(10 mL) and the mixture heated under reflux (nitrogen atmosphere) overnight. A workup in the usual way gave 4-hydroxy-6-methoxy-2-methyl-2,3-dihydrobenzofuran (**9**): 92% yield; as oil; ^{1}H NMR ($CDCl_3$) δ 1.43 (d, J = 6 Hz, CH_3), 2.63 (dd, J = 7, 14 Hz, H-3β), 3.18 (dd, J = 9, 14 Hz, H-3α), 3.70 (s, OMe), 4.94 (m, H-2α), 5.38 (br s, OH), 5.87 (d, J = 2 Hz, ArH), 5.98 (d, J = 2 Hz, H-5); exact mass m/e 180.0786 (calcd for $C_{10}H_{12}O_3$ m/e 180.0786).

A mixture of **8** and **9** was obtained with shorter reaction times in ether and tetrahydrofuran.

6-Methoxy-2-methyl-4,7-benzofurandione (Acamelin, 2). A solution of potassium nitrosodisulfonate (Fremy's salt, 705 mg) in water (60 mL) containing sodium acetate (280 mg) was added to a solution of the benzofuran **8** (200 mg) in methanol (6 mL) and the mixture stirred at room temperature for 30 min. The orange precipitate (150 mg, 70% yield) which formed was collected, washed with water, and recrystallized from chloroform–acetone (1:2) to give acamelin as bright orange-red needles: mp 253–255 °C;[9] IR (KBr) 1686, 1679, 1656, 1646, 1601, 1571, 1525 cm^{-1}; UV (EtOH) λ 219 nm (ϵ 21 000), 263 (9400), 307 (10 600), 417 (820); ^{1}H NMR ($CDCl_3$) δ 2.45 (d, J = 0.8 Hz, Me), 3.83 (s, OMe), 5.74 (s, H-5), 6.41 (d, J = 0.8 Hz, H-3). Anal. Calcd for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.25; H, 4.35.

α-Chloroethyl 2,4-Dihydroxy-6-methoxyphenyl Ketone (11). A solution of the 4-hydroxy-2,6-dimethoxyphenyl ketone **10** (2.6 g) in dichloromethane (125 mL) was added to aluminium chloride (5.31 g) in the same solvent (125 mL) and the mixture stirred under nitrogen at room temperature for 3 days. Ice–water (100 mL) was then added, the layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated to yield a solid (2.4 g) which was recrystallized from carbon tetrachloride to give the dihydroxymethoxyphenyl ketone as small yellow needles: 89% yield; mp 134–135.5 °C; an analytical specimen was obtained by sublimation: mp 137–139 °C; ^{1}H NMR ($(CD_3)_2CO$) δ 1.62 (d, J = 7 Hz, Me), 3.93 (s, OMe), 5.68 (q, J = 7 Hz, CHCl), 5.98 (d, J = 2 Hz, H-3), 6.04 (d, J = 2 Hz, H-5). Anal. Calcd for $C_{10}H_{11}O_4Cl$: C, 52.07; H, 4.81. Found: C, 52.11; H, 4.85.

6-Hydroxy-4-methoxy-2-methyl-2,3-dihydrobenzofuran-3-one (12). A solution of the α-chloroethyl phenyl ketone **11** (126 mg) and potassium acetate (720 mg) in water (30 mL) was heated under reflux for 3.5 h. After being stored overnight at room temperature, it was acidified (1 N hydrochloric acid) and worked up in the usual way via ether. Removal of solvent gave a solid (75 mg, 70% yield) which on recrystallization from benzene yielded the **dihydrobenzofuranone 12** as prisms: mp 194–196 °C; ^{1}H NMR ($(CD_3)_2CO$) δ 1.36 (d, J = 7 Hz, Me), 2.90 (br s, OH), 3.83 (s, OMe), 4.50 (q, J = 7 Hz, CHMe), 6.06 (s, H-5 and H-7). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.76; H, 5.32.

Methylation of **12** with dimethyl sulfate and potassium carbonate in 1,2-dimethoxyethane yielded the 4,6-dimethoxydihydrobenzofuranone **6** in 44% yield, identical with that prepared from **5**.

Acknowledgment. We are grateful to the National Institutes of Health (General Medical Sciences) for a research grant.

Registry No. **2**, 74161-27-6; **3**, 108-73-6; **4**, 500-99-2; **5**, 83949-03-5; **6**, 83949-04-6; **7**, 83949-05-7; **8**, 83949-06-8; **9**, 83949-07-9; **10**, 83949-08-0; **11**, 83949-09-1; **12**, 83949-10-4; 2-chloropropionitrile, 1617-17-0.

(9) This melting point, determined on a Fisher-Johns apparatus or in a sealed tube capillary differs from that reported (mp 175–176 °C) for the natural product. In correspondence with Dr. Hausen, he has expressed reservations regarding the correctness of his melting point determination. We have also observed sublimation of the compound at lower temperatures than the melting point.

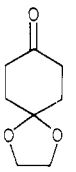
Convenient Monoketalization of 1,4-Cyclohexanedione. Synthesis of New Quinone Methides

John A. Hyatt

Research Laboratories, Eastman Chemicals Division, Eastman Kodak Company, Kingsport, Tennessee 37662

Received June 28, 1982

Considerable utility in the synthesis of natural products[1a-e] and of theoretically interesting molecules[1f] has been demonstrated for the ethylene monoketal (**1**) of 1,4-cyclohexanedione. Access to this extremely useful starting



1

material has not, in general, been easy. Routes employing partial reaction of 1,4-cyclohexanedione with ethylene glycol gave low (to 30%) yields of **1** after a difficult (extraction/derivatization or chromatographic) workup,[2,3] a route based on cyclohexanone ring formation gave a low yield,[4] and a process involving partial oxidation of 1,4-cyclohexanediol followed by ketalization and further oxidation also gave about 30% overall yield.[5] Marshall and Flynn[6] have recently described a high-yielding (88%) preparation of **1** from hydroquinone monomethyl ether. Although efficient and suitable for mole-scale operation, this route was quite time consuming[7] and involved some potential hazards.[8] The purpose of this paper is to suggest the use of a more accessible compound, 7,12-dioxaspiro-[5.6]dodecan-3-one (**2**), which is functionally equivalent to **1**. The use of **2** in synthesizing some new quinone methides is reported.

Reaction of 1,4-cyclohexanedione (**3**) with ethylene glycol, propylene glycol, neopentyl glycol, or 1,3-propanediol gave the expected, hard-to-separate mixtures of residual **3**, monoketal, and bisketal in proportions close to 1:2:1.[9] It was surprising to observe that **3**, upon reaction with 1 equiv of 1,4-butanediol under normal ketalization conditions, gave a product mixture comprising (as shown by VPC analysis) 6% **3**, 80% monoketal **2**, and 14% bisketal **4** (Scheme I). Most of the undesired crystalline bisketal **4** was removed by filtration, and vacuum fractional distillation of the filtrate gave pure **2** in 40–60% yield.[10]

(1) (a) Nicolaou, K.; Magolda, R.; Clareman, D. *J. Am. Chem. Soc.* **1980**, *102*, 1404. (b) Marshall, J.; Flynn, G. *J. Org. Chem.* **1979**, *44*, 1391. (c) Gronowitz, S.; Svensson, L. *Chem. Scr.* **1980**, *15*, 169. (d) Tice, C.; Heathcock, C. *J. Org. Chem.* **1981**, *46*, 9. (e) Piers, E.; Abeysekera, B.; Scheffer, J. *Tetrahedron Lett.* **1979**, 3279. (f) Heller, J.; Dreiding, A.; O'Conner, B.; Simmons, H.; Buchanan, G.; Raphael, R.; Taylor, R. *Helv. Chim. Acta* **1973**, *56*, 272.

(2) Courtot, P. *Bull. Soc. Chim. Fr.* **1962**, 1493.

(3) Lambert, J. *J. Am. Chem. Soc.* **1967**, *89*, 1836.

(4) Gardner, P.; Haynes, R.; Brandon, R. *J. Org. Chem.* **1957**, *22*, 1206.

(5) Haslanger, M.; Lawton, R. *Syn. Commun.* **1974**, *4*, 155.

(6) Marshall, J.; Flynn, G. *Syn. Commun.* **1979**, *9*, 123.

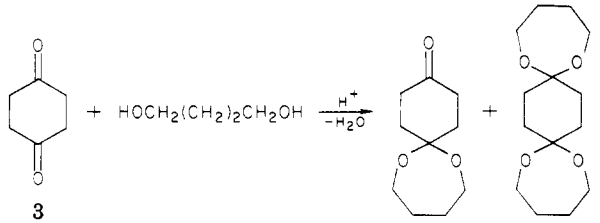
(7) The three-step sequence[6] involves a dissolving-metal reduction followed by a 2-day period of NH_3 evaporation before the workup.

(8) The authors[6] point out that a potential for uncontrolled reaction exists in the Birch reduction; large quantities of toxic chromium(VI) are used in the final step.

(9) Reactions were carried out with 0.1 mol each of **3** and diol, 0.2 g of *p*-toluenesulfonic acid, toluene solvent, and Dean–Stark water removal; washed and neutralized reaction mixtures were analyzed by VPC.

0022-3263/83/1948-0129$01.50/0

Scheme I



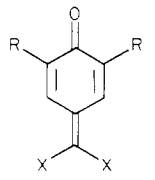
3 2 4

Mole quantities of **2** can thus be prepared in less than a single day; for some workers this facile procedure may be preferable to the higher yielding route to **1** reported by Marshall and Flynn.[6]

It is not clear why ketalization of **3** gives more monoketal with 1,4-butanediol than with other diols. Examination of models discloses no obvious steric resistance to bisketal formation. The flexibility of the seven-membered ring in **2** does allow orientations of the oxygen lone electron pairs that are precluded for the rigid five- and six-membered-ring ketals; subtle electronic effects may play a role in the reaction.

Compound **2** provides the basis of a new synthesis of quinone methides. Knoevenagel reactions of **2** with malononitrile and with ethyl cyanoacetate, followed by ketal hydrolysis, gave the keto olefins **6a** and **6b**. Further unsaturation by bromination–dehydrobromination or by Pt-catalyzed oxidation of **6a** and **6b** failed, but oxidation with active manganese dioxide[11] in chloroform gave satisfactory yields of the methides **7a** and **7b** (Scheme II).

Although **7b** was an unstable oil, **7a** was highly crystalline and stable.[12] Methides **7a** and **7b** are new, and **7a** may be the simplest known stable, isolable *p*-benzoquinone methide. Although 2,6-dialkyl-7,7-dicyano methides **8a**[13]

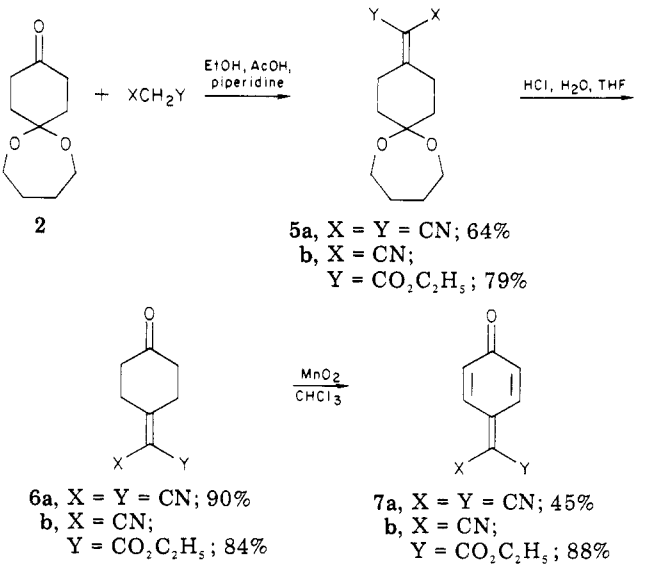


8a, R = CH_3; X = CN
b, R = *t*-Bu; X = CN
c, R = H; X = CF_3

and **8b**[14] are isolable (in very low yields from the corresponding phenol and quinone, respectively), the ring-unsubstituted 7,7-bis(trifluoromethyl) analogue **8c**[15] polymerizes at 25 °C.

The chemistry of **7a** was briefly examined (Scheme III). Catalytic hydrogenation yielded (*p*-hydroxyphenyl)-malononitrile (**9**); **7a** could be regenerated by MnO_2 treatment of **9**. Reaction with phenol and with *N*,*N*-dimethylaniline gave the diaryl malononitriles **10** and **11**. Diels–Alder reaction of **7a** with cyclopentadiene gave the product **12** by addition to the 2,3-double bond; no product was detected which resulted from addition to the 4,7-bond.

Scheme II



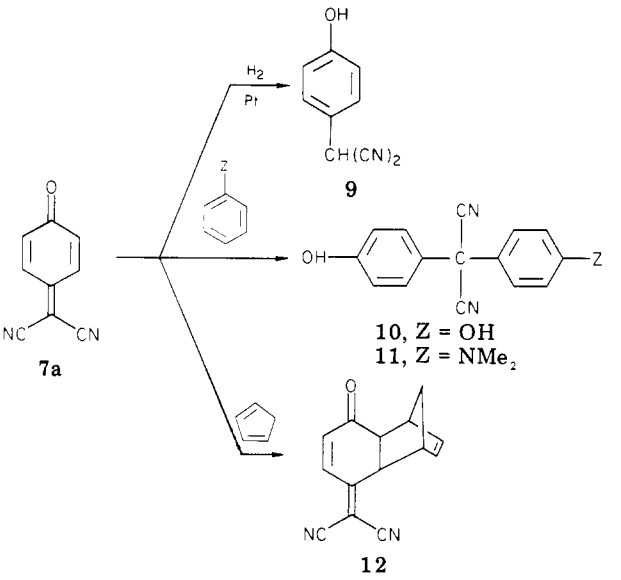
2

5a, X = Y = CN; 64%
b, X = CN; Y = $CO_2C_2H_5$; 79%

6a, X = Y = CN; 90%
b, X = CN; Y = $CO_2C_2H_5$; 84%

7a, X = Y = CN; 45%
b, X = CN; Y = $CO_2C_2H_5$; 88%

Scheme III



The ease of preparation of ketal **2** and the accessibility and stability of methide **7a** should make these substances useful tools in organic research. The study of charge-transfer complexes of **7a** might prove particularly interesting.

Experimental Section

General Methods. Melting and boiling points are uncorrected. IR spectra were taken on a Perkin-Elmer Model 137 spectrometer. ^1H NMR spectra were obtained with Varian EM-360 and JEOLCO MH-100 spectrometers and are reported in parts per million (δ) from internal tetramethylsilane. Mass spectra were recorded with a Consolidated Electrodynamics Corp. Model 21-110-B mass spectrometer. UV–visible spectra were recorded on a Cary 14 spectrophotometer.

7,12-Dioxaspiro[5.6]dodecan-3-one (2). A mixture of 112.0 g (1.0 mol) of 1,4-cyclohexanedione,[16] 0.5 g of *p*-toluenesulfonic acid, and 1 L of toluene was stirred at reflux under a Dean–Stark water separator. 1,4-Butanediol (90 g, 1.0 mol) was added dropwise over 3.5 h, during which 18.2 mL (104%) of water was evolved. The mixture was cooled, washed with ca. 20 mL saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and analyzed by VPC (6 ft, 2% OV-17 on Chrom P, 150–250 °C at 10 °C/min). The com-

(10) Some resinification of **2** occurred upon distillation; this accounts for the variation in yield.
(11) For previous examples of double-bond introduction via MnO_2 oxidation, see: (a) Hyatt, J.; Krutak, J. *J. Org. Chem.* **1977**, *42*, 169. (b) Chen, C.; Reynolds, G.; Cossar, B. *J. Org. Chem.* **1981**, *46*, 2752. (c) Fadiati, A. *Synthesis* **1976**, 133.
(12) Samples of **7a** stored in air at room temperature for 2 years show no evidence of decomposition.
(13) Takimoto, H.; Denault, G.; Krbechek, L. *J. Org. Chem.* **1974**, *29*, 1899.
(14) Rieker, A. *Chem. Ber.* **1970**, *103*, 656.
(15) Murray, J. *J. Org. Chem.* **1968**, *33*, 3306.
(16) Aldrich Chemical Co.

position (area percent) was 6% **3**, 80% **2**, and 14% **4**. The toluene was removed on a rotary evaporator, and the yellow oily residue was triturated with ethyl acetate and cooled in ice. Filtration afforded 20.4 g of bisketal **4**.[17] The filtrate was stripped of ethyl acetate and distilled (12-in. Vigreaux column) to give, after a small forerun of **3**, 109 g (59%) of **2** as a clear liquid: bp 109–114 °C (2.7 mmHg); IR (neat) 5.85, 8.00, 8.90, 11.72 μm; NMR ($CDCl_3$) δ 3.80 (m, 4 H), 2.50 (t, 4 H), 2.00 (t, 4 H), 1.72 (m, 4 H); mass spectrum, *m/e* 184 (calcd, 184). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.2; H, 8.76. Found: C, 64.9; H, 8.44.

1,4-Butylene Ketal of 4-(Dicyanomethylene)cyclohexanone (5a). A mixture of 25 g (0.136 mol) of ketal **2**, 250 mL of ethanol, 1.0 g of piperidine, 0.5 g of acetic acid, and 9.64 g (0.146 mol) of malononitrile was allowed to stand at 25 °C for 3 h and cooled to −5 °C, and the crystalline **5a** was filtered off. Recrystallization (charcoal, aqueous ethanol) gave 20.2 g (64%) of **5a** as a tan solid: mp 122–125 °C; IR (KBr) 4.50, 6.28, 8.84, 8.93, 9.19, 9.52, 9.96 μm; NMR ($CDCl_3$) δ 3.72 (m, 4 H); 2.80 (t, 4 H), 1.89 (t, 4 H), 1.81 (m, 4 H). Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.1; H, 6.94; N, 12.0. Found: C, 67.4; H, 7.05; N, 12.0.

Ketal 5b was prepared from **2** and ethyl cyanoacetate in the same way as **5a** (**5b** formed plates; mp 61–63 °C from aqueous ethanol): IR (KBr) 4.48, 5.82, 6.27, 8.25, 9.20, 10.00 μm; NMR ($CDCl_3$) δ 4.30 (q, 2 H), 3.70 (br m, 4 H), 3.14 (t, 2 H), 2.81 (t, 2 H), 1.70 (m, 8 H), 1.37 (t, 3 H). Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.2; H, 7.58; N, 5.01. Found: C, 64.5; H, 7.40; N, 5.01.

4-(Dicyanomethylene)cyclohexanone (6a). A mixture of 20.0 g of ketal **5a**, 200 mL of THF, and 25 mL of 10% aqueous HCl was refluxed 2.0 h, at which time TLC analysis indicated conversion to be complete. The mixture was cooled, stripped to ca. 50 mL, and partitioned between water and ethyl acetate. The organic phase was dried ($MgSO_4$) and stripped to give 12.5 g (90.5%) of **6a** as a tan solid, pure by TLC, IR, and NMR analysis. An analytical sample had the following: mp 42–44 °C (ether–hexane); IR (KBr) 4.39, 5.83, 6.28, 7.08, 8.70, 10.40, 12.35 μm; NMR ($CDCl_3$) δ 3.20 (t, 4 H), 2.64 (t, 4 H). Anal. Calcd for $C_9H_8N_2O$: C, 67.1; H, 5.00; N, 17.4. Found: C, 67.2; H, 4.90; N, 17.6.

Cyclohexanone 6b was prepared in 84% yield from **5b** by the same method as for **6a**: mp (ethanol) 72–73 °C; IR (KBr) 4.48, 5.80 (br), 6.24, 8.00, 12.33, 12.96 μm; NMR ($CDCl_3$) δ 4.32 (q, 2 H), 3.37 (m, 4 H), 2.70 (m, 4 H), 1.33 (t, 3 H). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.32; N, 6.76. Found: C, 63.8; H, 6.26; N, 6.74.

7,7-Dicyanobenzoquinone Methide (7a). A mixture of 14.0 g of ketone **6a**, 600 mL of chloroform, 120 g of active MnO_2,[18] and 100 g of 3A molecular sieves[19] was stirred at reflux for 0.5 h, cooled, and filtered (Celite), and the red filtrate was stripped to give crude **7a**. Recrystallization from ethanol gave 6.1 g (45%) of **7a** as beautiful red needles (0.5–1 cm long): mp 145–147 °C; IR (KBr) 4.48, 6.12, 6.14, 8.00, 9.18, 11.47 μm; NMR ($CDCl_3$) δ 7.90 (d, *J* = 10.5, 2 H), 6.80 (d, *J* = 10.5, 2 H); UV (CH_2Cl_2) λ_{max} 323 nm (ε 1.706); mass spectrum, *m/e* 156 (calcd, 156). Anal. Calcd for $C_9H_4N_2O$: C, 69.2; H, 2.58; N, 17.9. Found: C, 69.1; H, 2.85; N, 18.1.

7-Cyano-7-(ethoxycarbonyl)benzoquinone Methide (7b) was prepared from **6b** (3.0 g), MnO_2 (24 g), chloroform (150 mL), and 3A molecular sieves (24 g) in 88% yield. Methide **7b** was a yellow syrup that refused to crystallize and decomposed within 12 h at 25 °C: IR (neat) 4.50, 5.80 (br), 6.11, 8.15 (br), 11.5 μm; NMR ($CDCl_3$) δ 8.62 (dd, *J* = 3.0, 10.5 Hz, 1 H), 7.81 (dd, *J* = 3.0, 10.5 Hz, 1 H), 6.80 (dd, *J* = 2, 5 Hz, 1 H), 6.52 (dd, *J* = 2, 5 Hz, 1 H), 4.50 (q, 2 H); 1.45 (t, 3 H); mass spectrum, *m/e* 203 (calcd 203). Combustion analysis was not undertaken due to the instability of **7b**.

(*p*-Hydroxyphenyl)malononitrile (9). A solution of 0.5 g of methide **7a** in 15 mL of ethyl acetate was treated with 0.05 g of 5% Pd/C and hydrogenated at 25 °C (1 atm of H_2) for 1.5 h. Filtration and removal of solvent gave pink crude **9**; recrystallization (chloroform–hexane) gave 0.48 g (95%) of white **9**: mp 88–90 °C; IR (KBr) 2.94, 4.42, 6.21, 6.29, 6.63, 6.95, 7.88, 8.19, 8.28, 8.51, 9.02, 9.94, 11.95 μm; NMR ($CDCl_3$) δ 8.55 (br s, 1 H), 7.32 (center of AB q, *J* = 8 Hz, 4 H), 5.60 (br s, 1 H); mass spectrum, *m/e* 158 (calcd 158). Anal. Calcd for $C_9H_6N_2O$: C, 68.3; H, 3.82; N, 17.7. Found: C, 67.9; H, 3.93; N, 17.5.

Bis(*p*-hydroxyphenyl)malononitrile (10). A mixture of 0.1 g of methide **7a**, 0.1 g of phenol, 10 mL of THF, and 3 drops of concentrated HCl was allowed to stand at 25 °C for 18 h and was evaporated to dryness, and the residue was twice recrystallized from toluene to give 0.165 g (91%) of **10**, mp 139–144 °C (lit.[20] mp 144–146 °C).

(4-Hydroxyphenyl)[4-(dimethylamino)phenyl]malononitrile (11). A solution of 0.1 g of methide **7a** and 0.5 g of *N,N*-dimethylaniline in 10 mL of THF was treated with 0.5 g of acetic acid. After 1 h at 25 °C, the colorless mixture was poured into water, extracted with ethyl acetate, dried, and stripped of solvent and excess aniline in vacuo. Toluene/hexane trituration of the residue gave **11**: 0.22 g (78%); mp 109–111 °C; IR (KBr) 2.90, 4.41, 6.19, 6.60, 6.91, 7.30, 7.85, 8.18, 11.90, 12.22, 12.30 μm; NMR ($CDCl_3$) δ 8.8 (br s, 1 H), 7.10 (center of 7-line m, 8 H), 3.02 (s, 6 H); mass spectrum, *m/e* 277 (calcd 277). Anal. Calcd for $C_{17}H_{15}N_3O$: C, 73.6; H, 5.45; N, 15.2. Found: C, 73.7; H, 5.62; N, 15.1.

Diels–Alder Adduct 12. A mixture of 0.5 g of methide **7a** and 3 g of freshly distilled cyclopentadiene in 5 mL of toluene was allowed to stand at 25 °C for 1 h. The yellow mixture was cooled to 0 °C and the product filtered off to give 0.49 g (69%) of **12** as yellow needles: mp 123–127 °C dec; IR (KBr) 4.45, 6.00, 6.23, 6.46, 7.49, 8.00, 8.81, 9.50, 11.65, 11.89, 13.30 μm; NMR ($CDCl_3$) δ 7.50 (d, *J* = 10 Hz, 1 H), 6.36 (d, *J* = 10 Hz, 1 H), 6.13 (m, 2 H), 3.87 (m, 2 H), 3.64 (m, 1 H), 3.20 (m, 1 H), 1.60 (br s, 2 H); mass spectrum, *m/e* 222 (calcd 222). Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.7; H, 4.53; N, 12.6. Found: C, 75.6; H, 4.72; N, 12.7.

Registry No. **2**, 80427-20-9; **4**, 41561-14-2; **5a**, 83928-79-4; **5b**, 83928-80-7; **6a**, 83928-81-8; **6b**, 83928-82-9; **7a**, 83928-83-0; **7b**, 83928-84-1; **9**, 83928-85-2; **10**, 50778-50-2; **11**, 83928-86-3; **12**, 83928-87-4; 1,4-cyclohexanedione, 637-88-7; 1,4-butanediol, 110-63-4; malononitrile, 109-77-3; ethyl cyanoacetate, 105-56-6; phenol, 108-95-2; *N,N*-dimethylaniline, 121-69-7; cyclopentadiene, 542-92-7.

(17) An analytical sample of **4** had the following: mp 131–134 °C (recrystallized from ethyl acetate); IR (KBr) 6.95, 7.27, 8.05, 8.84, 8.95, 9.45, 9.82, 10.48, 11.63 μm; NMR ($CDCl_3$) δ 3.63 (br s, 8 H), 1.80 (m, 16 H). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.6; H, 9.43. Found: C, 65.9; H, 9.06.

(18) Active MnO_2 was purchased[16] or prepared according to: Attenburrow, A. B.; et al. *J. Chem. Soc.* **1952**, 1094. Moulton, R. W. U.S. Patent 2459714, 1949.

(19) Addition of the drying agent led to higher yields of **7a** and **7b**.

(20) Banucci, E. *Synthesis* **1973**, 671.