Opiate Dienes as Dienophiles in the Diels−Alder Reaction with 1-Cyano-*o*-quinodimethane

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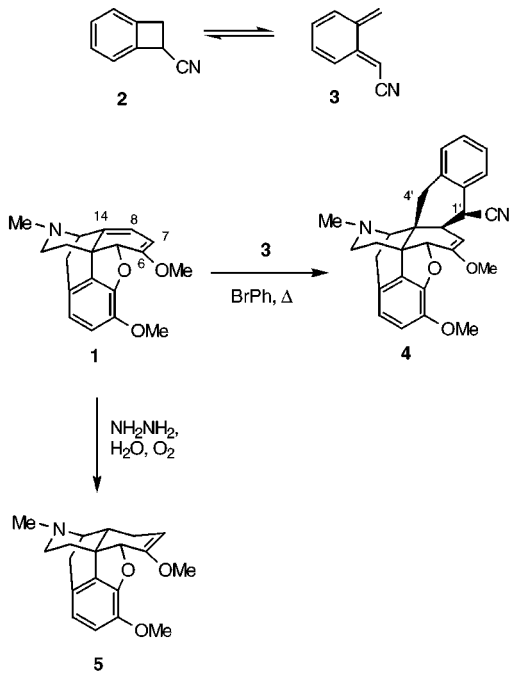
Introduction

Diels−Alder reactions of opiates have been extensively reported,[1] particularly thebaine (**1**), which functions as a diene in the cycloaddition reaction with dienophiles. There are, however, no reported examples of opiates functioning as dienophiles. The naturally occurring opiates contain at least one double bond in the C ring. Hence, by selective reduction, substitution, or other chemical modifications it should be possible to alter the reactivity of opiate dienes to allow for reactions at any of the available positions on the C ring. Here we describe an investigation of the Diels−Alder reactions of thebaine (**1**) and a related opiate **6** with the reactive diene, 1-cyano-*o*-quinodimethane (**3**), as a route to tetrahydronaphthalene-fused opiates. Also, the role of the 6-methoxy group of thebaine as a regiodirecting substituent for this reaction has been investigated.

Results and Discussion

It is well-known that the Diels−Alder reaction is enhanced by electron-withdrawing groups on the dienophile and by electron-donating groups on the diene.[2] Since the 6-methoxy substituent of thebaine (**1**) is an electron-donating moiety through resonance interaction with $\Delta^{6,7}$, and the opiate was expected to function as the dienophile, the Diels−Alder reaction was expected to take place predominantly at $\Delta^{8,14}$. To generate the diene for the Diels−Alder reaction leading to tetrahydronaphthalene-fused opiates, the thermal electrocyclic ring opening of 1-benzocyclobutenecarbonitrile (**2**) was employed.[3−5] When heated to temperatures above 160 °C, **2** affords the reactive diene **3**.[3−5] The reaction of **1** with the diene **3** in bromobenzene for 12 h in an inert atmosphere yielded **4** as the major cycloaddition product (57%) (Scheme 1). The cycloaddition was expected to take place from the sterically less hindered β-face of the opiate molecule. The

Scheme 1



regioselectivity of the cycloaddition was established to involve $\Delta^{8,14}$, inasmuch as the characteristic IR absorption for enol ethers at 1654 cm^{-1} was clearly present. The regiochemistry of the cyano group was determined from the ^1H NMR coupling of the proton α to the cyano group (H-1′, δ 4.13, doublet, J = 3.9 Hz) to H-8. If the cyano group had been present on the other benzylic carbon, the proton α to the cyano group would have appeared as a singlet.

On the basis of the β-face selectivity of the cycloaddition and mechanistically favored *exo*-ring opening of the diene,[4,5] the stereochemistry of the cyano group was expected to be α. However, the coupling constant between H-1′ and H-8 (J = 3.9 Hz) is consistent with a β configuration for the cyano group as estimated from the calculated diheral angles H-1′, C-1′, C-8, and H-8 from the energy-miminized structures (α, 78° vs β, 52°). It is conceivable that the initially formed α isomer, whose cyano group would be oriented in a pseudoaxial conformation, was epimerized to the energitically more favored β isomer under the Diels−Alder reaction conditions. In this regard, molecular modeling has revealed a 1.3 kcal difference between the two stereoisomers. The tertiary amine group may function as a base to catalyze Hα exchange to facilitate epimerization.

In an effort to direct cycloaddition to the $\Delta^{6,7}$ and to obtain additional insight into the role played by the 6-methoxy group in determining the regiospecificity, 6-demethoxythebaine (**6**)[9,10] was employed as the dienophile. The $\Delta^{6,7}$ regiospecificity was expected because the absence of the 6-methoxy group would render $\Delta^{6,7}$ more reactive to cycloaddition than $\Delta^{8,14}$ due to its lower substitution and lower electron density. Since thermal

(1) Casy, A. F.; Parfitt, R. T. 4,5-Epoxymorphinans. In *Opioid Analgesics*; Plenum Press: New York, 1986; Chapter I, pp 9−104 and references therein.
(2) Lowry, T. H.; Richardson, K. S. In *Mechanism and Theory in Organic Chemistry*, IIIrd ed.; Harper and Row: New York, 1987; pp 839−931.
(3) Charlton, J. L.; Alauddin, M. M. *Tetrahedron* **1987**, *43*, 2873.
(4) Niwayama, S.; Kallel, E. A.; Spellmeyer, D. C.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2813.
(5) Jefford, C. W.; Bernardinelli, G.; Wang, Y.; Spellmeyer, D. C.; Buda, A.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1157.
(6) Eppenberger, U.; Warren, M. E.; Rapoport, H. *Helv. Chim. Acta* **1968**, *51*, 381.
(7) Corey, E. J.; Pasto, D. J.; Mock, W. L. *J. Am. Chem. Soc.* **1961**, *83*, 2957.
(8) Pasto, D. J. In *Comprehensive Organic Chemistry; Selectivity, Stratergy, and Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds; Pergamon Press: New York, pp 471−478.
(9) Beyerman, H. C.; Crabbendam, P. R.; Lie, T. S.; Matt. L. *Recl. Trav. Chim. Pays-Bas* **1984**, *103*, 112.
(10) Lewis, J. W.; Readhead, M. J. *J. Med. Chem.* **1970**, *13*, 525.

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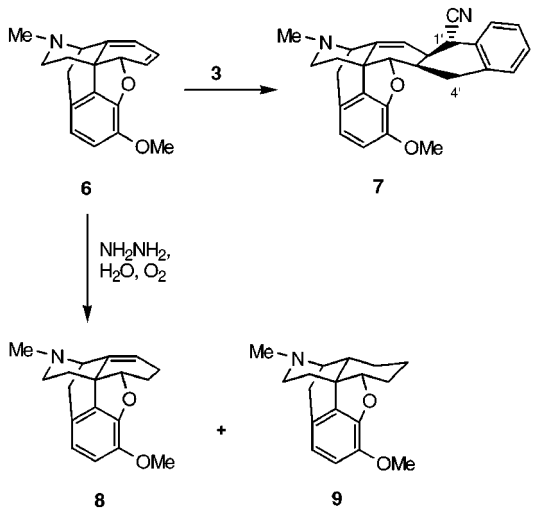
Scheme 2



decomposition studies in refluxing bromobenzene for 10 h indicated **6** was totally destroyed, the Diels–Alder reaction was quenched at 6 h to yield the $\Delta^{6,7}$ Diels–Alder adduct **7** (24%) as the major product together with starting material (Scheme 2). Detailed COSY studies indicated that H-6 was coupled to the two benzylic protons (H-4′). Thus, the cyano group was identified to be on the C-1′ benzylic carbon. Decoupling of H-6 permitted the identification of H-7 and subsequently a similar experiment unequivocally identified H-1′ ($J_{7,1'}$ = 6.9 Hz; $J_{7,8}$ = 6 Hz). The NOE observed between the H-5 and the H-1′ is consistent with an α configuration for the CN group in **7**. The pseudoequatorial α-CN group in **7** represents the most stable epimer, which is consistent with the cycloaddition of **6** with the transient diene obtained from the *exo*-ring opening of **2**. The *β*-CN epimer, if formed initially, may have epimerized to the observed α-CN epimer under the Diels–Alder reaction conditions. The coupling constant, $J_{5,6}$ = 11.7 Hz, corresponds to a *trans*-diaxial relationship and is in agreement with the cycloaddition occurring from the *β*-face of the opiate.

Significantly, reaction of the analogous $\Delta^{6,7}$ compound **5** with the dienophile **3** did not yield the expected Diels–Alder product even after prolonged heating at 156 or 180 °C. The lack of reactivity of **5** with the diene **3** is consistent with the unfavorable electron-donating effects of the methoxy group. The similar reaction of the $\Delta^{8,14}$ compound **8** with diene **3** also failed to yield the expected cycloaddition. Modeling studies indicate that the $\Delta^{8,14}$ in **8** is sterically hindered as compared to $\Delta^{8,14}$ in **1** since, in the latter, the presence of $\Delta^{6,7}$ maintains the C ring in a planar fashion. Thus, the lack of reactivity of the opiate dienophiles **5** and **8** when compared to **6** and **1**, respectively, can be rationalized on the basis of either the electronic effects of the 6-methoxy substituent or the steric effects of ring conformation, or a combination of these factors.

There are some parallels to the greater reactivity of $\Delta^{8,14}$ in the Diels–Alder reaction. Thebaine (**1**) also has been reported to be selectively reduced by diimide to afford **5**[6,7] (Scheme 1). In this reaction, *cis*-diimide is involved in hydrogen transfer across $\Delta^{8,14}$ from the less hindered *β* side of the double bond and the reduction is believed to proceed through a six-membered cyclic transition state by a concerted *syn*-addition.[8,12] In this connection, we have investigated the diimide reduction of **6** to determine if a similar relationship between the two reactions exists. We have found that diimide reduction of **6** afforded two products **8** and **9** in a ratio of 6:1 (51% yield) (Scheme 2). The fact that the major product (**8**) showed the presence of a single vinyl proton at *δ* 5.63 (H-8) indicated that $\Delta^{6,7}$ was reduced selectively. As is reported, in a diene system the diimide reduction of the less substituted bond is favored due to differences in torsional strain, bond angle bending strain, and α-alkyl substituent effects.[11,12] The greater accessibility of $\Delta^{6,7}$ in diene **8** relative to that in thebaine **1** for the Diels–Alder and the diimide reduction is due to the absence of the 6-methoxy substituent.

In conclusion, the Diels–Alder reaction of opiate dienophiles with *o*-quinodimethanes has led to the synthesis of tetrahydronaphthalene-fused opiates that are not easily accessible by other means. By manipulating the substitution on $\Delta^{5,6}$ it is possible to control the regioselectivity of the Diels–Alder reaction. Thus, a 6-methoxy group directed cycloaddition with $\Delta^{8,14}$, and in the absence of this group, $\Delta^{5,6}$ was favored.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF glass plates. Column chromatography was performed with silica gel (200–400 mesh, Aldrich Chemicals). The chromatographic solvent system is reported as volume/volume. All reagents and solvents employed were reagent grade and were used without further purification. Infrared spectra were recorded on a Perkin-Elmer 281 spectrometer. Nuclear magnetic resonance spectra were recorded on a GE Omega 300 MHz NMR instrument or on a Varian 300 MHz NMR instrument at room temperature (18–20 °C). The *δ* (ppm) scale was in reference to the deuterated solvent. The coupling constants are reported in Hz. The mass spectra were obtained from the Mass Spectrometry Laboratory of The Department of Chemistry, University of Minnesota. The modeling studies were carried out using Biosym–InsightII v. 2.3.0 software using the Builder program and using the method of steepest descent to generate the energy-minimized structures.

8*β*,14*β*-2′3′(1′*β*-Cyano-1′,2′,3′,4′-tetrahydronaphthyl)-6,7-dihydro-3,6-dimethoxy-4,5α-epoxy-17-methylmorphinan (4). To a solution of thebaine (**1**) (236 mg, 0.76 mmol) in bromobenzene (15 mL) was added 1-benzocyclobutenecarbonitrile (**2**) (Aldrich Chemical Co.)[3] (100 mg, 0.76 mmol). The reaction mixture was refluxed in an inert atmosphere with stirring. After 12 h, the reaction mixture was cooled and the solvent removed under reduced pressure. The residue was taken up in $CHCl_3$ (50 mL) and the organic layer washed with saturated aqueous $NaHCO_3$ (50 × 3 mL). The organic layer was then separated, dried, and filtered and the solvent removed. The residue was chromatographed on a silica gel column (CH_3OH–$CHCl_3$ 2:98) to yield an oil (**4** 160 mg, 57%), TLC R_f ($CHCl_3$–CH_3OH 97:3) = 0.5. A portion of the product was converted to the hydrochloride salt by treatment with ethereal HCl: mp >250 °C; ^{1}H NMR (300 MHz, $CDCl_3$, free base) *δ* 7.45 (m, 1H), 7.25 (m, 3H), 6.76 (d, *J* = 7.8 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 4.82 (s, 1H), 4.68 (d, *J* = 1.8 Hz, 1H), 4.13, (d, *J* = 3.9 Hz, 1H), 3.86 (s, 3H), 3.43 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) *δ* 155, 146, 145, 137, 132, 131, 129.5, 129, 128.5, 128, 127.5, 121, 119, 115, 98, 89, 59, 57, 56, 48, 47, 45, 41, 36, 34, 31, 30, 21; FTIR (KBr pellet) 1654.4 (enol ether) 2239.9 cm^{-1} (cyano); FABMS *m*/*z* 441.1 (M + 1).

(11) Siegel, S.; Foreman, M.; Fischer, R. P.; Johnson, S. E. *J. Org. Chem.* **1975**, *40*, 3599.
(12) Garbisch, E. W.; Schildcrout, S. M.; Patterson, D. B.; Sprecher, C. M. *J. Am. Chem. Soc.* **1965**, *87*, 2932.

6β,7β-2′,3′-(1′α-Cyano-1′,2′,3′,4′-tetrahydronahpthyl)-8,14-didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan (7). To a solution of 6-demethoxythebaine (**6**)[9,10] (281 mg, 1 mmol) in bromobenzene (20 mL) was added 1-benzocyclobutenecarbonitrile (**2**) (153 mg, 1.24 mmol). The reaction mixture was refluxed in an inert atmosphere with stirring. After 12 h, the reaction mixture was cooled and the solvent removed under reduced pressure. The residue was taken up in $CHCl_3$ (100 mL) and the organic layer washed with saturated aqueous $NaHCO_3$ (50 × 3 mL). The organic layer was then separated, dried, and filtered and the solvent removed. The residue was chromatographed on a silica gel column ($CH_3OH-CHCl_3$ 2:98) to yield an oil (**7**, 100 mg, 24%): TLC R_f ($CHCl_3-CH_3OH$ 19:1) = 0.5. A portion of the product was converted to the hydrochloride salt by treatment with ethereal HCl: mp >250 °C; ^{1}H NMR (300 MHz, $CDCl_3$, free base) δ 7.49 (m, 1H), 7.29−7.21 (m, 3H), 6.74 (d, 1H), 6.66 (d, 1H), 6.10 (d, J = 6.0 Hz, 1H), 4.44 (d, J = 10.8 Hz, 1H), 3.88 (s, 3H), 3.66 (d, J = 6.9 Hz, 1H), 3.01 (dd, 2H), 2.76 (m, 1H), 2.49 (s, 3H), 2.14 (m, 1H); NOE ($CDCl_3$) the irradiation of H-5 gave a positive enhancement for H-1′ and the irradiation of H-1′ gave a positive enhancement for H-5 and H-8; ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.06, 143.81, 141.67, 134.05, 132.50, 131.10, 129.11, 128.77, 128.42, 127.59, 121.73, 120.15, 119.19, 114.15, 89.70, 62.09, 57.16, 46.67, 45.33, 42.85, 37.60, 36.16, 34.80, 30.55, 28.52; FABMS m/z 411.3 (M + 1).

8,14-Didehydro-4,5α-epoxy-3-methoxy-17-methylmorphinan[12] (8). To a solution of 6-demethoxythebaine[9,10] **6** (400 mg, 1.48 mmol) in MeOH (20 mL) was added a solution of 85% hydrazine hydrate (5 mL). Through a syringe, oxygen was continuously bubbled through the solution. The reaction mixture was warmed to 70 °C and was stirred for 3 h at that temperature, after which time all the starting material had disappeared. The reaction mixture was then allowed to cool and was added to water (100 mL). To this was added $CHCl_3$ (100 mL), and the mixture was stirred. The organic layer was then separated and washed with saturated aqueous $NaHCO_3$. The organic layer was dried and evaporated to yield an oil that was chromatographed on a silica gel column ($CH_3OH-CHCl_3$ 1:20) to yield **8**[13] (182 mg, 44%), mp 58−60 °C (lit.[13] mp 61.2−62 °C), and dihydrodesoxycodiene[13] (**9**) (30 mg, 7%), mp 102−106 °C (lit.[13] mp 106−107 °C).

8: ^{1}H NMR (300 MHz, $CDCl_3$, free base) δ 6.69 (d, 1H), 6.60 (d, 1H), 5.63 (m, 1H), 4.76 (d, 1H), 3.80 (s, 3H), 3.54 (m, 1H), 2.41 (s, 3H); FABMS m/z 284.3 (M + 1). **9**: ^{1}H NMR (300 MHz, $CDCl_3$, free base) δ 6.74 (d, 1H), 6.65 (d, 1H), 4.64 (d, 1H), 3.61 (s, 3H), 3.17 (m, 1H), 2.40 (s, 3H); FABMS m/z 286.3 (M + 1).

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Supporting Information Available: ^{1}H NMR of compounds **4** and **7** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(13) (a) Bentley, K. W. In *The Chemistry of Morphine Alkaloids*; Clarendon Press: 1954; pp 126−165. (b) Small, L. F.; Morris, D. E. *J. Am. Chem. Soc.* **1933**, *55*, 2874. (c) Small, L. F.; Cohen, L. F. *J. Am. Chem. Soc.* **1931**, *53*, 2227. (d) Small, L. F.; Mallone, J. E. *J. Org. Chem.* **1940**, *5*, 350.