(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 $\delta$ 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 $\delta$ 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 $\delta$ 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 $\delta$ 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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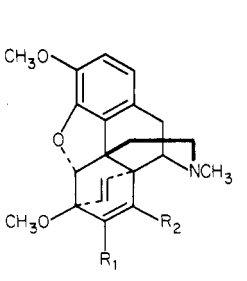
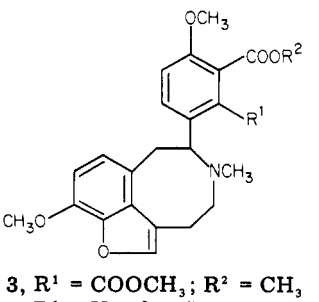
Thebaine and methyl propiolate (MP) in THF gave the enol ether **6** instead of the expected normal Diels–Alder adduct. Hydrolysis of **6** gave the ketone **8**, whose structure was established by a single-crystal X-ray structure determination. When MeOH was substituted for THF, the same reactants gave 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, $R^1 = COOCH_2H_5$, $R^2 = H$



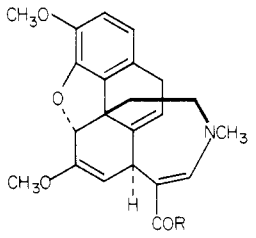

3, $R^1 = COOCH_3$; $R^2 = CH_3$
4, $R^1 = H$; $R^2 = C_2H_5$
5, $R^1 = H$; $R^2 = CH_3$

(1) Rapoport, H.; Sheldrick, P. *J. Am. Chem. Soc.* **1963**, *85*, 1636.
(2) Bidlack, J. M.; Abood, L. G.; Osei-Gyimah, P.; Archer, S. *Proc. Natl. Acad. Sci. U.S.A.* **1981**, *78*, 636. Osei-Gyimah, P.; Archer, S.; Gillan, M. G. C.; Kosterlitz, H. W. *J. Med. Chem.* **1981**, *24*, 212.

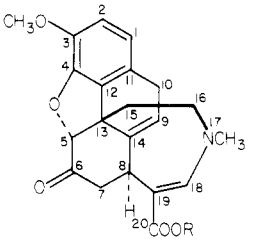
0022-3263/83/1948-0173$01.50/0 

described the results of a similar study.[4] Some of our findings differed from those reported by these investigators.

When thebaine was allowed to react with methyl propiolate (MP) in THF at 35 °C for 24 h, none of the normal Diels–Alder adduct corresponding to **2** was obtained. Instead, the enol ether **6** was isolated in 38% yield. Hydrolysis with the aid of 6 N HCl afforded the ketone **8**. The structure of the ketone **8** was secured by a single-crystal X-ray determination.[3]



**6**, R = $OCH_3$
**7**, R = $CH_3$



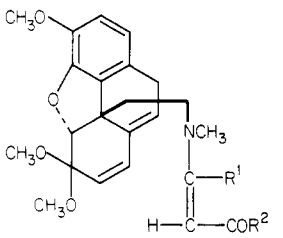
**8**, R = $CH_3$
**9**, R = $C_2H_5$

The IR and NMR spectra of **6** are in agreement with the assigned structure. The outstanding features of the $^1H$ NMR spectrum are the signals for the H-9 proton which appears as a doublet of doublets at $\delta$ 5.92 and that of the H-18 proton which is a downfield singlet appearing at $\delta$ 7.35 and which seems to be characteristic of the $\beta$ proton in $\beta$-amino acrylates.[4] Earlier and independently, Hayakawa et al.[4] assigned structures **6** and **8** primarily on the basis of spectroscopic data.

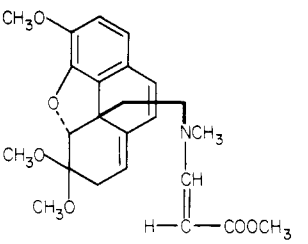
When thebaine and MP were allowed to react in refluxing THF for 40 h, the adduct, **6**, was isolated in 26% yield accompanied by the thermal rearrangement product, **5**, obtained in 12% yield. The spectral properties of **5** closely resemble those of its homologue **4**. The presence of this compound suggested strongly that the normal Diels–Alder product was formed but that prolonged heating effected the rearrangment. It should be noted that this thermal rearrangement occurred at lower temperatures than those employed by Rapoport and Sheldrick.[1]

In contrast to the report of Hayakawa et al.[4] in which MeOH, thebaine, and MP gave **6** quantitatively, we found that after 30 min in methanol at room temperature the same reactants gave **6** in only 32% yield. The major product, isolated in 62% yield, was the ether-soluble ketal **10**. The $^1H$ NMR spectrum showed signals for four methoxy groups, the coupled vinyl protons H-7 and H-8 ($J$ = 10 Hz), the H-9 proton at $\delta$ 5.94, and the H-18 proton at $\delta$ 7.35 coupled to the H-19 proton at $\delta$ 4.40 ($J$ = 13 Hz). The latter coupling constant suggested that these protons were trans to each other as in other aminoacrylate esters.[5] The IR and UV spectra supported structure **10** also. When alcohols such as *tert*-butyl alcohol or trichloroethanol were substituted for MeOH, the adduct **6** was the major product formed; no ketals corresponding to **10** could be isolated. In benzyl alcohol and (trimethylsilyl)ethanol, thebaine was recovered unchanged.

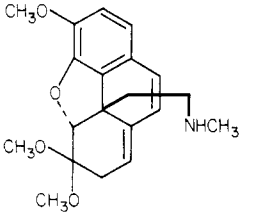
When DMAD and thebaine were allowed to react in refluxing THF, the normal Diels–Alder adduct **1** was obtained. When the reaction was carried out in MeOH at room temperature, the ketal **11** was isolated in 35% yield. The $^1H$ NMR spectrum of this ketal did not possess a signal for the downfield H-18 proton, and the H-19 proton now appeared as a singlet at $\delta$ 4.45. The other signals in the NMR spectrum as well as the IR and UV spectra supported the structural assignment. The reaction of thebaine with 3-butyn-2-one in methanol afforded the enol ether **7** in 34% yield accompanied by an oil whose mass and $^1H$ NMR spectrum were consistent with structure **12**. In THF, **7** was obtained in 46% yield.



**10**, $R^1$ = H, $R^2$ = $OCH_3$
**11**, $R^1$ = $COOCH_3$, $R^2$ = $OCH_3$
**12**, $R^1$ = H, $R^2$ = $CH_3$



**13**



**14**

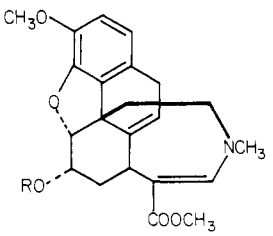
When **10** was treated with a slight excess of a strong acid such as HCl or *p*-toluenesulfonic acid, it cyclized almost instantaneously to the enol ether **6**. Longer exposure to strong acids resulted in the hydrolysis of **6** to the ketone **8**. Thebaine and EP in methanol presumably first formed the ketal analogous to **13** which was not isolated. In this instance, the reaction mixture was treated with HCl to give the ketone **9** directly.

When the ketal **10** was heated under reflux for 2 h in dilute methanol/NaOH, an isomeric compound was obtained whose structure was shown to be **13** on the basis of elementary analyses and spectroscopic data. The isomer was yellow rather than white, and the UV spectrum showed two maxima, $\lambda$ 282 nm (log $\epsilon$ 4.49) and 326 (3.81). The UV spectrum of the precursor ketal **10** showed one maximum $\lambda$ 280 nm (log $\epsilon$ 4.49) and a shoulder at 225 nm. The $^1H$ NMR spectrum had signals for only two protons in the $\delta$ 3.00–3.30 region which were assigned to the H-16 protons rather than signals for four protons as found in the spectrum of **10**. The H-10 proton in the spectrum of **13** appeared as a doublet at $\delta$ 6.30 coupled to the H-9 proton.

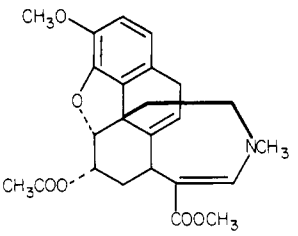
Prolonged basic hydrolysis of **13** or brief treatment with strong acid converted it to the oily secondary amine **14**, characterized as the crystalline fumarate salt. The spectral data were in agreement with the structural assignment. Furthermore, when the oily base **14** was allowed to react with MP, it was converted back to **13**, thus confirming the structure.

Sodium borohydride reduction of the ketone **8** furnished the corresponding alcohol **15**, which gave the crystalline acetate **16**. The presence of the H-6 proton signal in the $\delta$ 4.00–4.40 region suggested that it was a 6-$\beta$ proton.[6] Catalytic reduction of the acetate in the presence of Adams

(3) Singh, A.; Archer, S.; Hoogsteen, K.; Hirschfield, J. *J. Org. Chem.* **1982**, *47*, 752.
(4) Hayakawa, K.; Motohiro, S.; Fujii, I.; Kanematsu, K. *J. Am. Chem. Soc.* **1981**, *103*, 4605.
(5) Herkes, F. E.; Simmons, H. E. *J. Org. Chem.* **1973**, *38*, 2845. These authors found that tertiary amines added to MP to give carbomethoxy vinylalkylammonium compounds in which the vinyl protons are trans ($J$ = 13.8–14.0 Hz). Addition to DMAD occurred in a similar manner to give the corresponding maleate esters.
(6) Okuda, S.; Yamaguchi, S.; Kawazoe, Y.; Tsuda, K. *Chem. Pharm. Bull.* **1964**, *13*, 104.



15, R = H
16, R = $CH_3CO$



17

catalyst gave the dihydro ester **17**. Elementary analyses and the mass spectrum showed that 1 mol of hydrogen was absorbed. Since the signal for the H-9 proton remained while that for the C-18 proton disappeared, structure **17** was assigned to the dihydro compound. The UV spectrum of **17** showed that the maximum at 296 nm, due to the aminoacrylate function found in **16**, was absent, confirming this structural assignment.

Ring opening of a heterocyclic base by an acetylenic dienophile in the presence of an alcohol is unusual but not unprecedented. Winterfeldt and Dillinger[7] found that DMAD reacted with *N*-benzylaziridine in *tert*-butyl alcohol at room temperature to give the benzyl (*β*-*tert*-butoxyethyl)aminomaleate. As discussed above, thebaine and MP gave only **6** in *tert*-butyl alcohol.

## Experimental Section

Melting points were determined by using a Laboratory Device Melt-Temp apparatus and are corrected. The $^1H$ NMR spectra were run on a 100-MHz Varian HA-100 spectrometer with $CDCl_3$ as the solvent and $(CH_3)_4Si$ as the internal standard. The mass spectra were run on a JEOL O1SC mass spectrometer at the Sterling-Winthrop Research Institute. We thank Dr. S. Clemans and Ms C. Martini for these determinations. Microanalyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI. All analytical results were within ±0.4% of the theoretical values. [Analytical data, (C, H, N) were obtained for compounds **1**, **3**, **6**–**11**, and **13**–**17**.]

**Reaction of Thebaine and Methyl Propiolate. (A) In Tetrahydrofuran at 35 °C.** A solution of 5.0 g (1.6 mmol) of thebaine and 2 mL (2.3 mmol) of methyl propiolate in 100 mL of dry THF was stirred at 35–40 °C for 24 h. The reaction mixture was concentrated in vacuo to about 20 mL before 10 mL of ether was added. Chromatography on alumina with ether as the eluant furnished 2.4 g (30%) of the adduct **6**: mp 160–162 °C (lit.[4] mp 160–162 °C); $[\alpha]_D$ −325° ($CHCl_3$); UV (EtOH) $\lambda_{max}$ 296 nm (log $\epsilon$ 4.3); IR (KBr) 1675 $cm^{-1}$; $^1H$ NMR $\delta$ 1.90 (m, 2 H, H-15), 2.92 (s, 3 H, $NCH_3$), 3.04–3.40 (m, 4 H, H-10, H-16), 3.58 (s, 3 H, 6-$OCH_3$), 3.74 (s, 3 H, $COOCH_3$), 3.86 (s, 3 H, 3-$OCH_3$), 4.54 (d, 1 H, $J$ = 5 Hz, H-8), 4.98 (s, 1 H, H-5), 5.25 (d, 1 H, $J$ = 5 Hz, H-7), 5.92 (dd, 1 H, H-9), 6.65 (s, 2 H, H-1, H-2), 7.35 (s, 1 H, H-18).

Elution of the column with ethanol furnished 1.0 g of unreacted thebaine.

**(B) In Tetrahydrofuran at Reflux.** A solution of 10 g (3.2 mmol) of thebaine and 3.0 mL (3.6 mmol) of methyl propiolate in 200 mL of THF was refluxed for 40 h. The solvent was removed in vacuo. The residue was treated with 100 mL of ether. The insoluble, sticky material was dissolved in 5 mL of MeOH and treated with 10 mL of ether. The crystals that separated were filtered to give 0.2 g of **6**. The filtrate was combined with the ether solution, and after evaporation the residue was chromatographed on 150 g of alumina with ether as the eluant. The eluate was concentrated to 50 mL and cooled. An additional 3.1 g of the adduct **6** was obtained, making the total yield 3.3 g (26%). On further cooling for 2 days, 1.5 g (12%) of the thermal adduct **5** was obtained: mp 125 °C (after recrystallization from MeOH); UV (EtOH) $\lambda_{max}$ 236 nm (log $\epsilon$ 4.11), 255 (3.92), 289 (3.77); $^1H$ NMR $\delta$ 2.07 (s, 3 H, $NCH_3$), 2.66–3.80 (m, 7 H), 3.86, 3.91, 4.00 (9 H, 3 $OCH_3$), 6.73–7.70 (m, 6 H, aromatic H).

(7) Winterfeldt, E.; Dillinger, H. J. *Chem. Ber.* **1960**, *99*, 1558.

**(C) In Methanol.** A suspension of 35.0 g (0.11 mol) of thebaine in 1.5 L of MeOH was stirred at room temperature while 11.0 mL (0.13 mol) of methyl propiolate was added dropwise. After stirring at room temperature for 30 min, the solvent was removed, and the residue was dissolved in 300 mL of ether. After 5 h, the enol ether **6** was collected; 14.0 g (31.8%). The filtrate was concentrated to 70 mL and cooled. After 2 days the ketal **10** was collected by filtration: 25.0 g (61.9%); mp 117–118 °C (after recrystallization from MeOH); $[\alpha]_D$ −154° ($CHCl_3$); IR 1675 $cm^{-1}$; UV (EtOH) $\lambda_{max}$ 280 nm (log $\epsilon$ 4.49), 225 (sh, 4.26); $^1H$ NMR $\delta$ 1.83 (t, 2 H, H-15) 2.70 (s, 3 H, $NCH_3$), 2.92 (s, 3 H, $OCH_3$), 3.55 (s, 3 H, $OCH_3$), 3.64 (s, 3 H, $OCH_3$), 3.90 (s, 3 H, $OCH_3$), 3.00–3.50 (m, 4 H, H-10, H-16), 4.40 (d, 1 H, $J$ = 13 Hz, H-19), 4.80 (s, 1 H, H-5), 5.62 (d, 1 H, $J$ = 10 Hz, H-7), 5.94 (dd, 1 H, H-9), 6.60 (d, 1 H, $J$ = 10 Hz, H-8), 6.65 (s, 2 H, H-1, H-2), 7.35 (d, 1 H, $J$ = 13 Hz, H-18).

**(D) In *tert*-Butyl Alcohol.** A suspension of 5.0 g (16 mmol) of thebain in 100 mL of dry *t*-BuOH was treated with 1.7 mL (19 mmol) of methyl propiolate. After 40 h at room temperature the mixture was worked up as above to give a total of 2.5 g (44%) of the enol ether adduct **6**. No ketal was found.

**(E) In Trichloroethanol.** When 100 mL of this alcohol was substituted for *tert*-butyl alcohol and the solution was left at room temperature for 40 h and worked up in the usual way, a total of 4.6 g (73%) of the adduct **6** was obtained.

When either benzyl alcohol or (trimethylsilyl)ethanol was used as the solvent under similar conditions, thebaine was recovered unchanged.

**Reaction of Thebaine with Dimethyl Acetylenedicarboxylate (DMAD). (A) In Tetrahydrofuran.** Dimethyl acetylenedicarboxylate (5 g, 3.5 mmol) was added to a stirred suspension of 10.0 g (3.2 mmol) of thebaine in 100 mL of THF. After being refluxed for 16 h, the reaction mixture was concentrated to dryness. The residue was covered with 30 mL of benzene, cooled, and filtered to furnish 5.4 g of the adduct 1, mp 144 °C (after recrystallization from MeOH) (lit.[1] mp 141–142 °C). Cooling the benzene filtrate gave an additional 2.0 g of adduct: total yield 7.4 g (51%); IR (KBr) 1720, 1730 $cm^{-1}$; $^1H$ NMR, $\delta$ 1.67–2.06 (m, 2 H, H-15), 2.33 (s, 3 H, $NCH_3$), 2.40–2.70 (m, 3 H, H-9, H-10), 3.00–3.50 (br t, 2 H, H-16), 3.60, 3.76, 3.80, 3.83 (4 s, 12 H, 4 $OCH_3$), 4.76 (s, 1 H, H-5), 5.56 (d, 1 H, $J$ = 8 Hz vinyl H), 6.30 (d, 1 H, $J$ = 8 Hz vinyl H), 6.70 (d, 2 H), H-1, H-2).

**(B) In Methanol.** The same quantitites of reagents were used in 400 mL of MeOH. After the mixture was stirred 15 min at room temperature, the MeOH was removed in vacuo, and the residue was dissolved in 100 mL of ether. After being allowed to stand overnight, the solution deposited 5.5 g (35%) of the ketal **11**, mp 172–174 °C (after recystallization from MeOH). The ethereal filtrate was evaporated to dryness and the residue was dissolved in 30 mL of benzene. After 1 week at 4 °C, no crystalline material was deposited: UV (EtOH) $\lambda_{max}$ 284 (log $\epsilon$ 4.27), 225 (4.09); IR (KBr) 1690, 1740 $cm^{-1}$; $^1H$ NMR $\delta$ 1.83 (t, 2 H, H-15), 2.75 (s, 3 H, $NCH_3$), 2.93, 3.50, 3.66, 3.81, 3.88 (5 s, 15 H, 5 $OCH_3$), 3.00–3.40 (m, 4 H, H-10, H-16), 4.45 (s, 1 H, H-19), 4.75 (s, 1 H, H-5), 5.65 (d, 1 H, $J$ = 10 Hz, H-8), 5.95 (dd, 1 H, H-9), 6.63 (d, 1 H, $J$ = 10 Hz, H-7), 6.70 (s, 2 H, H-1, H-2).

**Cyclization of the Ketal 10. (A) To the Enol Ether 6.** A solution of 1.0 g (2.3 mmol) of the ketal **10** and 450 mg (2.3 mmol) of *p*-toluenesulfonic acid in 10 mL of MeOH containing 1.0 mL of $H_2O$ was evaporated to dryness almost immediately. The residue was dissolved in 10 mL of $H_2O$, and the solution was made slightly basic with a $Na_2CO_3$ solution. The crystalline material which separated with filtered, washed with $H_2O$, dried, and crystallized from MeOH to furnish 500 mg (50%) of the enol ether **6** (mp 160–162 °C) identical in all respects with an authentic sample, prepared as described above. The conversion could also be carried out in about the same yield by using 1.0 mL of 6 N HCl instead of pTSA.

**(B) To the Ketone 8.** The ketal **10** (1 g, 2.3 mmol) was dissolved in 10 mL of MeOH, and the solution was added to 5 mL of 6 N HCl. The mixture was stirred at room temperature for 5 min, made slightly basic with sodium carbonate solution, and filtered to give 600 mg (67%) of product. After crystallization from dioxane, **8** melted at 225 °C (lit.[4] mp 231–233 °C): $[\alpha]_D$ −307° ($CHCl_3$); mass spectrum, $m/e$ 381 ($M^+$); UV (EtOH) $\lambda_{max}$ 293 nm (log $\epsilon$ 4.28), IR (KBr) 1725, 1665 $cm^{-1}$; $^1H$ NMR $\delta$ 1.70–2.13 (m, 2 H, H-15), 2.40–2.90 (m, 2 H, H-7), 3.03 (s, 3 H, $NCH_3$), 3.20 (d,

2 H, H-10), 3.48 (m, 2 H, H-16), 3.73, 3.93 (2 s, 6 H, 2 $OCH_3$), 4.42 (br t, 1 H, H-8), 5.06 (s, 1 H, H-5), 5.90 (dd, 1 H, H-9), 6.68 (s, 2 H, H-1, H-2), 7.42 (s, 1 H, H-18).

The same ketone was prepared from thebaine and MP. To a stirred suspension of 8.0 g (25.7 mmol) of thebaine in 400 mL of MeOH was added 2.2 mL (26.2 mmol) of MP dropwise. The reaction mixture was stirred at room temperature for 30 min and then evaporated to dryness in vacuo. The residue was covered with 150 mL of ether, and the crude enol ether **6** was filtered off. The filtrate was concentrated to dryness, and the residue was combined with the crystalline material. The whole was dissolved in 80 mL of MeOH, and the solution was added to a stirred solution of 40 mL (240 mmol) of 6 N HCl. After 15 min, the solution was carefully neutralized with aqueous sodium bicarbonate until the ketone **8** had separated completely. The crystals were filtered, washed with $H_2O$ and then with a small amount of cold MeOH, and dried; yield 6.9 g (70%). The product was identical in all respects with the sample prepared above.

**Reaction of Thebaine with Ethyl Propiolate. Preparation of the Ketone 9.** To a stirred suspension of 30.0 g (96 mmol) of thebaine in 1.5 L of MeOH was added 9.4 (96 mmol) mL of ethyl propiolate dropwise. After 2 h at room temperature, the reaction mixture was concentrated in vacuo to 300 mL and then was added dropwise over 15 min to a stirred solution of 150 mL of 6 N HCl. The solution was made basic with sodium carbonate solution whereupon a tacky semicrystalline mass separated. The supernatant was carefully decanted, and 200 mL of MeOH was added to the residue which crystallized after stirring at room temperature for 2 h. The crystals were filtered, washed successively with $H_2O$ and MeOH, and then dried; yield 32.5 g (85%). After recrystallization from EtOH, pure **9** melted at 175–176 °C (lit.[4] mp 170–172 °C): IR (KBr) 1718, 1620 $cm^{-1}$; mass spectrum, *m/e* 395 ($M^+$); $^1H$ NMR $\delta$ 1.26 (t, 3 H, $OCH_2CH_3$), 1.60–2.20 (m, 2 H, H-15), 2.20–2.90 (m, 2 H, H-7), 3.00 (s, 3 H, $NCH_3$), 3.20 (d, 2 H, H-10), 3.40–3.62 (m, 2 H, H-16), 3.90 (s, 3 H, $OCH_3$), 4.18 (q, 2 H, $OCH_2CH_3$), 4.42 (br t, 1 H, H-8), 5.04 (s, 1 H, H-5), 5.92 (t, 1 H, H-9), 6.60 (s, 2 H, H-1, H-2), 7.42 (s, 1 H, H-19).

**Isomerization of 10 to the Ketal 13.** The ketal **10** (5 g) was dissolved in 100 mL of MeOH, and a solution of 1.3 g of NaOH in 10 mL of $H_2O$ was added. The mixture was heated under reflux for 2 h and then concentrated to 30 mL. It was cooled, diluted with 50 mL of $H_2O$ and allowed to stand. A semicrystalline mass separated. The supernatant was decanted, and the residue was washed with $H_2O$ by decantation and then dissolved in 20 mL of MeOH. When the mixture was allowed to stand, the ketal **13** separated; yield 4.0 g (80%). After crystallization from EtOH, the pale yellow crystals melted at 125–127 °C: $[\alpha]_D$ +265° ($CHCl_3$); UV (EtOH) $\lambda_{max}$ 282 (log $\epsilon$ 4.49), 326 (3.81); $^1H$ NMR $\delta$ 1.70–2.60 (m, 4 H, H-7, H-15), 2.66 (s, 3 H, $NCH_3$), 2.90, 3.50, 3.60, 3.90 (4 s, 12 H, 4 $OCH_3$), 3.00–3.30 (m, 2 H, H-16), 4.40 (d, 1 H, *J* = 13 Hz, H-19), 4.80 (s, 1 H, H-5), 5.60 (dd, 1 H, H-8), 6.00 (d, 1 H, *J* = 10 Hz, H-9), 6.30 (d, 1 H, *J* = 10 Hz, H-10), 6.60 (s, 2 H, H-1, H-2), 7.30 (d, 1 H, *J* = 13 Hz, H-18).

**Preparation of the Ketal 14. (A) From the Ketal 13.** A solution of 100 mg (0.2 mmol) of the ketal **13** and 50 mg (0.29 mmol) of *p*-toluenesulfonic acid in 2.0 mL at MeOH was allowed to stand at room temperature for 3 h. The MeOH was removed and replaced with 10 mL of $H_2O$. The aqueous solution was made basic with aqueous sodium carbonate and extracted with $CHCl_3$. The organic phase was dried and concentrated in vacuo to leave an oil, **13**: $^1H$ NMR $\delta$ 1.20 (s, 1 H, NH, exchangeable with $D_2O$), 1.60–2.06 (br t, 2 H, H-15), 2.06–2.70 (m, 7 H, $NCH_3$, s at 2.36, H-7, H-16), 2.91, 3.53, 3.90 (3 s, 9 H, 3 $OCH_3$), 5.00 (s, 1 H, H-5), 5.50–5.70 (dd, 1 H, H-8), 6.00 (d, 1 H, *J* = 10 Hz, H-9), 6.36 (d, 1 H, *J* = 10 Hz, H-10), 6.61 (s, 2 H, H-1, H-2).

The oil, dissolved in THF, was treated with a solution of fumaric acid in THF. The crystals of the fumarate salt were filtered, washed with THF, and recrystallized from MeOH–THF (1:4). The pure salt melted at 205 °C.

**(B) From the Ketal 11.** A solution of 500 mg of the ketal **11** in 30 mL of MeOH containing excess aqueous 5% KOH was refluxed for 84 h. The solvents were removed in vacuo, and the residue was dissolved in ether. The ethereal solution was washed with $H_2O$, dried, and concentrated to dryness to leave an oily base which was dissolved in THF. The solution was treated with fumaric acid in THF, and the crystals of the fumarate salt of **14** were collected and recrystallized from MeOH–THF to give 300 mg (65%) of the salt (mp 205 °C), identical with the sample described above.

**(C) From the Ketal 10.** The ketal **10** (4 g, 9.36 mmol) in 100 mL of EtOH was refluxed 20 days with a solution of 1.5 g of NaOH in 30 mL of $H_2O$. The mixture was worked up as described above to give 2.3 g (53%) of the fumarate salt of **14**.

**Conversion of 14 to 13.** A solution of 80 mg of the fumarate salt of **13** in 3 mL of $H_2O$ was converted to the free base **13**. The latter was dissolved in $CHCl_3$, dried over $Na_2SO_4$, and evaporated to dryness. The residue was dissolved in 2 mL of MeOH and treated with 2 drops of MP. After a few minutes, the reaction mixture was evaporated and the residue was dissolved in 3.0 mL of ether. When the mixture was allowed to stand in the cold overnight, there was obtained 35 mg (47%) of the ester **13**, mp 125–127 °C (after crystallization from EtOH). It was identical in all respects with the sample prepared previously.

**Preparation of the Alcohol 15 from the Ketone 8.** A solution of 4.0 g (10.5 mmol) of the ketone **8** in 100 mL of $CH_3OH$ was treated with 800 mg of $NaBH_4$. After 1 h at room temperature, the reaction mixture was concentrated in vacuo to about 30 mL, diluted with 50 mL of $H_2O$, and neutralized with acetic acid. The crystals that separated were collected, washed with $H_2O$, and recrystallized from $CH_3OH$: yield 3.6 g (90%); mp 164 °C; IR(KBr) 3900, 1640 $cm^{-1}$; $^1H$ NMR $\delta$ 1.70–2.00 (t, 2 H, H-15), 2.50–2.90 (m, 2 H, H-7), 2.94 (s, 3 H, $NCH_3$), 3.15–3.45 (m, 5 H, H-8, H-10, H-16), 3.75 (s, 3 H, $OCH_3$), 3.90 (s, 3 H, $OCH_3$), 4.00–4.40 (m, H-6, OH), 4.56 (d, 1 H, H-5), 5.85 (dd, 1 H, H-9), 6.68 (s, 2 H, H-1, H-2), 7.34 (s, 1 H, H-18).

The Alcohol **15** (500 mg) was converted to the corresponding acetate **16** by treatment in the usual way with acetic anhydride in pyridine. The acetate was crystallized from MeOH: yield 450 mg (82%); mp 235–237 °C; UV (EtOH) $\lambda_{max}$ 296 nm (log $\epsilon$ 4.28); IR (KBr) 1725, 1650 $cm^{-1}$; mass spectrum, *m/e* 425 ($M^+$); $^1H$ NMR $\delta$ 1.44 (s, 3 H, $COCH_3$), 2.50–2.88 (m, 2 H, H-7), 2.96 (s, 3 H, $NCH_3$) 3.18–3.40 (m, 2 H, H-10, H-16), 3.72, 3.86 (2 s, 6 H, 2 $OCH_3$), 4.04 (t, 1 H, H-8), 4.62 (d, 1 H, H-5), 5.50 (m, 1 H, H-6), 5.80 (m, 1 H, H-9), 6.67 (s, 2 H, H-1, H-2), 7.37 (s, 1 H, H-18).

**Catalytic Reduction of 16 to the Dihydro Ester 17.** A solution of 300 mg of the ester **16** in 40 mL of acetic acid was hydrogenated at 45 psi in the presence of 10 mg of Adams catalyst. After 5 h, the reaction was stopped, and the filtered reaction mixture was concentrated under reduced pressure. The residue was dissolved in $H_2O$ and filtered (Celite), and the clear filtrate was made slightly alkaline. The suspension was extracted with ether. Removal of the ether followed by trituration of the residue with a small amount of MeOH gave crystals of the ester, 160 mg (53%). After recrystallization from MeOH, pure **17** melted at 143–145 °C: UV (EtOH) $\lambda_{max}$ 232 (log $\epsilon$ 3.14); IR (KBr) 1713 $cm^{-1}$; mass spectrum, *m/e* 427 ($M^+$); $^1H$ NMR $\delta$ 1.34 (s, 3 H, $COCH_3$), 1.70–3.00 (m, 11 H, H-7, H-8, $NCH_3$, H-15, H-18, H-19), 3.70 (s, 3 H, $COOCH_3$), 3.85 (s, 3 H, $OCH_3$), 4.88 (d, 1 H, H-5), 5.43 (m, 1 H, H-6), 5.80 (dd, 1 H, H-9), 6.61 (s, 2 H, H-1, H-2).

**Reaction of Thebaine and 3-Butyn-2-one. Preparation of 7.** A suspension of 10.0 g (32 mmol) of thebaine in 200 mL of THF was stirred at 35–40 °C as 2.5 g (36 mmol) of 3-butyn-2-one was added dropwise. Stirring at these temperatures was continued for 60 h. The solvent was removed under reduced pressure, and the residue was covered with a small volume of ether. The crude crystalline adduct **7** weighed 8.0 g. After recrystallization from EtOH, there was obtained 5.7 g (46%) of the pure ketone **7**: mp 250 °C; IR (KBr) 1640 $cm^{-1}$; $^1H$ NMR $\delta$ 1.97 (m, 2 H, H-15), 2.26 (s, 3 H, $COOCH_3$), 3.00 (s, 3 H, $NCH_3$), 3.25 (m, 4 H, H-10, H-16), 3.58, 3.86 (2 s, 6 H, 2 $OCH_3$), 4.74 (br t, 1 H, H-8), 5.00 (s, 1 H, H-5), 5.20 (d, 1 H, H-7), 5.89 (br t 1 H, H-9), 6.67 (s, 2 H, H-1, H-2), 7.21 (s, 1 H, H-18).

When the reaction between 9.5 g of 3-butyn-2-one and 23.0 g of thebaine was carried out overnight at room temperature in 700 mL of MeOH, there was obtained 9.5 g (34%) of the adduct **7** as an ether-insoluble product. The ethereal filtrate was evaporated to leave an oily residue which was chromatographed on a column of 400 g of activated neutral alumina with ether as the eluant. There was obtained 15.0 g (50%) of the ketal, **12** as an oil: mass spectrum, *m/e* 411 ($M^+$); $^1H$ NMR 1.60–2.20 (m, 2 H, H-15, 3 H, $COCH_3$ singlet at 2.03), 2.73 (s, 3 H, $NCH_3$), 2.91 (s, 3 H, $OCH_3$), 3.00–3.50 (m, 4 H, H-10, H-16), 3.53, 3.90 (2 s, 6 H, 2 $OCH_3$), 4.73

(s, 1 H, H-5), 4.96 (d, 1 H, $J$ = 13 Hz, H-19), 5.60 (d, 1 H, $J$ = 10 Hz, H-7), 5.90 (br t 1 H, H-9), 6.60 (d, 1 H, $J$ = 10 Hz, H-8), 6.66 (s, 2 H, H-1, H-2), 7.40 (d, 1 H, $J$ = 13 Hz, H-18).

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**Registry No.** 1, 18651-71-3; (±)-5, 83967-54-8; 6, 78923-43-0; 7, 83967-55-9; 8, 78914-30-4; 9, 78914-29-1; 10, 80410-25-9; 11, 84025-04-7; 12, 83967-56-0; 13, 80410-27-1; 14, 80410-26-0; 14 fumarate, 84025-05-8; 15, 83967-57-1; 16, 83967-58-2; 17, 83967-59-3; thebaine, 115-37-7; MP, 922-67-8; DMAD, 762-42-5; EP, 623-47-2; 3-butyn-2-one, 1423-60-5; THF, 109-99-9; MeOH, 67-56-1.

# Synthesis and Reactions of *o*-Benzoquinone Monosulfonimides

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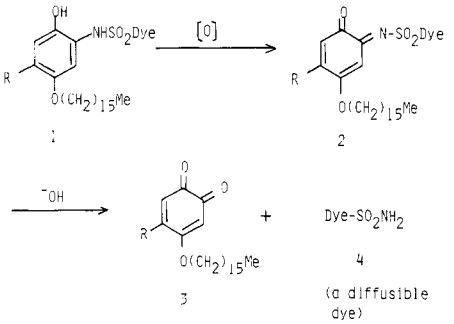
4-Alkoxy($R^2O$)-5-alkyl($R^1$)-*N*-[[2-(2-methoxyethoxy)-5-nitrophenyl]sulfonyl]-*o*-benzoquinone imines (**10a–d**: $R^1$, $R^2$; **a**, Me, Me; **b**, Me, *n*-$C_{16}H_{33}$; **c**, *t*-Bu, Me; **d**, *t*-Bu, *n*-$C_{16}H_{33}$) are synthesized by the oxidation of *o*-sulfonamidophenols **9a–d** with $MnO_2$. Reactions of **10a–d** with aqueous NaOH–MeOH result in 1,4-additions of $MeO^-$ to the imide groups, affording *p*-benzoquinone monoacetals **12a–d**. The subsequent hydrolyses (1,2-additions of $HO^-$ to **10** reproduced reversibly) give arenesulfonamides (**14**) in varying yields depending upon the 5-alkyl substituents. The formation rates ($t_{1/2}$) of **14** from **10b** and from **10d** are 1.3 and 0.4 h, respectively. Heterogeneous hydrolysis (aqueous NaOH–AcOEt) of **10b** affords 1,2-addition products [*o*-benzoquinone (**11b**) and **14**] and 1,4-addition products [*p*-benzoquinone imine (**15a**) and *p*-benzoquinone (**16a**)]. Similar compounds (**11d**, **14**, **15b**, and **16b**) are obtained by heterogeneous hydrolysis of **10d**, but the portion of 1,2-addition products (**11d** and **14**) is larger. While the redox and coupling reaction between **10b** and *N*-ethyl-*N*-(2-methanesulfonamidoethyl)-2-methylbenzene-1,4-diamine (**17**) gives the indoaniline dye **19**, no coupling reaction between the reduced **10d** and the oxidized **17** is observed.

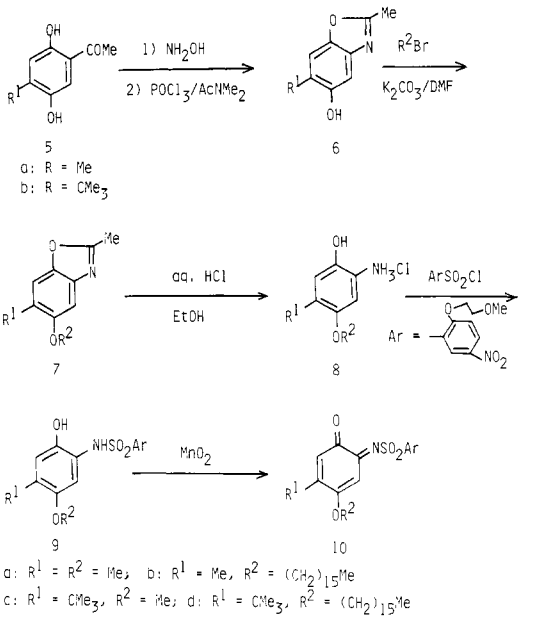
The chemistry of *p*-benzoquinone monosulfonimides was extensively studied by Adams[1] and recently revived with respect to their synthetic applications[2,3] and reaction mechanisms.[4] However, no reactions of the ortho analogues have ever been investigated. This is probably because they are so difficult to isolate. For example, Adams reported that, although he attempted the oxidation of 4- and 5-methyl-2-benzenesulfonamidophenol, he could not isolate the corresponding *o*-quinone monosulfonimides.[5]

*o*-Sulfonamidophenols **1** containing a dye moiety have been proposed as dye releasers for instant color photography.[6] Their main reactions have been presumed to be oxidation into the corresponding *o*-quinone monosulfonimides **2** and the subsequent hydrolysis to release the




diffusible dye **4**. However, the details of the dye-releasing processes have not been investigated so far. In this respect, studies on the behavior, particularly on the side reactions of the intermediates **2**, are significant in order to design dye-releasers of high efficiency.

Scheme I




The above-described organochemical and photographic interests prompted us to investigate the reaction of *o*-benzoquinone monosulfonimides. In this paper, we report the isolation and reactions of *o*-quinone monosulfonimides.[7] The isolation and structural determination of

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