tetrahydronaphtho adducts. Specifically, it was envisioned that electron-poor dienophiles such as codeinone (**9**) and 14-hydroxycodeinone (**10**) would readily react with **7**, whereas

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[1]) Portions of this manuscript have been included in the Ph.D. dissertation of *C. W. C.*, which was successfully defended on September 11, 2008.

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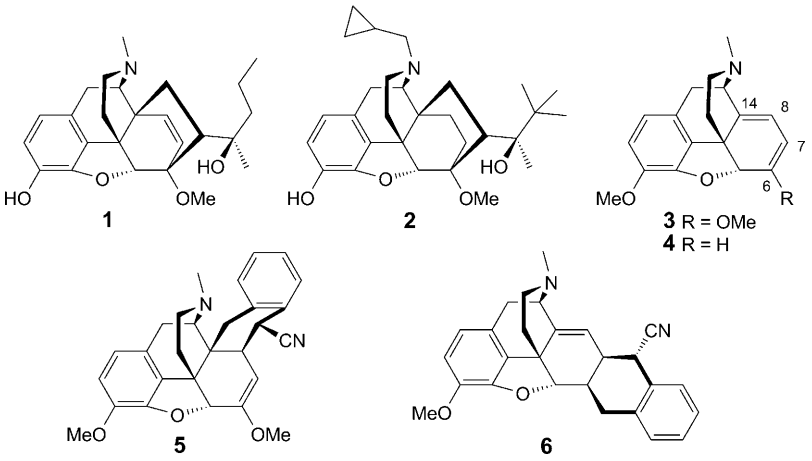
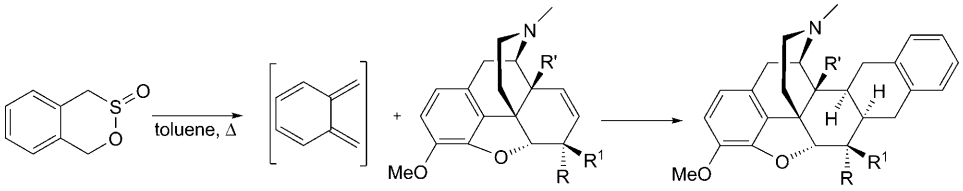


Figure. *Etorphine* (**1**), *buprenorphine* (**2**), *thebaine analogs* **3** *and* **4**, *and products* **5** *and* **6** *of* Diels–Alder *cycloadditions to thebaine*

unconjugated dienophiles such as codeine (**11**) would be less reactive. Despite the fact that *Diels–Alder* reactions typically proceed slowly with cyclic ketones [5], it was hypothesized that the high reactivity of **7** would overcome any steric or electronic limitations to give the desired cycloadducts without the need for additional catalysts.

Results and Discussion. – The diene *o*-quinodimethane (**7**) was formed *in situ* by thermolytic cleavage of the corresponding sultine **8** in toluene, as described by *Hoey* and *Dittmer* [6]. Diene **7** was then trapped by the presence of excess dienophiles **9**–**11** (*Scheme*). Opioids **9** [7] and **10** [8] were synthesized by known procedures, and codeine (**11**) was a generous gift from *Mallinckrodt*, *Inc.* (St. Louis, MO).

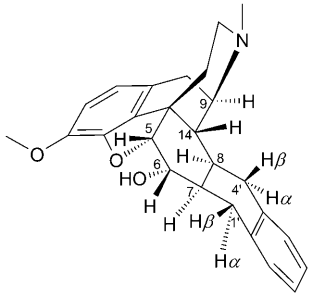
Scheme. Diels–Alder *Cycloaddition of* **9**, **10**, *and* **11** *with* **7**



Inspection of the crude product of the reaction of **7** and 6-keto analogs **9** and **10** showed no evidence of cycloaddition by MS or TLC. In the case of **9**, instability of the starting material was likely responsible for the lack of reactivity, as degradation products were seen during a control experiment of refluxing **9** alone in toluene. For **11**, evidence of a cycloadduct **12** was observed by MS (*m*/*z* 404, $[M+H]^+$), as well as by

TLC. Portions of this product were isolated by prep. TLC (silica gel (*Analtech*, *Inc.*), $CHCl_3$/MeOH 95:5) and identified by both 1D- (^{1}H- and ^{13}C-NMR) and 2D- (COSY, NOESY, HSQC) NMR techniques. Peak assignments pertinent for structure identification are shown in *Table 1*.

Table 1. *^{1}H- and ^{13}C-NMR, ^{1}H,^{1}H-COSY, and NOESY Assignments Involved in the Structure Determination of* **12**



	δ(H)[a])	δ(C)[a])[b])	^{1}H,^{1}H-COSY	NOESY[c])
H−C(5)	4.65	91.2	3.50, 1.50	2.43
H−C(6)	3.50	70.4	4.65, 1.50	2.76, 2.43
H−C(9)	3.34	58.0	2.30, 1.98	2.60, 2.38
H_α−C(1′)	2.76	31.3	2.43, 1.50	3.50, 2.60, 1.19
H_α−C(4′)	2.60	32.3	2.38, 1.19	3.34, 2.76, 1.98, 1.50
H_β−C(1′)	2.43	31.3	2.76, 1.50	4.65, 3.50
H_β−C(4′)	2.38	32.3	2.60, 1.19	3.34, 1.98
H−C(14)	1.98	42.0	3.34, 1.19	2.60, 2.38
H−C(7)	1.50	33.6	4.65, 3.50, 2.76, 2.43, 1.19	2.60
H−C(8)	1.19	32.8	2.60, 2.36, 1.98, 1.50	3.34, 2.76

[a]) δ(H) and δ(C) in ppm. [b]) H−C correlations determined by HSQC. [c]) Shifts which exhibit NOESY but no COSY cross-peaks.

The stereochemistry of the C(7),C(8) addition was determined by several methods. First, inspection of the ^3J(H,H) coupling constants of H−C(6) with H−C(5) and H−C(7) revealed large (10.9 Hz) and small (4.5 Hz) couplings. The known *syn*-periplanar orientation between H−C(5) and H−C(6) correlates with a small *J* value in 4,5-epoxymorphinans, indicating that ^3J(6,7) is 10.9 Hz, suggesting a large dihedral and an *anti*-periplanar orientation (*Table 2*). This suggests that H−C(7) is located below the plane of the ring, in an α orientation. Futher, no NOESY correlation was observed between H−C(14) and H−C(7), in light of a NOESY cross-peak between axial H−C(14) and equatorial H−C(6). This supports the conclusion that H−C(7) is located in a pseudoequatorial position below the plane of the *C*-ring, opposite to H−C(14).

The configuration at C(8) was determined through ^3J(H,H) following identification of the benzylic H-atoms H_α−C(4′) and H_β−C(4′). H_α−C(4′) and H_β−C(4′) were identified as showing correlations with the benzylic C(4′) atom (δ 32.3; HSQC) and COSY cross-peaks with H−C(8) (δ 1.19). The identity of these H-atoms was

Table 2. *Prediction of* ^{3}J*(H,H) Values for Selected H-Atoms of* **12**[a])

Dihedral	Θ [°]	^3J(H,H) [Hz]	
		predicted[b])	observed
$\mathbf{H_5}$–C(5)–C(6)–$\mathbf{H_6}$	–41.7	4.0	4.5
$\mathbf{H_6}$–C(6)–C(7)–$\mathbf{H_7}$	–178.5	9.9	10.9
$\mathbf{H_{1'\alpha}}$–C(1′)–C(7)–$\mathbf{H_7}$	–37.8	6.8	6.3
$\mathbf{H_{4'\alpha}}$–C(4′)–C(8)–$\mathbf{H_8}$	62.8	2.8	5.6

[a]) Dihedral values (θ) determined by using ChemBio3D Ultra 11.0. [b]) Predicted ^3J(H,H) determined by using parameters outlined in [9].

differentiated by NOESY. The signal for H_α–C(4′) at δ 2.60 shows a NOESY cross-peak with H–C(7) (δ 1.50) which was not seen by its geminal partner, indicating that δ 2.60 arises from the H–C(4′) located below the plane of the *C*-ring, *i.e.*, from H_α–C(4′). Additionally, this axial H-atom is NOESY-coupled with H_α–C(1′) (δ 2.76), which is NOESY-coupled with H–C(8) (δ 1.19). This suggests that H–C(8) is, like H–C(7) and H_α–C(1′), located below the plane of the *C*-ring, in an α orientation. Further, the *J* values for H_α–C(4′), $J = 14.8$ and 5.6 Hz correspond to a geminal $^2J(4'\alpha,4'\beta)$ coupling constant and to a vicinal $^3J(4'\alpha,8)$ coupling constant (*syn*-periplanar arrangement), respectively. Finally, analysis of the NOESY spectrum indicated that there was no correlation between the axial H_β–C(5) and H–C(8), suggesting that H–C(8) is not located above the plane of the *C*-ring. Combined, it was determined that H–C(8) is in an α position at the ring, *syn*-periplanar to H–C(7).

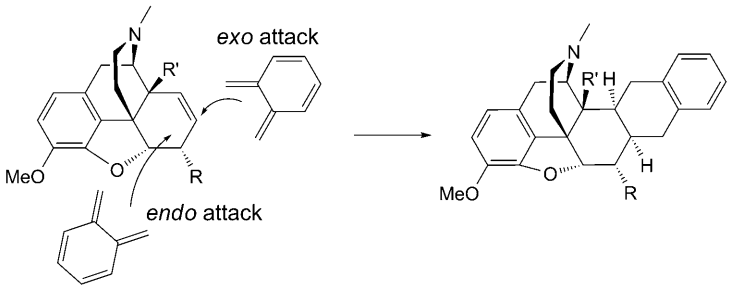
These data indicate that the *Diels–Alder* addition occurred across the less-hindered β-face of the *C*-ring of codeine. To further confirm this determination, ^3J(H,H) values for **12** were predicted with an algorithm described by *Serianni* and co-workers [9]. Predicted and observed ^3J(H,H) values are shown in *Table 2*. As these predicted figures correlate well with experimentally determined *J* values, the combined results allow us to assign the configuration at C(7) and C(8) of **12** as (7*R*,8*R*) (*Table 1*).

As *Diels–Alder* reactions generally proceed more readily with ketone-conjugated olefins, the fact that codeine (**11**), and not keto derivatives **9** and **10**, gave rise to cycloaddition led us to consider that there were appreciable energetic differences required to reach their respective transition states during condensation with diene **7**. Specifically, it was hypothesized that oxidation of the 6- and 14-positions introduced steric interference which would disfavor reactions with these opioids. Quantum mechanical (QM) calculations were therefore performed to determine the energy barrier facing the formation of each product under both gas-phase and solvated (toluene)-phase conditions. Barriers were evaluated as the difference in free energy between transition state and product (ΔE_{ts}) for both *endo* and *exo* additions. For completeness, the energetics of 14-hydroxycodeine (**13**) were also predicted.

The transition states and products for each reaction were geometry-optimized in the gas phase with the B3LYP/6-31G* level of theory [10][11]. The gas-phase-optimized structures were then used for single-point calculations at the B3LYP/6-31G* level of theory in the presence of toluene by using the polarized continuum model (PCM) [12]. All quantum-mechanical calculations were performed with GAUSSIAN 03 [13]. The

preference for *endo vs. exo* transition states is given as $\Delta\Delta E_{endo\text{-}exo}$, and the results are shown in *Table 3*.

Table 3. *Energy Barriers* (ΔE) *of* Diels–Alder *Codeine Cycloaddition Reactions Through* endo- *and* exo-*Mechanisms*[a])



Gas phase			E [kcal/mol]			$\Delta\Delta E$ ($E_{ts}-E_{prod}$) [kcal/mol]		
	R	R′	$E_{ts}(endo)$	$E_{ts}(exo)$	E_{prod}	ΔE_{endo}	ΔE_{exo}	$\Delta\Delta E_{endo\text{-}exo}$
11	OH	H	– 808562.5	– 808549.4	– 808625.5	63.0	76.0	– 13.0
9	=O	H	– 807815.6	– 807813.6	– 807884.6	69.0	71.0	– 2.0
13	OH	OH	– 855759.5	– 855761.7	– 855838.4	78.9	76.7	2.2
10	=O	OH	– 855008.8	– 855013.6	– 855085.4	76.6	71.8	4.8
Solvated phase			E [kcal/mol]			$\Delta\Delta E$ ($E_{ts}-E_{prod}$) [kcal/mol]		
	R	R′	$E_{ts}(endo)$	$E_{ts}(exo)$	E_{prod}	ΔE_{endo}	ΔE_{exo}	$\Delta\Delta E_{endo\text{-}exo}$
11	OH	H	– 808566.6	– 808553.6	– 808629.7	63.2	76.1	– 12.9
9	=O	H	– 807820.1	– 807818.2	– 807888.7	68.6	70.5	– 1.9
13	OH	OH	– 855763.1	– 855766.2	– 855843.0	79.9	76.8	3.0
10	=O	OH	– 855013.1	– 855018.1	– 855090.0	76.9	71.9	5.1

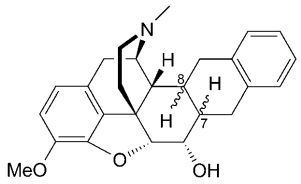
[a]) Free energies (E) calculated for gas phase, and single-point calculations in toluene by using PCM, with T 353 K, $\varepsilon = 2.2597$, TSARE = 0.25.

There was no significant difference between $\Delta\Delta E$ for gas phase and solvated (toluene) phase of **9**, **10**, and **11**, indicating that toluene solvation did not appreciably affect the kinetics of the reaction, regardless of *endo* or *exo* attack. The energy barrier between transition states and products in toluene was lowest for *endo* addition with **11** (63.2 kcal/mol), which was approximately 8.7 kcal/mol lower than the lowest energy barrier for **10** (*exo*) and 5.4 kcal/mol lower than that for **9** (*endo*). This indicates that oxidation from **11** to the 6-ketone **9** has a modest detrimental effect on ΔE_{endo} (63.2 kcal/mol for **11** *vs.* 68.6 kcal/mol for **9**), which was unexpected. As anticipated, this energy barrier for *endo* addition was increased upon addition of a 14β-OH group to the structure (**11** *vs.* **13**, **9** *vs.* **10** by 15 and 7 kcal/mol, resp.). The effect of a 14β-OH group on ΔE_{exo} was minimal, suggesting that 14-OH substitution had a greater effect on the ability of **7** to approach the alkene from the *endo* orientation compared to the *exo*. Comparison between the *endo*- and *exo*-transition-state energies ($\Delta\Delta E_{endo\text{-}exo}$) for these four compounds also suggested that the presence of the 14-OH group caused the *exo* pathway to be energetically more favorable as seen in **13** and **10** (positive $\Delta\Delta E_{endo\text{-}exo}$)

as compared to **11** and **9** where the *endo* attack is favored (negative $\Delta\Delta E_{endo\text{-}exo}$). These results support the observation that the presence of a 14-OH group hindered the *endo* reaction pathway. However, the QM results did not confirm the hypothesis that the 6-OH group had a detrimental effect on the reaction.

The cyclic opioid dienophile exhibits a *cis*-orientation, therefore the [4+2] cycloaddition product was anticipated to result from a *syn*-addition across C(7)=C(8) [14]. As the exact mechanism of *Diels–Alder* cycloaddition is the subject of much debate [15], it was conceived that *anti*-addition products may be energetically favorable, and could potentially be formed by a nonconcerted addition mechanisms. *Table 4* shows the relative energies of all possible (*R*) and (*S*) configurations at C(7) and C(8) of **12**. *syn*-Addition products (*Entries 3* and *4*) gave rise to relatively higher-energy products. The configuration of **12** at C(7) and C(8) was determined to be (7*R*,8*R*), which is 8.1 kcal/mol higher in energy than the lowest-energy product ((7*R*,8*S*), *Entry 1*) and 4.5 kcal/mol higher than the (7*S*,8*S*) *syn*-addition product (*Entry 3*). The fact that the highest-energy cycloaddition product is preferentially formed supports the hypothesis that the α-face of the olefin is sufficiently hindered to prevent the formation of the energetically more favorable products. Together, these results indicate that the *Diels–Alder* cycloaddition of highly reactive dienes occurs across the more accessible β-face of the C(7)=C(8)-olefin, most likely through an *endo* transition state.

Table 4. *Potential Energy* ($E - E_{min}$ [kcal/mol]) *for the (7*S*,8*R*)-, (7*S*,8*S*)-, and (7*R*,8*R*)-Diastereoisomer Relative to the Minimum-Energy (7*R*,8*S*)-Diastereoisomer of Cycloaddition Product* **12**[a])



Entry	Configuration	$E_x - E(7R,8S)$ [kcal/mol]	
		Gas phase	Solvated (toluene) phase
1	(7*R*,8*S*)	0	0
2	(7*S*,8*R*)	2.0	1.6
3	(7*S*,8*S*)	4.0	3.6
4	(7*R*,8*R*)	7.8	8.1

[a]) Free energies (E) calculated for gas phase, and single-point calculations in toluene by using PCM, with T 353 K, $\varepsilon = 2.2597$, TSARE = 0.25.

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Experimental Part

1. *General.* Analogs **9** [7] and **10** [8] were synthesized according to known procedures. Codeine (**11**) was a generous gift from *Mallinckrodt, Inc.* (St. Louis, MO). Prep. TLC: 20 × 20 cm silica-gel-coated glass plates (*Analtech, Inc.*, Newark, DE). NMR Experiments (^{1}H- and ^{13}C-NMR, COSY, NOESY, HSQC): *Varian* NMR spectrometer (500 MHz); δ in ppm, J in Hz. ESI-MS: *LCQ instrument* (*Thermo Scientific*, Waltham, MA); in m/z.

2. *(7*R*,8*R*)-1′,4′,7,8-Tetrahydronaphtho[2′,3′:7,8]-codeine* (*=(5α,6α,7*R*,8*R*)-7,8-Didehydro-4,5-epoxy-1′,4′,7,8-tetrahydro-3-methoxy-17-methylnaphtho[2′,3′:7,8]morphinan-6-ol*; **12**). To a soln. of **8** (135 mg, 0.8 mmol) in toluene (5 ml) was added codeine (**11**; 1.20 g, 4.0 mmol, 5 equiv.) in toluene (5 ml). The soln. was stirred under reflux for 24 h, cooled to r.t., washed with H_2O, and concentrated *in vacuo* to give a brown foam (1.45 g). Prep. TLC ($CHCl_3$/MeOH 95:5) of 50 mg (34%) of the crude product resulted in unreacted **11** (18.8 mg) and **12** (6.4 mg, 2% isolated yield; 7.7% theoretical yield from crude product) as a yellow oil. ^{1}H-NMR ($CDCl_3$): 6.99–7.10 (*m*, 4 H); 6.62 (*d*, *J* = 8.4, 1 H); 6.50 (*d*, *J* = 8.4, 1 H); 4.67 (*d*, *J* = 4.9, 1 H); 3.78 (*s*, 3 H); 3.50 (*dd*, *J* = 11.2, 5.0, 1 H); 3.34 (*m*, 1 H); 2.95 (*d*, *J* = 19, 1 H); 2.76 (*dd*, *J* = 16, 6.3, 1 H); 2.60 (*dd*, *J* = 15, 5.6, 1 H); 2.34–2.51 (*m*, 4 H); 2.38 (*s*, 3 H); 2.20–2.34 (*m*, 2 H); 1.98 (*m*, 1 H); 1.87 (*m*, 1 H); 1.67 (*dd*, *J* = 13, 2.0, 1 H); 1.50 (*m*, 1 H); 1.19 (*m*, 1 H). ^{13}C-NMR ($CDCl_3$): 127.5; 127.4; 127.0; 126.1; 119.3; 113.4; 91.2; 70.4; 58.0; 56.3; 46.2; 43.1; 42.0; 37.5; 33.6; 32.8; 32.3; 31.3; 20.4. ESI-MS: 404.2 ($[M+H]^+$).

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