(−)-β-pinene, 18172-67-3; (methoxymethylene)cycloheptane, 66051-09-0; 2-cyclopentenone, 930-30-3; 2-cyclohexenone, 930-68-7; 2-cycloheptenone, 1121-66-0; 2-cyclooctenone, 1728-25-2; methyl 9-oxo-10-octadecenoate, 87070-66-4; methyl 10-oxo-8-octadecenoate, 87070-67-5; 4-methyl-3-oxo-1-pentene, 1606-47-9; (−)-pinocarvone, 19890-00-7; (−)-myrtenal, 18486-69-6; 1-(methoxycarbonyl)-1-cycloheptene, 56745-53-0.

Diels–Alder Reaction of β-Dihydrothebaine and Its 4-Phenyl Ether with Methyl Vinyl Ketone: Synthesis of 6,14-*exo*-Ethenomorphinans[1]

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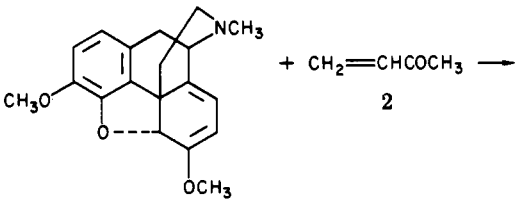
Bentley and co-workers[2-5] studied the Diels–Alder reaction of thebaine (1) with various dienophiles and concluded that 6,14-*endo*-etheno derivatives are formed, since the dienophiles can approach from the relatively exposed β-face of thebaine. Thus, the reaction with methyl vinyl ketone (2) formed the oripavine 3 with the stereochemistry as shown. This led these workers to synthesize a series of extremely potent 6,14-*endo*-etheno- and 6,14-*endo*-ethanotetrahydrooripavine type analgesics.

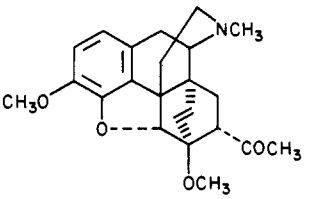
As part of an on-going program on analgesics in the morphine/morphinan area, we have reported[6] a practical synthesis of β-dihydrothebaine (**4a**) from thebaine (1). The Diels–Alder reaction of β-dihydrothebaine with **2** was of considerable interest to us, since this could provide an entry into a novel class of potential analgesic intermediates. Interestingly, Bentley[5] had mentioned in a review article that β-dihydrothebaine (**4a**) undergoes a Diels–Alder reaction with **2**. He assigned endo stereochemistry to the adduct **5** presumably by analogy with the oripavines. No experimental details have since appeared in the literature.

We have reexamined this reaction. A close examination of the Dreiding models of thebaine and β-dihydrothebaine shows that the strain on the thebaine molecule is considerably released by opening the 4,5-α-epoxide ring. Thus the addition of the dienophile to the exposed face of the diene in **4a** can be envisioned from both faces, unlike in the closed ring system of thebaine (1). In our hands the reaction between β-dihydrothebaine and **2** proved to be very sluggish and did not give the adduct as a clean product under a variety of conditions. In some instances, the adduct was formed as evidenced by NMR, but the yield was extremely poor.

Better results were obtained when the 4-phenyl ether **4b** was substituted for **4a**, since the adduct **6b** was isolated



1 (thebaine) 2



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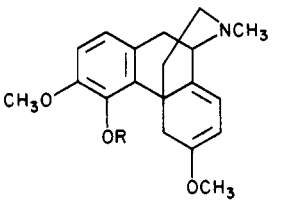
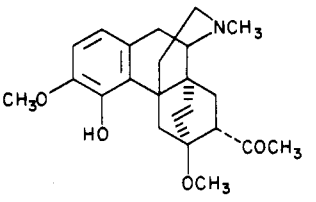


4a, R = H = β-dihydrothebaine
b, R = Ph



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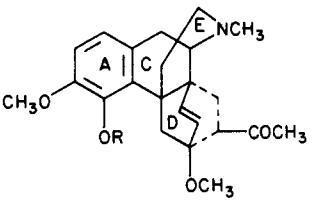
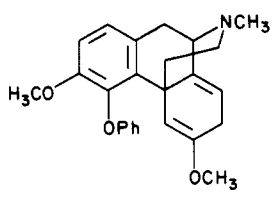
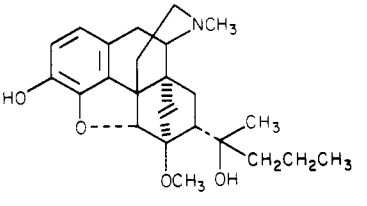


6a, R = H
b, R = Ph

in 33% yield (procedure A) after chromatography. On the basis of a report by Hudlicky[7] that Diels–Alder reaction can be conducted under mild reaction conditions by adsorbing a solution of the diene and dienophile on silica gel or alumina, **4b** was reacted with **2** on an alumina column (procedure B) and the yield was increased to 80%. On scale-up, this procedure gave poor yields and the following simplified procedure was therefore developed. The product **6b** could be readily prepared, albeit in lower but reproducible yields, by refluxing a slurry of **4b**, alumina (neutral, grade 1), **2**, and benzene for 20 h, as long as **2** was added at intervals. This process had the added advantage that the reaction could be readily carried out by using a mixture of **4b** and **7**. Fractional crystallization of the product after workup gave 41% of the Diels–Alder product.



7



8 (etorphine)

It was apparent from the results of a large series of experiments that the Diels–Alder reaction between **4b** and **2** was more complicated than the facile reaction observed between thebaine and **2**. Therefore a crystalline sample

(1) Part 7 in the series Novel Opiates and Antagonists. For part 6, see: Quick, J.; Herlihy, P.; Howes, J. F., submitted for publication.
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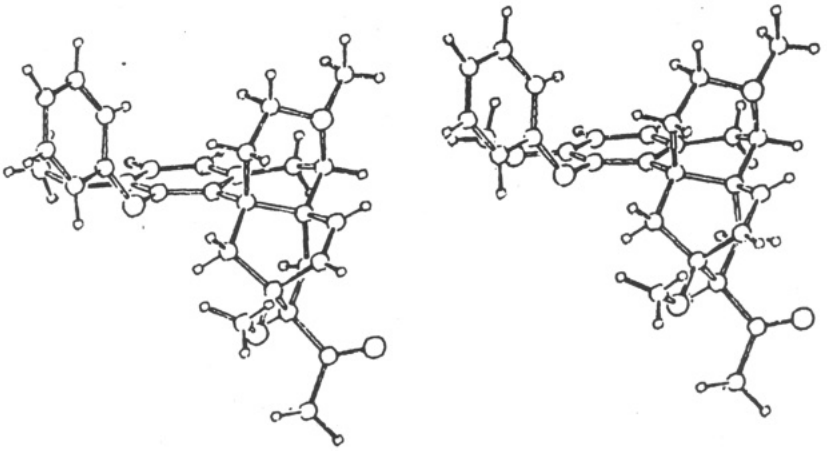

Figure 1. Stereodiagram[8] of the Diels–Alder product **6b**.

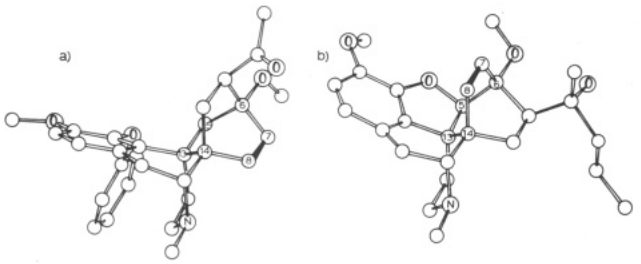

Figure 2. Comparison of the structures of (a) the *exo*-ethenomorphinan adduct **6b** and (b) the *endo*-ethenomorphinan structure of etorphine (**8**).[9] Note the difference in location of the darkened double bond in the two structures.

of the Diels–Alder adduct **6b** was submitted for X-ray crystallographic studies to establish its absolute stereochemistry. It was found to be *exo*-ethenomorphinan, as shown in structure **6**, and contains a 6,14 ring junction, which is opposite of that found in the adduct **3** from thebaine. The relative stereochemistry of the asymmetric centers is illustrated in Figure 1. The bond lengths and angles are unexceptional. For example, the range of lengths of the bonds in the benzene ring is 1.384–1.411 Å. The C ring has a conformation midway between a C(11) sofa and a C(11)–C(14) half-chair, the D ring has a nearly perfect boat conformation with C(6) and C(14) on the bow spirits, and the E ring has a simple chair conformation. The difference in the stereochemistry of the C/D ring junction between this Diels–Alder product and etorphine (**8**)[9] is clearly illustrated in Figure 2.

These results are somewhat unexpected and provide the possibility of developing a novel series of morphinans of type **6** which are related to the potent analgesics of oripavine type.

Experimental Section

Melting points were recorded on Thomas-Hoover capillary melting point apparatus. IR spectra were recorded on a Perkin-Elmer Model 700 instrument. UV spectra were recorded on a Varian 635 UV–visible spectrophotometer, and a Varian T-60 instrument was used for NMR spectra with Me_4Si as an internal standard. A Waters Associates ALC-202 chromatograph equipped with a Model 6000 solvent delivery system was used for high-pressure liquid chromatographic analysis. Microanalyses were performed by Heterocyclic Chemical Corp., Harrisonville, MO. Precoated TLC plates (silica gel 60F, EM Reagent) were used for thin-layer chromatographic analysis.

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β-Dihydrothebaine 4-Phenyl Ether (4b). To a stirred solution of 6.28 g (20 mmol) of β-dihydrothebaine[6] in 20 mL of dry pyridine under N_2 were added 3.46 g (22 mmol) of dry (molecular sieves) bromobenzene, 3.04 g (22 mmol) of anhydrous 200-mesh K_2CO_3, and 2.3 g of anhydrous active copper powder. The brown mixture was stirred and refluxed under N_2 for 20 h. After filtration, the residue was washed twice with 20 mL of hot pyridine. The filtrate was concentrated by vacuum distillation at 55 °C (20 mm) to give a black gum. It was dissolved in 250 mL of benzene and filtered, and the filtrate was washed three times with 75 mL of saturated NaCl solution and dried (K_2CO_3). After filtration and concentration, 7.6 g of a brown oily foam was obtained. It was column chromatographed (100 g of Woelm neutral alumina, grade 1) using benzene, followed by benzene–ethyl acetate (5% and 10%) mixtures to give 5.26 g (68%) of **4b** as a pale yellow glass: NMR ($CDCl_3$) δ 4.85 (d, 1 H, olefin), 5.82 (d, 1 H, olefin); single spot on TLC (10% MeOH–$CHCl_3$; R_f 0.33).

Anal. Calcd for $C_{25}H_{27}NO_3 \cdot {}^1/_2H_2O$: C, 75.34; H, 7.08; N, 3.52. Found: C, 75.36; H, 7.28; N, 3.33.

(−)-7α-Acetyl-3,6-dimethoxy-*N*-methyl-4-phenoxy-6,14-*exo*-ethenomorphinan (6b). Procedure A. A mixture of 9.6 g (25 mmol) of β-dihydrothebaine 4-phenyl ether (**4b**), 20.3 g (289 mmol) of methyl vinyl ketone (stored under molecular sieves), a small amount of hydroquinone, and a few boiling chips was refluxed for 2.5 h (oil bath 115 °C), and then the volatile components were removed first by vacuum distillation at 55 °C (20 mm) and finally at room temperature under high vacuum. A dark gum was obtained to which 50 mL of diisopropyl ether was added and the mixture stirred well for 30 min. After filtration, the solution was evaporated to give a viscous red syrup, which was stirred with 250 mL of absolute ether. The small amount of undissolved tan floccular solid was gravity filtered and to the red filtrate was added 15 mL of an ether solution that had been saturated with dry HCl gas. Vigorous stirring was carried out during this slow addition. The precipitated salt was filtered and washed with 100 mL of absolute ether. The solid was then dissolved in 200 mL of H_2O and a second layer of 200 mL of ether added. With vigorous stirring, solid K_2CO_3 was added until the aqueous layer lost its red color or was saturated. The layers were separated, and the aqueous layer was extracted with 150 mL of ether. The combined ethereal layers were dried (Na_2SO_4), filtered, and concentrated to give 11.3 g of dark red tar. Purification by column chromatography (silica gel) with $CHCl_3$ as elution solvent yielded 3.79 g (33%) of **6b** as a light red viscous material: IR ($CHCl_3$) 1710 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 6.57–7.53 (m, 7 H, Ar H); 6.36 (d, 1 H, olefin), 6.00 (d, J_{AB} = 8 Hz, 1 H, olefin), 3.67 (s, 3 H, OCH_3), 3.13 (s, 3 H, OCH_3), 2.60–3.03 (m, 4 H), 2.37 (s, 3 H, NCH_3), 2.10 (s, 3 H, $COCH_3$), 1.13–2.03 (m, 8 H). Trituration of this viscous material with hexanes caused crystallization and an analytical sample was prepared by recrystallization from hexanes: mp 151.5–153.5 °C; λ_{max} (EtOH) 222 nm (log ε, 4.23). 2.66 (sh, 3.26), 272 (3.40), 278 (3.48), 287 (sh, 3.34).

Anal. Calcd for $C_{29}H_{33}NO_4$: C, 75.79; H, 7.24; N, 3.05. Found: C, 75.65; H, 7.21; N, 3.06.

Procedure B. A chromatographic column was assembled by pouring a slurry prepared from 14 mL of neutral alumina powder

Table I. Atomic Coordinates ($\times 10^4$) for the Phenyl Ether of 6,14-*exo*-Ethenotetrahydrothebaine

atom	$X/A(\sigma)$	$Y/B(\sigma)$	$Z/C(\sigma)$
C(1)	96 (2)	6129 (1)	4861 (1)
C(2)	−963 (2)	5546 (1)	3978 (1)
C(3)	−1662 (1)	4634 (1)	4211 (1)
C(4)	−1248 (1)	4321 (1)	5329 (1)
C(5)	708 (1)	3335 (1)	7610 (1)
C(6)	2463 (2)	3126 (1)	8552 (1)
C(7)	3865 (2)	3562 (1)	8114 (1)
C(8)	3567 (1)	4732 (2)	7938 (1)
C(9)	1667 (2)	6256 (1)	8071 (1)
C(10)	1578 (2)	6555 (1)	6880 (1)
C(11)	520 (2)	5824 (1)	5978 (1)
C(12)	−105 (1)	4872 (1)	6220 (1)
C(13)	321 (2)	4515 (-)	7439 (1)
C(14)	1973 (1)	5088 (1)	8222 (1)
C(15)	−1200 (2)	4838 (1)	7810 (1)
C(16)	−1432 (2)	6010 (2)	7762 (1)
C(17)	2309 (2)	4736 (2)	9410 (1)
C(18)	2560 (2)	3734 (2)	9582 (1)
C(19)	5693 (2)	3299 (2)	8911 (1)
C(20)	6476 (2)	2323 (2)	8683 (2)
C(21)	−99 (3)	7661 (2)	8364 (2)
C(22)	−3412 (4)	4360 (3)	2305 (2)
C(23)	1661 (3)	1499 (2)	9171 (2)
C(24)	−3736 (1)	3375 (1)	5320 (1)
C(25)	−4408 (2)	2406 (1)	5385 (2)
C(26)	−6153 (2)	2306 (2)	5216 (2)
C(27)	−7226 (2)	3155 (2)	4969 (2)
C(28)	−6550 (2)	4116 (2)	4921 (2)
C(29)	−4794 (2)	4233 (2)	5099 (2)
N(1)	178 (2)	6541 (1)	8388 (1)
O(3)	−2758 (2)	3995 (1)	3428 (1)
O(4)	−1970 (1)	3410 (1)	5538 (1)
O(6)	2780 (1)	2044 (1)	8731 (1)
O(19)	6474 (2)	3864 (2)	9671 (1)

(Woelm, activity grade 1) and excess benzene into a 50-mL buret. To the column was introduced a solution of 0.5 g (1.3 mmol) of crude **4b** and 1.22 mL (1.04 g, 15 mmol, 11.5 equiv) of **2** (dried over molecular sieves) in 10 mL of dry benzene. While the solution was being adsorbed into the alumina, the column became quite hot, especially toward the lower end where there was no coloration. The material was allowed to stand for 40.5 h, the adsorbent washed off with MeOH, and the material concentrated under reduced pressure. The dark red, gummy residue was taken up in $CHCl_3$, filtered, and again concentrated to give 1.45 g of dark reddish brown resin.

This crude product was worked up and then chromatographed as in procedure A to give 0.47 g (80%) of **6b**.

Crystal Data. A single crystal of dimensions 0.4 × 0.4 × 0.6 mm crystallized from acetone was used in the analysis. The crystals were determined to be in the monoclinic space group $P2_1$ with cell dimensions of a = 8.236 (2) Å, b = 12.950 (1) Å, c = 12.745 (3) Å, and β = 110.25 (3)°. Intensities of 2729 independent reflections were measured, of which 2597 had intensities greater than twice their standard deviation (σ_F). Monitoring of four standard reflections revealed no significant decay of the crystal over the course of intensity collection. Lorentz and polarization corrections were applied to the integrated intensities. Structure determination was achieved through use of the direct-methods program MULTAN.[10]

Hydrogen atoms were introduced at geometrically expected positions. In the final cycles of full-matrix least-squares refinement, positional parameters for all the atoms, anisotropic thermal vibration parameters for the nonhydrogen atoms, and isotropic thermal parameters for the hydrogen atoms were varied.

The quantities $(1/\sigma_F^2)$, where σ_F, was as defined by Stout and Jensen[11] but with an instrumental instability factor of 0.06, were used to weight the least-squares differences for the observed data; differences for data determined to be unobserved $2\sigma_F$ were given zero weight. The refinement converged to a residual ($R = \sum||F_o| - |F_c||/\sum|F_o|$) of 0.039 for the observed data and 0.042 for all data. Positional parameters are given in Table I.

Acknowledgment. This work was supported by a joint development program with Miles Laboratories, Inc., Elkhart, IN. X-ray work was supported by NIH Grant No. RR05716.

Registry No. **2**, 78-94-4; **4a**, 63944-52-5; **4b**, 87101-22-2; **6b**, 87101-23-3; bromobenzene, 108-86-1.

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Solvent Dependence of the Conformation and Chiroptical Properties of *trans*-9,10-Dihydroxy-9,10-dihydrophenanthrene and Its Monoglucuronides

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Vicinal *trans*-dihydro diols are important intermediates in the metabolism of polycyclic aromatic hydrocarbons. Stereoselective enzymatic formation of *trans*-dihydro diols from arene oxides can often influence their subsequent metabolism and biological activity.[1] Hence, considerable interest exists in determining the absolute configurations and preferred solution conformations of these metabolites. Chiroptical techniques often employed to deduce absolute configurations of *trans*-dihydro diols or their derivatives can be extremely sensitive to shifts in conformer populations influenced by stereoelectronic[2,3] and, as demonstrated here, solvent effects. In addition, the previously reported[4] solution conformations (solvent not specified) of *trans*-9,10-dihydroxy-9,10-dihydrophenanthrene (**1**) and the diacetate (**2**) deduced from the chiroptical properties of the 9*S*, 10*S* antipodes (**1b** and **2b**) have been shown inconsistent with both the predicted ORD spectra as well as ^1H NMR data from a series of closely related 9,10-disubstituted-9,10-dihydrophenanthrenes,[2a] raising at least some doubt about the original assignment of absolute configuration.[4] Moreover, although the dramatic solvent dependence of the CD spectrum of **1b**[5] is most reasonably attributed to a shift in conformer populations, additional experimental evidence supporting this conclusion is de-

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