mg (46%); yellow solid; mp 194.5–195 °C (acetone–petroleum ether); ^{1}H NMR (acetone-d_6) δ 1.6 (m, 12 H, $NCH_2CH_2CH_2$), 3.1 (m, 8 H, $NCH_2CH_2CH_2$), 3.53 (s, 3 H, NCH_3), 7.50 (s, 1 H); EI mass spectrum, m/e 292 (M^+); UV (CH_3CN) λ_{max} 225, 294 nm. Anal. Calcd for $C_{15}H_{24}N_4O_2$: C, 61.62; H, 8.27; N, 19.16. Found: C, 61.9; H, 8.30; N, 19.2. Spectroscopic data agree with the formation of 1-methyl-3-nitro-4,5-dipiperidinopyrrole.

Dehydrogenation of 4b with Chloranil. The procedure involved the use of a pyrroline **4b** suspension in benzene but was otherwise similar to that above described. A shorter time was required (15 h). Two main reaction products were separated after chromatography: the first one to be eluted was 1-methyl-2-morpholino-4-nitropyrrole (yield 37%); the other product was a dimorpholinonitro-1-methylpyrrole, presumably 1-methyl-2,3-dimorpholino-4-nitropyrrole: yield 8%; mp 247–249 °C dec [petroleum ether (bp 40–70 °C)–chloroform]; ^{1}H NMR ($CDCl_3$) δ 3.1 (m, 8 H, NCH_2CH_2O), 3.49 (s, 3 H, NCH_3), 3.8 (m, 8 H, NCH_2CH_2O), 7.29 (s, 1 H); EI mass spectrum, 296 m/e (M^+); UV (CH_3CN) λ_{max} 224, 290 nm. Also a minor amount of an unidentified blue compound, presumably formed upon interaction between chloranil and morpholine, was isolated.

1-Methyl-3-nitro-4-piperidinopyrrole (6a). Pyrroline **4a** (0.4 g) was dissolved in 50 mL of benzene and refluxed 8 h with an equivalent amount of sodium methoxide (2.6 M in MeOH). After removal of the solvent and inorganic products, the residue was purified by chromatography on a silica gel column, with benzene/1:1 benzene–ethyl acetate, to give a red oil. This was crystallized from hexane to give **6a**: 100 mg (35%); orange solid; mp 69.5–70 °C; ^{1}H NMR ($CDCl_3$) δ 1.7 (m, 6 H, $NCH_2CH_2CH_2$), 2.9 (m, 4 H, $NCH_2CH_2CH_2$), 3.59 (s, 3 H, NCH_3), 6.08 (d, 1 H, J = 3 Hz), 7.36 (d, 1 H, J = 3 Hz); UV λ_{max} (see Table I); mass spectrum, calcd for $C_{10}H_{15}N_3O_2$ (M^+) m/e 209.1164, found 209.1152.

1-Methyl-3-morpholino-4-nitropyrrole (6b). A solution of pyrroline **4b** (80 mg) in 15 mL of benzene was refluxed 10 h with an equivalent amount of sodium methoxide (2.6 M in MeOH). The reaction mixture was filtrated from salts, benzene was removed from the solution. The residue was purified by chromatography upon silica gel with ethyl acetate, and crystallized from CCl_4, to give **6b** (27 mg, 47%) as an orange solid: mp 114.5–115 °C (CCl_4); ^{1}H NMR ($CDCl_3$) δ 3.0 (m, 4 H, NCH_2CH_2O), 3.64 (s, 3 H, NCH_3), 3.9 (m, 4 H, NCH_2CH_2O), 6.14 (d, 1 H, J = 3 Hz), 7.46 (d, 1 H, J = 3 Hz); mass spectrum, calcd for $C_9H_{13}N_3O_3$ (M^+) m/e 211.0957, found 211.0956; UV λ_{max} (see Table I).

Acknowledgment. We thank Prof. G. Illuminati for helpful discussions, Dr. Marina Attinà and Prof. P. Giacomello for the CI mass spectra, and Mr. E. Brancaleoni and the MS service of the CNR Area delle Ricerche (Roma) for the high-resolution mass spectra.

Registry No. 1, 68712-54-9; **2a**, 74460-26-7; **2b**, 83831-96-3; **3a**, 19985-38-7; **4a**, 83831-97-4; **4b**, 83831-98-5; **6a**, 83831-99-6; **6b**, 83832-00-2; piperidine, 110-89-4; methylamine, 74-89-5; morpholine, 110-91-8; 1-methyl-3-nitro-4,5-dipiperidinopyrrole, 83832-01-3.

Addition Reaction of Thebaine and Related Compounds with Acetylenic Dienophiles: The Structure–Reactivity Relationship

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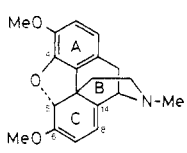
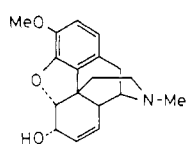
Received May 25, 1982

The addition reaction of thebaine (1) with methyl propiolate (MP) and dimethyl acetylenedicarboxylate (DMAD) has been shown to give different products depending on the solvent used. While the Diels–Alder adducts **3** and **4** were the only products obtained in benzene, the reaction with MP in acetonitrile gave the novel 1:1 adduct **8**, and that with DMAD in methanol afforded the methanol-added product **11**, both in high yields. These novel products were derived from the initial C(9)–N bond scission of 1. 6-Demethoxythebaine (**17**) gave only the Diels–Alder adduct **18**. β-Dihydrothebaine acetate (**21**) gave no Diels–Alder adducts, but C–N bond cleavage predominantly occurred to give the 1:1 adducts **22** and **23** in benzene or acetonitrile or **25** and **26** in methanol, respectively. Similar reactions of neopinone dimethyl ketal (**27**) resulted in the C–N bond cleavage to give the 1:1 adducts **28** and **29**, whereas the reaction of northebaine (**30**) afforded the 1,2-addition products **31** and **32** with no C–N bond scission. On the basis of these observations, structure–reactivity relationships in these reactions are discussed.

Thebaine (1), one of the minor constituents of opium, is a highly toxic alkaloid[1] and has been mainly used in the synthesis[2-4] of codeine (2) which is the medicinally most important opiate with a low abuse potential. However, it was recently discovered that the opium-free poppy *Papaver bracteatum* contains 1 as the major constituent, constituting more than 90% of total alkaloids.[5] This fact has stimulated studies on chemical modification of thebaine (1) as a potential new raw material for analgesic agents.[5b]



1



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A unique feature of thebaine (1) is the electron-rich diene moiety in the C ring. As a result, a number of Diels–Alder reactions of 1 with olefinic dienophiles and molecular rearrangements of the resulting adducts into

(1) Ginsburg, D. "The Opium Alkaloids"; Interscience: New York, 1962.
(2) (a) Krauz, F. U.S. Patent 3 112 323, 1963. (b) Garad, J. P.; Krauz, F.; Rull, T. *Bull. Soc. Chim. Fr.* **1965**, 486.
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(4) Dauben, W. G.; Baskin, C. P.; van Riel, H. C. H. A. *J. Org. Chem.* **1979**, *44*, 1567.
(5) (a) Nyman, U.; Bruhn, J. G. *Planta Med.* **1979**, *35*, 97. (b) Anonymous *Science* **1975**, *190*, 1274.

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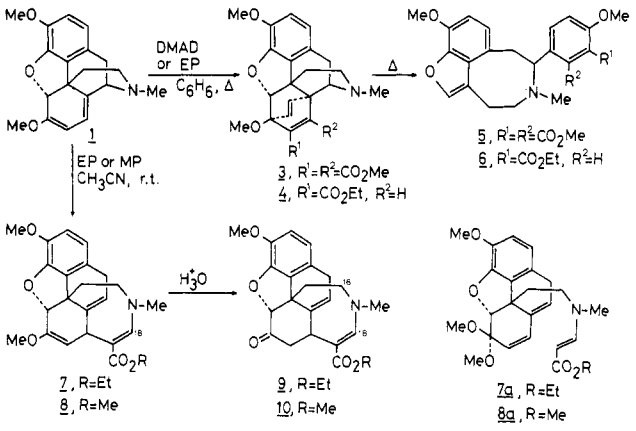
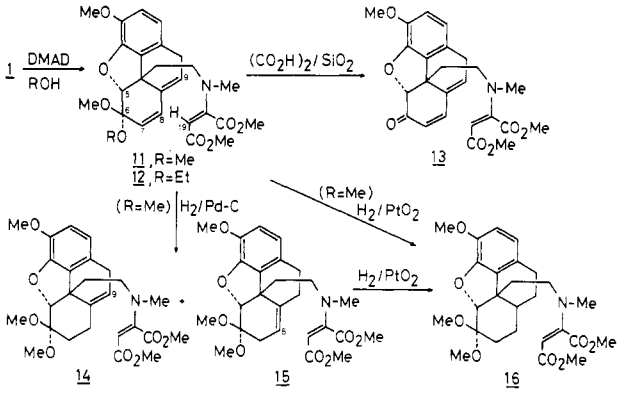
Scheme I



Scheme II



complex polycyclic molecules have been extensively investigated.[6-14] There have been only a few reports concerning the reaction of 1 with acetylenic dienophiles.[8,11,15] Recently we have found interesting solvent effects in the reaction of 1 with propiolic esters, leading to the formation of new types of adducts in the polar solvents.[16] In order to clarify the factors controlling these addition reactions, the reactions of thebaine (1) with acetylenic dienophiles have been systematically studied in various solvents. The similar reactions of some structurally related morphine derivatives were also investigated. We now report the full details of this work,[16] including the previously undisclosed structure–reactivity relationship in the addition reactions of these morphine alkaloids.

Results and Discussion

Reaction of Thebaine (1). Rapoport and Sheldrick[15] reported that 1 and dimethyl acetylenedicarboxylate (DMAD) react smoothly in benzene at 50 °C to give the Diels–Alder adduct 3 in high yield, whereas the similar reaction of ethyl propiolate (EP) gives the adduct 4 only in very poor yield (Scheme I). The low reactivity of the latter was attributed to a rapid polymerization of EP under the reaction conditions employed.[15] Therefore, we have reexamined the same reaction under milder conditions using different solvents. Surprisingly, 1 was found to react very readily with EP in polar solvents. Thus, reaction of 1 with 1.1 equiv of EP in acetonitrile at room temperature was complete within 30 min and gave almost quantitative yields of the crystalline adduct 7 (mp 168–170 °C; Scheme I). The structural proof of the novel adduct 7 was based on the spectroscopic data. Its nature as a 1:1 adduct was apparent from the elemental analysis and mass spectrum which displayed an intense molecular ion peak at m/z 409. The IR spectrum showed a characteristic absorption at 1680 cm^{-1} for the enamino ester (>NC=CCO_2Et) moiety. The ^1H NMR spectrum exhibited signals for ethyl group at δ 1.28 (t) and 4.14 (q), three methyl groups at δ 2.91, 3.55, and 3.82 (each s), and a characteristic olefinic proton of enamino ester moiety at δ 7.33 (s, H-18). The ^{13}C NMR spectrum also confirmed the assigned structure by showing signals for an ester carbonyl (δ 169.3), twelve sp^2 carbons, three methine carbons, three methylene carbons, and four methyl carbons. The product 7 was also obtained by a similar reaction in CH_2Cl_2 (64%). However, the reaction in benzene resulted in the formation of several minor products including 7 (21%) and the known Diels–Alder adduct 3[15] (6%) along with the recovery of a large amount of unreacted 1. The reaction in methanol gave a quantitative yield of solid product which showed a homogenous spot with the same R_f value as 7 on TLC (silica gel and alumina) with various solvent systems. However, a recent investigation by Singh et al. indicated this to be a mixture of 7 and a methanol-added product **7a**.[32] Actually, the ^1H NMR analysis showed that the product is composed of 7 and **7a** in a 1:2 ratio. The structural assignment of the latter was made by spectral comparison with methyl ester **8a** reported by Singh et al.[32] While 3 easily undergoes the retro-Diels–Alder reaction at 140 °C to give 6[15], compounds 7 and **7a** are stable under the above thermolytic conditions. The reaction of 1 with methyl propiolate (MP) in acetonitrile similarly proceeded at room temperature to afford the 1:1 adduct 8 (mp 160–162 °C) in almost quantitative yield. The reaction in methanol gave a mixture of 8 and methanol-added product **8a**[32] (Scheme I; see above as for the mixture of 7 and **7a**).

The structure of these adducts was further confirmed by the following chemical conversions. While 7 (or 8) was recovered unchanged from the catalytic hydrogenation (H_2, 5% Pd/C), the exposure of the enol ether functionality in 7 and 8 to the acid hydrolysis gave the corresponding ketones 9 (mp 170–172 °C) and 10 (mp 231–233 °C) in 88% and 86% yields, respectively. Compound 9 (M^+, m/z 395) showed typical carbonyl bands at 1735 and 1680 cm^{-1}, consistent with the ketone and enamino ester, in its IR spectrum. The ^1H NMR spectrum clearly indicated the disappearance of the enol ether moiety by showing only two singlets for methyl groups at δ 3.02 and 3.88 and the new appearance of two methylene proton signals (H-7) at δ 2.51 (dd, J = 14.2, 8.1 Hz) and 2.75 (dd, J = 14.2, 9.0 Hz). The ^{13}C NMR spectrum of 9 is very similar to that of 7 except for the new appearance of a carbonyl signal at δ

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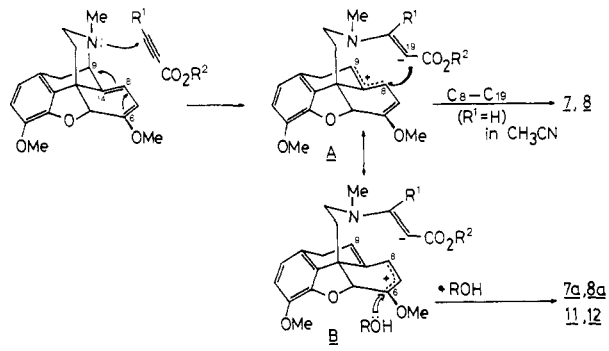
205.8 (s, C-6) and a methylene signal at δ 44.4 (t, C-7). The ketone structure of **10** was recently confirmed by the X-ray analysis.[32]

The observation of the above remarkable solvent effects in the reactions of propiolic esters prompted us to reexamine further the reaction of **1** with DMAD in different solvents. While **1** and DMAD smoothly reacted in benzene to give the Diels–Alder adduct **3** (Scheme I) in a high yield as Rapoport and Sheldrick reported,[15] the reaction in acetonitrile rapidly consumed **1** at room temperature but gave **3** only in a low yield (~20%) along with the several unidentified minor products. On the other hand, the reaction in methanol proceeded rapidly at the ambient temperature to give the new crystalline product **11** (mp 159–162 °C) in 68% yield (Scheme II). The similar result was also observed independently by Singh et al.[32] The structure of **11** was established as follows. Both elemental analysis and the mass spectrum (M^+, m/z 485) indicated **11** to be the 1:1:1 adduct of **1**, DMAD, and methanol. The IR spectrum showed two carbonyl bands at 1740 and 1690 cm^{-1}. The ^1H NMR spectrum displayed signals of an *N*-methyl group at δ 2.72 and five methoxy groups at δ 2.91, 3.62, 3.68, 3.76, and 3.88 (each s). The strong upfield shift of one methyl signal (δ 2.91, CH_3O-6_α) can be attributed to the anisotropic effect of the proximate aromatic ring. The chemical shift of H-19 (δ 4.46) is indicative of the *E* configuration at the enamino ester moiety.[17] The ^{13}C NMR spectrum also showed fully compatible signals, including two carbonyl carbons at δ 165.3 (s) and 167.5 (s) and a characteristically shielded vinyl carbon (C-19) of the enamino ester[18,19] at δ 84.3 (d). The same reaction in ethanol instead of methanol afforded the corresponding ethanol-added product **12** in 43% yield. A diagnostic feature of the ^1H NMR spectrum of **12**, which is very similar to that of **11**, is the abnormal upfield shift of ethoxy signal [δ 0.80 (t, 3 H) and 3.16 (q, 2 H)], indicating its α configuration at the C-6 position as shown.

Further structural confirmations of these products were obtained by the following chemical conversions (Scheme II). The deketalization of both **11** and **12** with wet silica gel in the presence of oxalic acid[20] gave the same ketone **13** (mp 102–105 °C) in moderate yields: MS, m/z 439 (M^+); IR 1740, 1690 cm^{-1}. Catalytic hydrogenation of **11** over 5% Pd/C afforded a quantitative yield of the inseparable mixture of dihydro derivatives **14** and **15** in a variable ratio which could be determined by the ^1H NMR analysis with the aid of the olefinic signals at δ 5.74 (H-9) of **14** and at δ 5.36 (H-8) of **15**. While **14** was the major product of the brief hydrogenation, **15** gradually increased at the cost of **14**.[21] Prolonged treatment gave only **15**: mp 139–141 °C; MS, m/z 487 (M^+); IR 1745, 1695 cm^{-1}. The ^1H NMR spectrum showed partial structural similarity of **15** to neopinone dimethyl ketal[4] (see Experimental Section). On the other hand, the hydrogenation of the mixture of **14** and **15** on PtO_2 gave the tetrahydro derivative **16** in a quantitative yield: MS, m/z 489 (M^+); IR 1740, 1690 cm^{-1}. Compound **16** was also obtained by the catalytic hydrogenation of **11** over PtO_2.

The above results indicate that the reactions of thebaine (**1**) with acetylenic dienophiles are strongly influenced by the polarity of reaction media, suggesting the alteration of the reaction mechanism depending on the solvent employed. In a nonpolar solvent such as benzene, the [4 + 2] cycloaddition reaction preferentially occurs to give the Diels–Alder adducts (**3**, **4**) as usually seen in the reaction with olefinic dienophiles.[6] In contrast, the reaction proceeds very rapidly in polar solvents to afford different types of adducts (**7**, **8**, **11**, **12**). The formation of these novel products can be most reasonably explained by the stepwise mechanism involving ionic species shown in Scheme III.[22] The reaction may be initiated by the nucleophilic attack of **1** to the electron-deficient acetylenes followed by the cleavage of the C(9)–N bond, which is stereoelectronically favored by its almost parallel arrangement to the p orbital of the adjacent C(8)=C(14) double bond. Thus-formed zwitterionic intermediates would be fairly stabilized by conjugation through the vinyl ether moiety in the C ring (A and B).[22] In the case of reactions of EP and MP (R^1 = H), these intermediates collapse at the sterically most favorable position (C-8) to give adducts **7** and **8**. In methanol, the intermolecular trapping reaction of these intermediates by the solvent competes substantially with this intramolecular process to give the ketals **7a** and **8a**. On the other hand, in the reaction with DMAD, the initially formed zwitterions (A and B; R^1 = CO_2Me) appear to be hindered from a similar intramolecular cyclization probably due to both steric and electronic factors caused by the second ester group (R^1). This is indicated by no formation of such cyclization product in acetonitrile. When methanol or ethanol was used as the solvent, this ionic intermediate could be effectively trapped by these nucleophilic solvents. In this event, an alcohol molecule (ROH) attacks the most stabilized cationic center (C-6) from the less hindered α side of the molecule to give exclusively the products (**11** and **12**) with the RO group in the α position. The selective formation of the *E* enamino ester in products **11** and **12** is also not inconsistent with the intermolecular protonation mechanism.[23]

Scheme III



Reaction of 6-Demethoxythebaine (17). On consideration of the above interesting behavior of thebaine (**1**) in the reaction with acetylenic dienophiles, we have also investigated the similar reaction of 6-demethoxythebaine (**17**) which was prepared from codeine (**2**) by the procedure of Rapoport et al.[24] Since **17** possesses the same structural features as **1** except for the lack of a methoxy group at C-6,

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(18) Hori, M.; Kataoka, T.; Shimizu, H.; Imai, E.; Matsumoto, Y. *Tetrahedron Lett.* **1981**, *22*, 1259.
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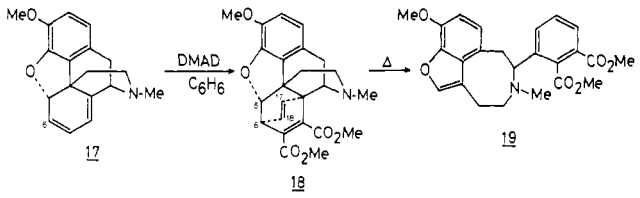
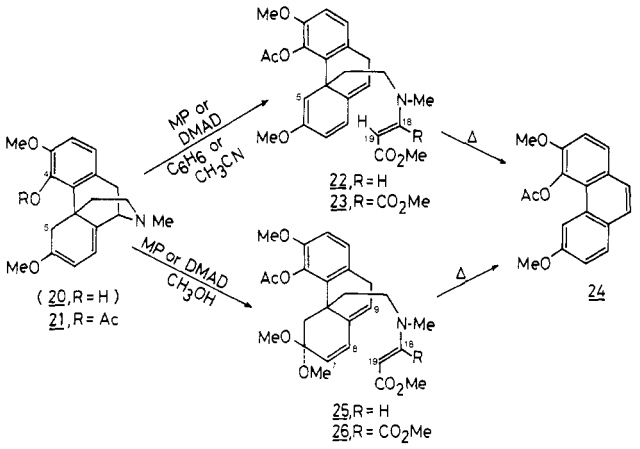
(22) The exact configuration of vinyl anion in the zwitterionic intermediates is not known at this stage. The recent ab initio calculations of the related systems suggested the slight preference of the anti form over the syn form with a low inversion barrier. See: Houk, K. N.; Strozier, R. W. Rozeboom, D.; Nagase, S. *J. Am. Chem. Soc.* **1982**, *104*, 323.
(23) Huisgen, R.; Giese, B.; Huber, H. *Tetrahedron Lett.* **1967**, 1883.
(24) Hutchins, C. W.; Cooper, G. K.; Purro, S.; Rapoport, H. *J. Med. Chem.* **1981**, *24*, 773.

Scheme IV



Scheme V

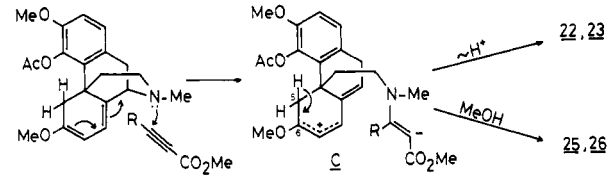


analogous reactivities might be expected for **17**. However, when **17** was treated with an excess (~3 equiv) of MP under various conditions, most of the **17** was recovered unchanged, and only MP was rapidly consumed to give the dimeric product[25] (in benzene or acetonitrile) or the solvent-addition product[17] (in alcoholic solvents) in high yields. Similarly, the reaction of **17** and DMAD in methanol or acetonitrile resulted in the recovery of **17** and formation of the products derived from only DMAD and solvents.[17] On the other hand, treatment of **17** with DMAD in refluxing benzene afforded the Diels–Alder adduct **18** (Scheme IV): mp 150–151 °C; 72% yield; MS, m/z 423 (M^+); IR 1730, 1720 cm^{-1}. The ^1H NMR spectrum of **18** confirmed its skeletal similarity to **3** (or **4**), showing the characteristic signals at δ 4.51 (m, H-6), 4.63 (d, J = 4.0 Hz, H-5), 5.50 (dd, J = 8.0, 1.7 Hz, H-17), and 6.06 (dd, J = 8.0, 5.7 Hz, H-18). As was expected, adduct **18** easily underwent the retro-Diels–Alder fragmentation at 140 °C to give **19** (mp 164–166 °C) in a quantitative yield.

It is a sharp contrast to **1** that **17** has no tendency to react with acetylenic esters in an ionic manner even in polar solvents. These results clearly indicate that the methoxy group at C-6 in **1** plays an important role in its novel reactions leading to the C–N bond-cleavaged products (**7**, **8**, **11**, **12**).

Reaction of β-Dihydrothebaine Acetate (21). In order to develop structure–reactivity relationships in these reactions, we studied the reaction of β-dihydrothebaine acetate (**21**) which is free of the 4,5-oxy bridge connecting the A and C rings as seen in **1** and **17**. The acetate **21** was prepared by acetylation of β-dihydrothebaine (**20**)[26] which was obtained by the $LiAlH_4$ reduction of **1**.[27] Reaction of **21** with MP (1.5 equiv) in acetonitrile or benzene at room temperature (30 min) afforded the thermally labile adduct **22** in 58% and 31% yields, respectively (Scheme V). While **22** could be isolated in a pure form by a quick chromatography on silica gel, the isolated **22** decomposed gradually at ambient temperature or instantaneously at

Scheme VI



50 °C to give 3,6-dimethoxy-4-acetoxyphenanthrene (**24**).[28] This aromatic compound, **24**, is also known to be obtained as the final product by the degradative treatment of the methiodide of **1** with acetic anhydride and sodium acetate.[1,28] In contrast, the reaction of **21** with MP in methanol proceeded rapidly at room temperature to give the methanol-added product **25** (91%) which was also thermally labile and easily coverted to **24** at 70 °C (Scheme V). The reaction of **21** with DMAD gave rise to the very similar results as outlined in Scheme V. Thus, the adduct **23** was obtained as the only product in acetonitrile (60%) or benzene (47%), whereas the dimethyl ketal **26** was formed in 86% yield in methanol. Both **23** and **26** aromatized on heating to give **24**.

All these products were isolated pure and were fully characterized on the basis of the spectroscopic data. Adduct **22** showed typical carbonyl bands at 1775 and 1680 cm^{-1} consistent for the acetyl and enamino ester. In the ^1H NMR spectrum, the 12.0-Hz value for $J_{18,19}$ and the chemical shift of H-19 (δ 4.33)[17] confirmed the E olefin geometry of the enamino ester moiety.

Compound **25** exhibited strong IR bands at 1768 and 1675 cm^{-1} for the acetyl and enamino ester groups. The ^1H NMR spectrum revealed the E enamino ester geometry by the coupling constant ($J_{18,19}$ = 12.8 Hz) and the upfield shift of H-19 (δ 4.34).[17] The characterization of **23** and **26** appears in the Experimental Section.

As indicated above, the reaction of **21** with acetylenic dienophiles readily takes place at the ambient temperature but gives none of the Diels–Alder adducts. These results can be understood by considering the initial formation of zwitterionic intermediate C which arises from the similar nucleophilic addition of **21** to acetylenes as discussed previously (Scheme VI).[22] In nonnucleophilic solvents such as acetonitrile and benzene, zwitterion C undergoes, instead of cyclization, deprotonation at the C-5 position adjacent to the stabilized cationic center (C-6) and protonation of the vinyl anion to give products **22** and **23**. In the case of zwitterions A and B resulting from **1** (Scheme III), this protonation–deprotonation process is considered to be suppressed by the presence of the oxy bridge at C-5. On the other hand, a nucleophilic solvent such as methanol may attack the stabilized zwitterion C at the C-6 position as before, prior to the deprotonation, to give products **25** and **26**. In support of this mechanism, when *tert*-butyl alcohol was used as the protic but nonnucleophilic solvent, only **22** or **23** was formed in the reactions of **21** with MP or DMAD, respectively.

While β-dihydrothebaine (**20**) showed similar behavior in the reaction with acetylenic esters, the products were not characterized because of their instability.

Reaction of Neopinone Dimethyl Ketal (27). Having observed the facile C(9)–N bond cleavage in **1** and **21**, we next focused our attention on the effect of conjugated diene moiety in the C ring which might have some influence on the reactivity of these alkaloids. For this purpose we prepared neopinone dimethyl ketal (**27**) from **1** by the method of Dauben et al.[4] and studied its reaction with

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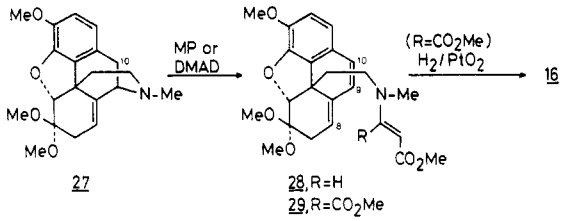
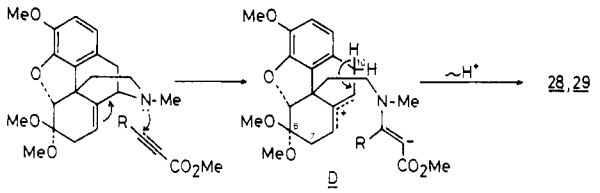
(28) Pschorr, R.; Seydel, C.; Stohre, W. *Ber.* **1902**, *35*, 4400.

Scheme VII



Scheme VIII



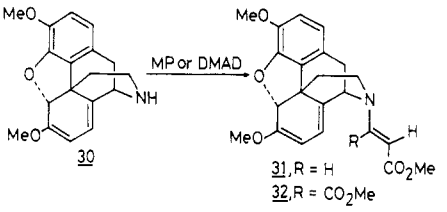
acetylenic dienophiles. In contrast to **1** and **21**, attempted reaction of **27** with MP under the similar conditions only caused the dimerization of MP, and **27** was recovered unchanged. However, treatment of **27** with a large excess of MP (~20 equiv) in acetonitrile at room temperature gave adduct **28** in 48% yield along with the dimers of MP.[25] Similarly, reaction of **27** with excess DMAD in polar solvents such as acetonitrile and methanol afforded the corresponding adduct **29** in 42% and 53% yields, respectively (Scheme VII).

The structure of **28** (M^+, m/z 427) was determined on the basis of its spectroscopic data. The IR spectrum exhibited a characteristic absorption at 1680 cm^{-1} for the enamino ester. The ^1H NMR spectrum indicated the signals of three olefinic protons at δ 5.61 (dd, J = 8.0, 3.8 Hz, H-8) and at 6.10 and 6.37 (AB q, J = 9.6 Hz, H-9, 10) besides the characteristic signals of the E enamino ester moiety at δ 4.41 and 7.30 (each d) with a coupling constant of J = 12.8 Hz. The absence of the benzylic methylene signals as well as the small chemical shift difference ($\Delta\beta$ = 0.27) between two vicinal olefinic protons (i.e., AB system) in **28** compared with that ($\Delta\beta$ = 1.01) in **11** (i.e., AX system) were compatible with the assigned double bond position in **28**.[29] The assignments were further confirmed by double-resonance experiments.

The ^1H NMR spectrum of **29** was very similar to that of **28** except for the substitution of the H-18 signal with that of a carbomethoxy group (δ 3.88) and the collapse of H-19 signal to a singlet (δ 4.47). Furthermore, on catalytic hydrogenation over PtO_2, **29** was quantitatively converted into **16** which was identical in all respects with the previous sample of **16** prepared from **11** (Schemes II and VII).

The formation of **28** and **29** can be uniformly explained by the stepwise mechanism via the zwitterionic intermediate D which arises from the nucleophilic addition of **27** to the electron-deficient acetylenes (Scheme VIII).[22] The intermediate D would be short-lived compared with the above-mentioned zwitterions A–C, since no additional stabilization is available for the allyl cation in D because of the lack of a double bond at the C-6,C-7 position. As a result, the deprotonation occurs rapidly at the most favorable benzylic position (C-10) to provide the products **28** and **29**, and neither a cyclization product nor a solvent-addition product could be obtained even in methanol solution. A similar type of elimination is known in the Hofmann degradation of a series of morphine alkaloids.[1] In addition, the remarkably lowered reactivity of **27** compared with **1** and **21** suggests that the diene functionality in the C ring has some effect on increasing the nucleophilicity of the nitrogen atom.

Scheme IX



Finally, the reaction of northebaine (**30**)[30] was also studied. The secondary amine **30** underwent a smooth reaction with MP and DMAD at room temperature to afford the syn 1,2-addition products[17,23] **31** and **32**, respectively, in almost quantitative yields (Scheme IX), and neither the C–N bond cleavage nor Diels–Alder reaction was observed.

In conclusion, we have been able to demonstrate that the reaction of thebaine (**1**) and related compounds with acetylenic dienophiles potentially possesses two competitive reaction pathways: (a) the symmetry-allowed [4 + 2] cycloaddition (Diels–Alder) reaction[31] and (b) the stepwise addition reaction initiated by the nucleophilic attack of a nitrogen atom accompanied by the C(9)–N bond scission. The choice of a reaction path strongly depends on the reaction medium. While the former reaction seems to be little affected by the solvent polarity, the latter is much favored in the polar solvents. This dichotomy in reaction mechanism is unique to the reaction with acetylenic dienophiles and is not observed for the reaction with olefinic dienophiles.

Experimental Section

The melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were determined in the indicated solvent on a JASCO IR A-1 infrared spectrophotometer and are reported in reciprocal centimeters. ^1H nuclear magnetic resonance (^1H NMR) spectra were taken in deuteriochloroform on a JEOL PS-100 (100 MHz) spectrometer. Chemical shifts are reported in δ units (parts per million downfield from tetramethylsilane). Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; br, broad. Coupling constants are regarded in herts. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were obtained on a JEOL FX-100 spectrometer. Chemical shifts are reported in δ units, and splitting patterns are designated as with ^1H NMR. Mass spectra (MS) were determined on a JEOL D-300 equipped with a JMA 3100/3500 at an ionization voltage of 70 eV unless otherwise noted. Data are reported as m/z (relative intensity) values. Analytical and preparative thin-layer chromatography was performed by using E. M. Merck silica gel 60 PF-254 or aluminum oxide 60 F 254 (neutral), and column chromatography was done by using 70–230-mesh silica gel 60 or aluminum oxide 90 (E. M. Merck). Analytical data (±0.4% for C, H and N, except as noted) were provided for all compounds with the designation. Anal. (C, H, N).

Reaction of Thebaine (1) with Ethyl Propiolate (EP). In Acetonitrile. To a stirred solution of **1** (1.0 g, 3.21 mmol) in 30 mL of acetonitrile in an ice–water bath was added a solution of EP (345 mg, 3.53 mmol) in 5 mL of acetonitrile. The mixture was stirred at room temperature for 30 min. The solvent was removed in vacuo, and the residual yellow solid was recrystallized from ethyl acetate to give pure adduct **7**: 1.27 g (97%); colorless prisms; mp 168–170 °C; IR (Nujol) 1680 cm^{-1}; ^1H NMR δ 1.28 (3 H, t, J = 6.8 Hz, CH_3), 1.91 (2 H, m, H-15), 2.91 (3 H, s, NCH_3),

(29) Matter, U. E.; Pascual, C.; Pretsch, E.; Pross, A.; Simon, W.; Sternhell, S. *Tetrahedron* **1969**, *25*, 691.

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(31) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 781.

3.15–3.24 (4 H, m), 3.55 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 4.14 (2 H, q, J = 6.8 Hz, CH_2), 4.50 (br d, J = 5.2 Hz, H-8), 4.97 (d, J = 1.2 Hz, H-5), 5.25 (dd, J = 5.2, 1.2 Hz, H-7), 5.93 (dd, J = 5.4, 2.7 Hz, H-9), 6.65 (2 H, s, Ar H), 7.33 (s, H-18); ^{13}C NMR δ 169.7 (s), 150.7 (d), 150.5 (s), 144.6 (s), 142.3 (s), 140.9 (s), 133.6 (s), 128.3 (s), 124.5 (d), 118.6 (s), 111.8 (s), 104.4 (s), 102.2 (d), 86.1 (d), 59.47 (t), 56.2 (q), 54.4 (q), 53.1 (t), 50.2 (q), 44.3 (q), 38.4 (d), 37.9 (s), 29.4 (t), 14.53 (q); MS m/z 409 (M^+, 100), 408 (28), 394 (31), 336 (22), 124 (32), 31 (22). Anal. ($C_{24}H_{27}NO_5$): C, H, N.

In Methanol. A mixture of 1 (500 mg, 1.60 mmol) and EP (173 mg, 1.77 mmol) in 20 mL of methanol was stirred at room temperature for 30 min. After evaporation of the solvent, the ^1H NMR analysis of the crude solid (641 mg) showed it to be a mixture of 7 and **7a** in a 1:2 ratio. ^1H NMR of **7a**:[32] δ 1.27 (3 H, t, J = 7.0 Hz, CH_3), 2.69 (3 H, s, NCH_3), 2.91 (3 H, s, OCH_3), 3.54 (3 H, s, OCH_3), 3.63 (3 H, s, OCH_3), 3.89 (3 H, s, OCH_3), 4.00 (2 H, q, J = 7.0 Hz, CH_2), 4.43 (d, J = 13.2 Hz, H-19), 4.77 (s, H-5), 5.61 (d, J = 10.2 Hz, H-7), 5.93 (dd, J = 5.4, 2.7 Hz, H-9), 6.60 (d, J = 10.2 Hz, H-8), 6.67 (2 H, s, Ar H), 7.37 (d, J = 13.2 Hz, H-18).

In Methylene Chloride. A mixture of 1 (3.0 g, 9.64 mmol) and EP (1.42 g, 14.5 mmol) in 60 mL of CH_2Cl_2 was stirred at room temperature for 1 h. The solvent was removed in vacuo, and the residual oil was chromatographed on silica gel with ethyl acetate–hexane (1:3) to give 7 (2.4 g, 64%).

In Benzene. A mixture of 1 (300 mg, 0.94 mmol) and EP (283 mg, 2.9 mmol) in 20 mL of benzene was stirred at room temperature for 12 h. The solvent was removed, and the residue was chromatographed on silica gel with ethyl acetate–hexane to give Diels–Alder adduct 3[15] (20 mg, 5%) and 7 (79 mg, 20%) and with chloroform–methanol (8:1) to give unreacted 1 (185 mg, 62%).

Reaction of Thebaine (1) with Methyl Propiolate (MP). In Acetonitrile. To a stirred solution of 1 (3.0 g, 9.65 mmol) in 60 mL of acetonitrile in an ice–water bath was added a solution of MP (891 mg, 10.6 mmol) in 10 mL of acetonitrile. The mixture was stirred at room temperature for 30 min, and the solvent was removed in vacuo. Recrystallization of the residual solid from ethyl acetate gave adduct 8: 3.6 g (95%); colorless crystals; mp 160–162 °C; IR (Nujol) 1680 cm^{-1}; ^1H NMR δ 1.86–2.40 (2 H, m, H-15), 2.91 (3 H, s, NCH_3), 3.15–3.24 (4 H, m), 3.55 (3 H, s, CH_3), 3.72 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 4.50 (br d, J = 5.2 Hz, H-8), 4.97 (d, J = 1.2 Hz, H-5), 5.25 (dd, J = 5.2, 1.2 Hz, H-7), 5.93 (dd, J = 5.4, 2.7 Hz, H-9), 6.65 (2 H, s, Ar H), 7.33 (s, H-18); ^{13}C NMR δ 169.7 (s), 150.7 (d), 150.5 (s), 144.6 (s), 142.3 (s), 140.9 (s), 133.6 (s), 128.3 (s), 124.5 (d), 111.8 (d), 104.4 (s), 102.2 (d), 86.1 (d), 56.2 (q), 54.4 (t), 53.1 (t), 51.0 (q), 50.2 (q), 44.3 (q), 38.4 (d), 37.9 (s), 29.4 (t); MS, m/z 395 (M^+, 100), 394 (28), 380 (44), 336 (20), 124 (35), 42 (23). Anal. ($C_{23}H_{25}NO_5$): C, H, N.

In Methanol. A mixture of 1 (500 mg, 1.60 mmol) and MP (149 mg, 1.76 mmol) in 20 mL of methanol was stirred at room temperature for 30 min. After evaporation of the solvent, the ^1H NMR analysis of the crude product (613 mg) showed it to be a mixture of 8 and **8a** in a 6:11 ratio. Compound **8a** was identified by spectral comparison with that reported by Singh et al.[32]

Hydrolysis of Adduct 7. To a stirred solution of adduct 7 (425 mg, 1.04 mmol) in 15 mL of THF was added 1 mL of concentrated HCl, and the solution was stirred at room temperature for 3 h. The mixture was diluted with 20 mL of water, and then saturated aqueous K_2CO_3 was added to pH 11 under ice cooling. The resulting suspension was extracted with CH_2Cl_2, and organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated. Column chromatography of the residue on silica gel with ethyl acetate–hexane (1:1) gave **9** (361 mg, 88%), which was recrystallized from ethyl acetate to give colorless crystals: mp 170–172 °C; IR (Nujol) 1735, 1680 cm^{-1}; ^1H NMR δ 1.27 (3 H, t, J = 6.9 Hz, CH_3), 1.68–2.00 (2 H, m), 2.51 (dd, J = 14.2, 8.1 Hz, H-7β), 2.75 (dd, J = 14.2, 9.0 Hz, H-7α), 3.02 (3 H, s, NCH_3), 3.20 (2 H, d-like m, H-10), 3.40–3.50 (2 H, m, H-16), 3.88 (3 H, s, OCH_3), 4.15 (2 H, q, J = 6.9 Hz, CH_2), 4.39 (br t, J = 8.5 Hz, H-8), 5.05 (s, H-5), 5.90 (m, H-9), 6.69 (2 H, s, Ar H), 7.42 (s, H-18); ^{13}C NMR δ 205.8 (s), 168.7 (s), 150.4 (d), 143.9 (s), 142.3 (s), 138.5 (s), 132.2 (s), 126.3 (s), 126.3 (d), 119.6 (d), 112.7 (d), 105.7 (s), 89.5 (d), 59.7 (t), 56.5 (q), 54.2 (t), 53.3 (t), 44.4 (t), 41.5 (q), 37.4 (s), 37.4 (d), 29.2 (t), 14.5 (q); MS, m/z 395 (M^+, 59), 61 (21), 43 (100). Anal. ($C_{23}H_{25}NO_5$): C, H, N.[33]

Hydrolysis of Adduct 8. Adduct 8 (1.2 g, 3.03 mmol) was dissolved in 40 mL of THF and 2.5 mL of concentrated HCl, and the resulting solution was stirred at room temperature for 2.5 h. The extractive workup afforded the crude solid which was recrystallized from ethyl acetate to give **10**: 992 mg (86%); colorless crystals; mp 230–233 °C; IR (Nujol) 1735, 1670 cm^{-1}; ^1H NMR δ 1.68–2.00 (2 H, m), 2.50 (dd, J = 13.8, 8.0 Hz, H-7β), 2.82 (dd, J = 13.8, 9.0 Hz, H-7α), 3.00 (3 H, s, NCH_3), 3.18 (2 H, d-like m), 3.40–3.60 (2 H, m), 3.67 (3 H, s, OCH_3), 3.86 (3 H, s OCH_3), 4.37 (br t, J = 8.5 Hz, H-8), 5.03 (s, H-5), 5.90 (m, H-9), 6.88 (2 H, s, Ar H), 7.40 (s, H-18); ^{13}C NMR δ 205.7 (s), 169.4 (s), 150.6 (d), 143.9 (s), 142.3 (s), 138.5 (s), 132.2 (s), 126.3 (s), 126.3 (d), 119.6 (d), 112.8 (d), 105.4 (s), 89.4 (d), 56.5 (q), 54.2 (t), 53.3 (t), 51.1 (q), 44.5 (q), 41.5 (t), 37.4 (d), 37.4 (s), 29.2 (t); MS, m/z 381 (M^+, 100), 296 (17), 44 (18), 42 (18). Anal. ($C_{22}H_{23}NO_5$): C, H, N.

Reaction of Thebaine (1) with Dimethyl Acetylenedicarboxylate (DMAD). In Methanol. To a stirred solution of 1 (2.0 g, 6.43 mmol) in 60 mL of methanol in an ice–water bath was added a solution of DMAD (1.0 g, 7.07 mmol) in 10 mL of methanol. The mixture was stirred at room temperature for 30 min, and then the solvent was removed in vacuo. The residual solid was recrystallized from ethyl acetate–hexane to give 11: 2.12 g (68%); colorless crystals; mp 159–162 °C; IR (Nujol) 1740, 1690 cm^{-1}; ^1H NMR δ 1.84 (2 H, t, J = 7.6 Hz, H-15), 2.72 (3 H, s, NCH_3), 2.91 (3 H, s, OCH_3), 3.03 (2 H, d-like m, H-10), 3.33 (2 H, t, J = 7.6 Hz, H-16), 3.52 (3 H, s, OCH_3), 3.58 (3 H, s, OCH_3), 3.75 (3 H, s, OCH_3), 3.87 (3 H, s OCH_3), 4.46 (s, H-19), 4.74 (s, H-5), 5.57 (d, J = 10.0 Hz, H-7 or H-8), 5.93 (dd, J = 5.4, 2.7 Hz, H-9), 6.58 (d, J = 10.0 Hz, H-8 or 7), 6.67 (2 H, s, Ar H); ^{13}C NMR δ 167.5 (s), 165.3 (s), 154.1 (s), 145.8 (s), 141.7 (s), 138.3 (s), 132.0 (s), 130.9 (d), 128.5 (d), 126.4 (s), 124.2 (d), 119.1 (d), 114.1 (d), 84.3 (d), 97.4 (s), 92.2 (d), 57.1 (q), 52.5 (q), 50.6 (q), 50.4 (q), 49.7 (t), 48.9 (q), 47.3 (s), 37.3 (q), 37.3 (t), 29.5 (t); MS, m/z 485 (M^+, 30), 269 (26), 254 (21), 253 (36), 201 (27), 200 (100), 173 (21), 169 (65), 142 (25), 141 (25), 114 (25), 82 (30). Anal. ($C_{26}H_{31}NO_8$): C, H, N.

In Ethanol. A mixture of 1 (500 mg, 1.61 mmol) and DMAD (251 mg, 1.76 mmol) in 25 mL of ethanol was stirred at room temperature for 30 min, and then the solvent was removed in vacuo. The brown residue was chromatographed on silica gel with ethyl acetate–hexane (1:3) to give adduct 12: 345 mg (43%); viscous oil; IR ($CHCl_3$) 1740, 1690 cm^{-1}; ^1H NMR δ 0.80 (3 H, t, J = 8.0 Hz, CH_3), 1.86 (2 H, t, J = 7.6 Hz, H-15), 2.72 (3 H, s, NCH_3), 3.16 (2 H, q, J = 8.0 Hz, CH_2), 2.96–3.44 (4 H, m), 3.62 (3 H, s, OCH_3), 3.68 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.47 (s, H-19), 4.67 (s, H-5), 5.57 (d, J = 9.8 Hz, H-7 or H-8), 5.93 (dd, J = 5.8, 2.7 Hz, H-9), 6.59 (d, J = 9.8 Hz, H-8 or H-7), 6.68 (2 H, s, Ar H); ^{13}C NMR δ 167.6 (s), 165.3 (s), 154.0 (s), 146.5 (s), 141.8 (s), 138.6 (s), 132.4 (s), 130.8 (d), 128.8 (s), 126.8 (d), 124.0 (d), 118.9 (d), 115.2 (d), 97.2 (s), 92.6 (d), 84.3 (d), 57.7 (q), 56.5 (t), 52.6 (q), 50.6 (t), 50.6 (q), 49.7 (q), 47.5 (s), 37.3 (q), 37.1 (t), 29.6 (t), 14.9 (q).

Hydrolysis of Adduct 11. To a vigorously stirred suspension of silica gel (2.4 g) and 10% aqueous oxalic acid (0.24 mL) in CH_2Cl_2 (3 mL) was added a solution of 11 (250 mg, 0.52 mmol) in 1 mL of CH_2Cl_2, and stirring was continued at room temperature for 45 min. After neutralization by solid $NaHCO_3$ (ca. 0.2 g), the mixture was filtered on a suction filter, and the solid was washed several times with CH_2Cl_2. The combined filtrate was concentrated under reduced pressure and chromatographed on silica gel with ethyl acetate–hexane (1:2) to give 13 (92 mg, 40%) which was recrystallized from CH_2Cl_2–ether to afford colorless prisms: mp 102–105 °C; IR ($CHCl_3$) 1740, 1690 cm^{-1}; ^1H NMR δ 1.94–2.12 (2 H, m), 2.76 (3 H, s, NCH_3), 2.86–3.36 (3 H, m), 3.44 (d-like m, H-10), 3.36 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 3.85 (3 H, s, OCH_3), 4.49 (s, H-19), 4.89 (s, H-5), 5.93 (d, J = 10.0 Hz, H-7), 6.36 (dd, J = 6.0, 2.7 Hz, H-9), 6.64, 6.76 (2 H, AB q, J = 8.0 Hz, Ar H), 7.20 (d, J = 10.0 Hz, H-8); ^{13}C NMR δ 192.9 (s), 167.5 (s), 165.4 (s), 153.9 (s), 144.5 (s), 143.4 (d), 142.6 (s), 138.9

(32) After completion of this work, a similar work appeared. See: Singh, A.; Archer, S.; Hoogsteen, K.; Hirshfield, J. *J. Org. Chem.* **1982**, *47*, 754.

(33) Anal. Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.10; H, 6.65; N, 3.27.

(s), 133.2 (d), 130.7 (s), 126.1 (s), 124.6 (d), 120.0 (d), 113.5 (d), 86.5 (d), 84.9 (d), 56.5 (q), 52.7 (q), 50.7 (q), 49.4 (t), 47.5 (s), 37.5 (q), 36.8 (t), 30.4 (t); MS, m/z 439 (M^+, 26), 409 (20), 407 (29), 350 (22), 266 (59), 251 (38), 240 (29), 186 (100), 113 (40), 82 (44), 45 (42). Anal. ($C_{24}H_{25}NO_7$): C, H, N.

Catalytic Hydrogenation of Adduct 11. A solution of 11 (100 mg, 0.206 mmol) in 15 mL of methanol was hydrogenated over 5% Pd/C (52 mg) under an atmospheric pressure of hydrogen for 12 h to give a mixture of **14** and **15** (97 mg, 97%) as colorless prisms. ^1H NMR shows the following methyl singlets: δ 2.72, 2.77, 2.96, 3.00, 3.42, 3.45, 3.56, 3.60, 3.76, 3.78, 3.82, 3.86.

A solution of 11 (300 mg, 0.62 mmol) in 30 mL of ethyl acetate was hydrogenated over 5% Pd/C (100 mg) under an atmospheric pressure of hydrogen, and the product was recrystallized from ether to give pure **15**: 290 mg (97%) as colorless prisms: mp 139–141 °C; IR (Nujol) 1743, 1695 cm^{-1}; ^1H NMR δ 1.30–3.40 (10 H, m), 2.77 (3 H, s, NCH_3), 2.96 (3 H, s, OCH_3), 3.45 (3 H, s, OCH_3), 3.60 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.51 (s, H-19), 4.72 (s, H-5), 5.36 (d-like m, H-8), 6.56, 6.68 (2 H, AB q, J = 8.0 Hz, Ar H); MS, m/z 487 (M^+, 47), 428 (27), 299 (21), 288 (26), 287 (100), 286 (36), 257 (30), 256 (49), 255 (72), 254 (22), 240 (25), 200 (62), 186 (77), 181 (63), 169 (49), 101 (58). Anal. ($C_{26}H_{33}NO_8$): C, H, N.

A solution of 11 (100 mg, 0.21 mmol) in 15 mL of methanol was hydrogenated over PtO_2 (20 mg) under an atmospheric pressure of hydrogen for 4 h. The mixture was filtered, and the solvent was evaporated to give **16**: 100 mg (99%); viscous oil; IR ($CHCl_3$) 1740, 1690 cm^{-1}; ^1H NMR δ 1.12–3.00 (13 H, m), 2.75 (3 H, s, NCH_3), 3.14 (3 H, s, OCH_3), 3.31 (3 H, s, OCH_3), 3.59 (3 H, s, OCH_3), 3.79 (3 H, s, OCH_3), 3.86 (3 H, s, OCH_3), 4.48 (s, H-19), 4.52 (s, H-5), 6.56, 6.72 (2 H, AB q, J = 8.0 Hz, Ar H); ^{13}C NMR δ 167.6 (s), 165.4 (s), 154.2 (s), 146.8 (s), 141.2 (s), 129.3 (s), 126.0 (s), 119.9 (d), 114.8 (d), 99.3 (s), 90.2 (d), 84.0 (d), 56.9 (q), 52.6 (q), 50.6 (q), 49.3 (q), 48.7 (q), 47.9 (s), 45.9 (t), 37.6 (t), 37.3 (q), 32.9 (d), 26.0 (t), 24.0 (t), 22.5 (t), 20.6 (t); MS, m/z 489 (M^+, 12), 458 (14), 457 (15), 398 (19), 258 (38), 257 (60), 186 (41), 101 (100), 82 (34).

A mixture of **14** and **15** (145 mg, 0.29 mmol) was hydrogenated over PtO_2 (20 mg) to give **16** (140 mg, 98%).

Reaction of 6-Demethoxythebaine (17) with DMAD. A solution of **17**[24] (50 mg, 0.178 mmol) and DMAD (75 mg, 0.534 mmol) in 4 mL of benzene was heated at reflux for 12 h. The mixture was concentrated under reduced pressure and subjected to preparative TLC on silica gel with ethyl acetate–hexane (1:2) to give adduct **18**: 50 mg (72%); colorless solid; mp 150–151 °C; IR ($CHCl_3$) 1730, 1720 cm^{-1}; ^1H NMR δ 1.83–1.96 (2 H, m), 2.35 (3 H, s, NCH_3), 2.44–2.63 (3 H, m), 3.25 (d, J = 18.0 Hz, H-10β), 3.75 (3 H, s, OCH_3), 3.78 (3 H, s, OCH_3), 3.81 (3 H, s, OCH_3), 3.74–3.88 (1 H, overlapped, H-9), 4.51 (m, H-6), 4.63 (d, J = 4.0 Hz, H-5), 5.50 (dd, J = 8.0, 1.7 Hz, H-17), 6.06 (dd, J = 8.0, 5.7 Hz, H-18), 6.54, 6.66 (2 H, AB q, J = 8.0 Hz, Ar H); MS, m/z 423 (M^+, 100), 408 (47), 254 (31), 230 (49), 188 (46). Anal. ($C_{24}H_{25}NO_6$): C, H, N.

Thermolysis of Adduct 18. A solution of **18** (90 mg, 0.21 mmol) in 3 mL of xylene was heated at reflux for 10 min. The solvent was removed in vacuo to give analytically pure **19**: 90 mg (100%); pale yellow solid; mp 164–166 °C; IR ($CHCl_3$) 1730 cm^{-1}; ^1H NMR δ 2.04 (3 H, s, NCH_3), 2.92–3.67 (6 H, m), 3.88 (6 H, s, 2 OCH_3), 3.95 (3 H, s, OCH_3), 6.38, 6.55 (2 H, AB q, J = 8.0 Hz, Ar H), 6.88–7.33 (2 H, m, Ar H), 7.39 (1 H, s, furan), 7.85 (dd, J = 8.0, 2.2 Hz, Ar H); MS, m/z 423 (M^+, 12), 269 (34), 257 (100), 215 (68), 214 (86), 200 (36), 120 (38), 119 (57), 105 (60).

Preparation of 4-Acetoxy-β-dihydrothebaine (21). To a solution of β-dihydrothebaine (**20**;[27] 395 mg, 1.26 mmol) and 4-(dimethylamino)pyridine (216 mg, 1.76 mmol) in 8 mL of CH_2Cl_2 was added a solution of acetic anhydride (193 mg, 1.89 mmol) in 4 mL of CH_2Cl_2. The resulting mixture was stirred at room temperature for 8 h and then washed with water and brine. After evaporation of the solvent, the residue was chromatographed on alumina with ether to give **21**: 327 mg (72%); viscous oil; IR ($CHCl_3$) 1770 cm^{-1}; ^1H NMR δ 1.68–3.42 (9 H, m), 2.29 (3 H, s, OAc), 2.33 (3 H, s, NCH_3), 3.52 (3 H, s, OCH_3), 3.74 (3 H, s, OCH_3), 4.79 (d, J = 7.2 Hz, H-7), 5.75 (d, J = 7.2 Hz, H-8), 6.74, 6.98 (2 H, AB q, J = 8.0 Hz, Ar H).

Reaction of 21 with MP. In Acetonitrile. To a stirred solution of **21** (100 mg, 0.28 mmol) in 4 mL of acetonitrile was added an acetonitrile solution of MP (35 mg, 0.42 mmol). The resulting solution was stirred at room temperature for 30 min, and then the solvent was removed in vacuo without heating. Column chromatography of the residue on alumina with ether–hexane (1:2) gave thermally unstable **22**: 72 mg (58%); pale yellow crystals; IR ($CHCl_3$) 1775, 1680 cm^{-1}; ^1H NMR δ 1.84–2.15 (2 H, m), 2.38 (3 H, s, OAc), 2.59 (3 H, s, NCH_3), 2.64–3.68 (4 H, m), 3.53 (3 H, s, OCH_3), 3.60 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 4.33 (d, J = 12.0 Hz, H-19), 5.67 (br s, H-5), 5.78 (dd, J = 9.6, 1.8 Hz, H-7), 6.08 (br t, J = 5.2 Hz, H-9), 6.24 (d, J = 9.6 Hz, H-8), 6.86, 7.02 (2 H, AB q, J = 8.0 Hz, Ar H), 7.24 (d, J = 12.0 Hz, H-18).

A solution of **22** (60 mg, 0.14 mmol) in chloroform (1 mL) was heated at 50 °C for 5 min, and then subjected to preparative TLC on silica gel with ethyl acetate–hexane (1:2) to give **24**: 27 mg (64%); pale yellow oil; IR ($CHCl_3$) 1775 cm^{-1}; ^1H NMR δ 2.48 (3 H, s, OAc), 3.93 (6 H, s, 2 OCH_3), 7.15–7.81 (6 H, m), 8.63 (d, J = 2.6 Hz, H-5); MS, m/z 296 (M^+, 47), 254 (98), 239 (48), 149 (77), 83 (100), 57 (74).

In Benzene. A mixture of **21** (55 mg, 0.15 mmol) and MP (18 mg, 0.23 mmol) in benzene (4 mL) was stirred at room temperature for 3 h and a similar workup gave **22** (21 mg, 31%).

In Methanol. A mixture of **21** (80 mg, 0.28 mmol) and MP (35 mg, 0.42 mmol) in 6 mL of methanol was stirred at room temperature for 10 min, and then the quick workup as described above afforded thermally unstable **25**: 97 mg (91%); colorless crystals; IR ($CHCl_3$) 1768, 1675 cm^{-1}; ^1H NMR δ 1.84–2.19 (2 H, m), 2.38 (3 H, s, OAc), 2.48–3.58 (6 H, m), 2.59 (3 H, s, NCH_3), 3.22 (3 H, s, OCH_3), 3.28 (3 H, s, OCH_3), 3.61 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 4.34 (d, J = 12.8 Hz, H-19), 5.76 (d, J = 9.8 Hz, H-7 or H-8), 5.98 (br t, J = 4.0 Hz, H-9), 6.25 (d, J = 9.8 Hz, H-8 or 7), 6.86, 6.97 (2 H, AB q, J = 8.0 Hz, Ar H), 7.26 (d, J = 12.8 Hz, H-18).

Adduct **25** decomposed at 71 °C during measurement of the melting point to give **24**.

Reaction of 21 with DMAD. In Acetonitrile. A mixture of **21** (93 mg, 0.26 mmol) and DMAD (55 mg, 0.39 mmol) in 7 mL of acetonitrile was stirred at room temperature for 30 min, and a similar workup afforded thermally unstable adduct **23**: 78 mg (60%); pale yellow crystals; IR ($CHCl_3$) 1775, 1745, 1680 cm^{-1}; ^1H NMR δ 1.86–3.08 (4 H, m), 2.38 (3 H, s, OAc), 2.62 (3 H, s, NCH_3), 3.40–3.65 (2 H, m), 3.54 (3 H, s, OCH_3), 3.58 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 4.43 (s, H-19), 5.69 (br s, H-5), 5.80 (dd, J = 9.6, 1.8 Hz, H-7), 6.09 (br t, J = 5.2 Hz, H-9), 6.24 (d, J = 9.6 Hz, H-8), 6.86, 7.02 (2 H, AB q, J = 8.0 Hz, Ar H).

Adduct **23** decomposed at 60 °C during measurement of the melting point to give **24**.

In Benzene. A reaction of **21** (55 mg, 0.15 mmol) and DMAD (32 mg, 0.23 mmol) in 4 mL of benzene at room temperature for 5 h afforded 36 mg (47%) of **23**.

In Methanol. A solution of **21** (80 mg, 0.28 mmol) and DMAD (80 mg, 0.56 mmol) in 7 mL of methanol was stirred at room temperature for 5 min, and then a workup similar to that above gave thermally unstable **26**: 103 mg (86%); colorless crystals; IR ($CHCl_3$) 1775, 1745, 1680 cm^{-1}; ^1H NMR δ 1.84–2.23 (2 H, m), 2.40 (3 H, s, OAc), 2.45–3.68 (6 H, m), 2.62 (3 H, s, NCH_3), 3.23 (3 H, s, OCH_3), 3.27 (3 H, s, OCH_3), 3.58 (3 H, s, OCH_3), 3.80 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 4.42 (s, H-19), 5.76 (d, J = 9.8 Hz, H-7 or H-8), 6.01 (m, H-9), 6.26 (d, J = 9.8 Hz, H-8 or H-7), 6.86, 7.08 (2 H, AB q, J = 8.0 Hz, Ar H); MS, m/z 497 ($M^+ - CH_3OH$, 6), 296 (29), 254 (50), 186 (100), 82 (41).

Adduct **26** decomposed at 73–75 °C during measurement of the melting point to give **24**.

Reaction of Neopinone Dimethyl Ketal (27) with MP. A mixture of **27**[4] (115 mg, 0.34 mmol) and MP (281 mg, 3.35 mmol) in 6 mL of acetonitrile was stirred at room temperature for 8 h. Then 281 mg (3.35 mmol) of MP was added, and the mixture was stirred for an additional 4 h. After evaporation of the solvent, the residue was chromatographed on silica gel with ethyl acetate–hexane (1:2) to give adduct **28**: 67 mg (48%); viscous oil; IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR δ 1.76–3.24 (6 H, m), 2.68 (3 H, s, NCH_3), 2.91 (3 H, s, OCH_3), 3.50 (3 H, s, OCH_3), 3.60 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 4.41 (d, J = 12.8 Hz, H-19), 4.79 (s, H-5), 5.60 (dd, J = 8.0, 3.8 Hz, H-8), 6.08 (d, J = 9.6 Hz, H-9), 6.37 (d, J = 9.6 Hz, H-10), 6.64 (2 H, s, Ar H), 7.30 (d, J = 12.8 Hz, H-18); MS (30 eV), m/z 427 (M^+, 26), 343 (19), 257 (100), 214

(91), 198 (44), 119 (46), 83 (48).

Reaction of 27 with DMAD. A mixture of **27** (400 mg, 1.16 mmol) and DMAD (1.65 g, 11.7 mmol) in 20 mL of methanol was stirred at room temperature for 8 h. More DMAD (1.65 g, 11.7 mmol) was added, and the mixture was stirred for an additional 4 h. A workup as described above followed by recrystallization from CH_2Cl_2–ether afforded **29**: 300 mg (53%); colorless crystals; mp 175–177 °C; IR ($CHCl_3$) 1740, 1680 cm^{-1}; ^1H NMR δ 1.74–3.24 (6 H, m), 2.68 (3 H, s, NCH_3), 2.92 (3 H, s, OCH_3), 3.48 (3 H, s, OCH_3), 3.58 (3 H, s, OCH_3), 3.82 (3 H, s, OCH_3), 3.88 (3 H, s, OCH_3), 4.47 (s, H-19), 4.75 (s, H-5), 5.61 (dd, J = 8.0, 3.8 Hz, H-8), 6.10 (d, J = 9.6 Hz, H-9), 6.37 (d, J = 9.6 Hz, H-10), 6.63 (2 H, s, Ar H); ^{13}C NMR δ 167.6 (s), 165.4 (s), 154.0 (s), 145.0 (s), 143.4 (s), 140.2 (s), 129.2 (s), 124.5 (d), 124.1 (d), 123.5 (s), 120.9 (d), 118.0 (d), 113.3 (d), 100.5 (s), 92.9 (d), 84.5 (d), 56.7 (q), 52.6 (q), 50.9 (q), 50.6 (q), 48.9 (t), 48.4 (q), 48.3 (s), 37.4 (q), 35.6 (t), 30.2 (t); MS, m/z 485 (M^+, 78), 286 (48), 211 (49), 186 (49), 74 (54), 59 (100). Anal. ($C_{26}H_{31}NO_8$): C, H, N.

A reaction of **27** (85 mg, 0.24 mmol) and DMAD (703 mg, 4.95 mmol) in 6 mL of acetonitrile at room temperature (24 h) also afforded 50 mg (42%) of **29**.

Catalytic Hydrogenation of 29. A solution of **29** (50 mg, 0.103 mmol) in methanol (10 mL) was hydrogenated over PtO_2 (30 mg) under an atmospheric pressure of hydrogen and gave 49 mg (97%) of **16** which was identified by IR and ^1H NMR spectra.

Reaction of Northebaine (30) with MP. To a stirred solution of **30**[34] (1.50 g, 5.05 mmol) in 30 mL of acetonitrile was added MP (466 mg, 5.55 mmol) at 0 °C, and the resulting solution was stirred at room temperature for 30 min. Evaporation and column chromatography on silica gel with ethyl acetate–hexane (1:2) followed by recrystallization from the same solvents gave **31**: 1.87 g (97%); colorless needles; mp 208–209 °C; IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR δ 1.74–2.33 (2 H, m, H-15), 3.06 (2 H, d, J = 4.0 Hz, H-10), 3.28–3.45 (2 H, m, H-16), 3.59 (3 H, s, OCH_3), 3.65 (3 H, s, OCH_3), 3.84 (3 H, s, OCH_3), 4.34 (t, J = 4.0 Hz, H-9), 4.74 (d, J = 12.8 Hz, H-9), 5.02 (d, J = 6.5 Hz, H-7), 5.28 (s, H-5), 5.58 (d, J = 6.5 Hz, H-8), 6.57, 6.69 (2 H, AB q, J = 8.0 Hz, Ar H), 7.42 (d, J = 12.8 Hz, H-18); MS, m/z 381 (M^+, 100), 366 (38), 267 (54), 114 (28). Anal. ($C_{22}H_{23}NO_5$): C, H, N.

Reaction of 30 with DMAD. A mixture of **30** (1.00 g, 3.36 mmol) and DMAD (526 mg, 3.70 mmol) in acetonitrile (40 mL) was stirred at room temperature for 30 min. The same workup as above and recrystallization from ethyl acetate–hexane gave **32**: 1.40 g (95%); colorless needles; mp 191–194 °C; IR ($CHCl_3$) 1740, 1690 cm^{-1}; ^1H NMR δ 1.72–2.33 (2 H, m, H-15), 3.10 (2 H, fused d, H-10), 3.21–3.52 (2 H, m, H-16), 3.58 (3 H, s, OCH_3), 3.63 (3 H, s, OCH_3), 3.83 (3 H, s, OCH_3), 3.92 (3 H, s, OCH_3), 4.32 (m, H-9), 4.84 (s, H-19), 5.02 (d, J = 6.5 Hz, H-7), 5.27 (s, H-5), 5.58 (d, J = 6.5 Hz, H-8), 6.57, 6.69 (2 H, AB q, J = 8.0 Hz, Ar H); MS, m/z 439 (M^+, 100), 380 (26), 267 (40), 254 (34), 242 (36), 172 (55), 140 (53). Anal. ($C_{24}H_{25}NO_7$): C, H, N.

Acknowledgment. We are grateful to Mr. Shigenori Motohiro for the contribution to the early stage of this research.

Registry No. **1**, 115-37-7; **3**, 18651-71-3; **7**, 78914-28-0; **7a**, 83967-43-5; **8**, 78923-43-0; **8a**, 80410-25-9; **9**, 78914-29-1; **10**, 78914-30-4; **11**, 84025-04-7; **12**, 83967-44-6; **13**, 83967-45-7; **14**, 83984-01-4; **15**, 83967-46-8; **16**, 83967-47-9; **17**, 73294-93-6; **18**, 83967-48-0; (±)-**19**, 83967-49-1; **20**, 63944-52-5; **21**, 83967-50-4; **22**, 83984-02-5; **23**, 83984-04-7; **24**, 47192-97-2; **25**, 83984-03-6; **26**, 83984-05-8; **27**, 32398-20-2; **28**, 80410-27-1; **29**, 83967-51-5; **30**, 2579-67-1; **31**, 83967-52-6; **32**, 83967-53-7; EP, 623-47-2; MP, 922-67-8; DMAD, 762-42-5; benzene, 71-43-2; acetonitrile, 75-05-8; methanol, 67-56-1.

Thebaine and Acetylenic Dienophiles

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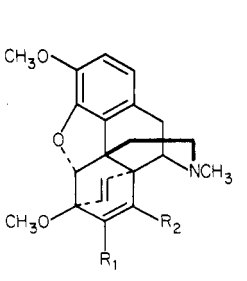
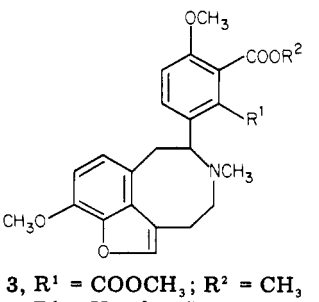
Received July 16, 1982

Thebaine and methyl propiolate (MP) in THF gave the enol ether **6** instead of the expected normal Diels–Alder adduct. Hydrolysis of **6** gave the ketone **8**, whose structure was established by a single-crystal X-ray structure determination. When MeOH was substituted for THF, the same reactants gave the ketal, **10**, as the major product accompanied by **6**. Treatment of **10** with base yielded the isomer **13** which gave **14** on hydrolysis. Addition of MP to **14** furnished **13**. Reduction of the ketone **8** with $NaBH_4$ gave the alcohol **15** characterized as its acetate, **16**. Catalytic reduction of **16** in the presence of Adams catalyst gave the dihydro ester **17**. The addition of other acetylenic dienophiles such as dimethyl acetylenedicarboxylate, ethyl propiolate, and 3-butyn-2-one to thebaine gave either enol ethers analogous to **6** or ketals corresponding to **10**. It appears that cleavage of the piperidine ring of thebaine with acetylenic dienophiles is general.

Rapoport and Sheldrick[1] found that heating thebaine and dimethyl acetylenedicarboxylate (DMAD) in benzene at 50 °C for 1 h gave the normal Diels–Alder adduct, **1**, in 90% yield but that under comparable conditions, ethyl propiolate (EP) furnished **2** in only 6% yield. They reported that these adducts readily underwent a thermal rearrangement to afford **3** and **4**, respectively. In connection with out continuing efforts to prepare opioids of biological interest from thebaine,[2] we had occasion to reexamine the reaction of thebaine with a number of acetylenic dienophiles. This turned out to be far more complex than originally reported,[1] and some of our observations were published in a preliminary communication.[3] While our work was in progress, Hayakawa et al.



1, $R^1 = R^2 = COOCH_3$
2, $R^1 = COOCH_2H_5$, $R^2 = H$



3, $R^1 = COOCH_3$; $R^2 = CH_3$
4, $R^1 = H$; $R^2 = C_2H_5$
5, $R^1 = H$; $R^2 = CH_3$

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0022-3263/83/1948-0173$01.50/0