J = 9, 3 Hz), 3.68 (3 H, m) 3.14 (1 H, dq, J = 9, 7 Hz), 3.03 (1 H, dq, J = 7, 7 Hz), 1.96 (3 H, s), 1.95 (3 H, s), 1.94 (1 H, m), 1.60–1.44 (2 H, m), 1.26 (3 H, d, J = 7 Hz), 1.15 (3 H, d, J = 7 Hz), 0.99 (3 H, t, J = 7 Hz), 0.95 (3 H, d, J = 7 Hz); MS, m/z 326 (M^+), 268, 180.

Conversion of 2 to 7. The triol **2** (14 mg) was dissolved in 2,2-dimethoxypropane (4 mL). A crystal of TsOH was added and the reaction refluxed for 3 h. The reaction was diluted with dry benzene (10 mL). The organic layer was evaporated to give **7** (10 mg): crystals from hexane; mp 134–135 °C; high-resolution mass measurement, obsd 584.372, calcd 584.3715 for $C_{35}H_{52}O_7$.

X-ray Analysis of 7. Precession photographs of a single crystal (0.10 × 0.10 × 0.25 mm) of ilikonapyrone acetonide ($C_{35}H_{52}O_7$) revealed orthorhombic symmetry ($P2_12_12_1$). Latice translations, a = 19.380 (3), b = 23.031 (4), c = 7.831 (1) Å, were determined by least-squares fitting of 24 automatically centered (Picker FACS-I diffractmeter) reflections (39° < 2θ < 48°) measured with Ni-filtered Cu Kα radiation (λ = 1.5405 Å) at 291 K. Crystal density (1.108 g/cm^3, flotation, KI–H_2O), lattice parameters, and space group symmetry reveal that there are four molecules per unit cell and one per asymmetric crystallographic unit. Intensity data (2$\theta \leq$ 100°) were measured in the $\theta/2\theta$ scan mode. Of 2089 unique reflections, 1697 were considered observed by using the criterion $I_0 \geq 3\sigma(I_0)$ after correction for Lorentz, polarization, background, decay (6%), and absorption (ψ-scan, μ = 6.16 cm^{-1}, 8.2% maximum at 15,2,2) effects. The structure was solved by direct methods. Repeated cycles of structure factor and difference Fourier synthesis provided acceptable positional parameters for all 42 non-hydrogen atoms. Anisotropic refinement converged at R = 0.12, minimizing $\sum w[|F_o| - |F_c|]^2$ where $w = 1/\sigma^2$. Repeated cycles of refinement and difference Fourier synthesis revealed positions for 25 hydrogen atoms. Positional parameters for 20 additional hydrogen atoms could be calculated on the basis of geometrical constraints. In the final cycles of refinement, hydrogen atom positional parameters were fixed. Throughout, thermal parameters for hydrogen atoms were also fixed and were assigned values of $8\pi^2(\sum_{i=1}^{3} U_{ij}/3)$ of the atoms to which they were bonded. Hydrogen atoms of the hydroxyl group and the methyl groups C(1) and C(24) could not be satisfactorily located. Refinement converged (shift/error ≤ 0.5) at $R = 0.072$ ($R = \sum(||F_o| - |F_c||)/\sum|F_o|$) and $wR = 0.079$ ($wR = [\sum w(|F_o| - |F_c|^2/\sum w|F_o|^2]^{1/2}$. Additional crystallographic details (structure factor table, atomic positional and thermal parameters, bond distances, bond angles, and torsion angles) can be found in the supplementary material.

Calculations were performed on IBM 370/168 and DEC PDP-10 computers. Atomic scattering factors were taken from Cromer and Weber (Cromer, D. T.; Weber, J. T. *Acta Crystallogr.* **1965**, *18*, 104–109) and Stewart et al. (Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175–3187). The principle programs used were the following: XRAY72, the X-ray system of crystallographic programs (Stewart, J. M.; Kruger, G. J.; Ammon, H. L.; Dickinson, C.; Hall, S. R. Technical Report TR-192, Computer Science Center, University of Maryland, College Park, MD, 1972); ORTEP-II, crystallographic illustration program (Johnson, K. C. Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, TN, 1976); MULTAN, programs for solution of crystal structures from X-ray diffraction data (Declercq, J. P.; Germain, G.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1975**, *31*, 367–372); ORFLS, full-matrix least-squares program for refinement of crystal structures (Busing, W. R.; Martin, K. O.; Levy, H. A. Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, TN, 1962); and ABS, a locally modified absorption correction program (North, A. C. T.; Phillips, D. C.; Mathews, F. S. *Acta Crystallogr., Sect. A* **1968**, *24*, 351–359.

Acknowledgment. This study was supported in part by a grant from the National Institutes of Health to CMI (CA 29821). ^{1}H and ^{13}C NMR spectra were obtained on the Bruker WM-500 at the Northwest Regional NSF–NMR Facility, Yale University, partially supported by the National Science Foundation (Grant CHE 79-16210). We thank David Sesin for technical assistance in preparing ilikonapyrone acetonide and Deborah Roll for additional collections of *O. verruculatum*.

Registry No. **2**, 88130-78-3; **3**, 88130-79-4; **4**, 88130-80-7; **5**, 88130-81-8; **6**, 88130-82-9; **7**, 88130-83-0; 2,2-dimethoxypropane, 77-76-9.

Supplementary Material Available: Tables I and II listing structure factors, atomic positional and thermal parameters, bond distances, bond angles, and torsion angles (11 pages). Ordering information is given on any current masthead page.

Isolation of the Key Intermediate in the Formation of *cis*-Bicyclo[3.3.0]octane-3,7-diones from Dimethyl 3-Ketoglutarate and 1,2-Dicarbonyl Compounds

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The reaction of 2 equiv of dimethyl 3-ketoglutarate (*1*) with 1 equiv of a 1,2-dicarbonyl compound **2**[1] provides a convenient approach to tetramethoxycarbonyl compounds,[2,3] which in turn yield *cis*-bicyclo[3.3.0]octane-3,7-diones on acid-catalyzed hydrolysis–decarboxylation. Examination of this process in our laboratories has resulted in a facile, general route for the preparation of more complex polyquinanes,[1-6] some of which are illustrated in Scheme I, as well as for compounds of pharmaceutical interest.[7] The versatility of this approach has been amply illustrated recently by reports of the syntheses of gymnomitrol,[8a] isocomene,[8b] and modhephene.[5]

The formation of the *cis*-bicyclo[3.3.0]octane-3,7-dione system from **1** and **2** can be easily rationalized[9] through the sequence of aldolization and Michael reactions shown in Scheme II. In agreement with this, Bertz has suggested that in mildly acidic media (pH 5) the aldol product **3** undergoes cyclization to **4**, which eventually leads to the *cis*-bicyclo[3.3.0] system,[10] while under less acidic conditions evidently elimination to a *trans*-olefin is observed.[10] We have now found that at pH >8 the 4-hydroxycyclo-

(1) Weiss, U.; Edwards, J. M. *Tetrahedron Lett.* **1968**, 4885.
(2) Yang, S.; Cook, J. M. *J. Org. Chem.* **1976**, *41*, 1903. Weber, R. W.; Cook, J. M. *Can. J. Chem.* **1978**, *56*, 189.
(3) Bertz, S. H. Ph.D. Thesis, Harvard University, Cambridge, MA, 1978.
(4) Mitschka, R.; Oehldrich, J.; Takahashi, K.; Weiss, U.; Cook, J. M. *Tetrahedron* **1981**, *37*, 4521.
(5) Wrobel, J.; Takahashi, K.; Honkan, V.; Bertz, S.; Lannoye, G.; Cook, J. M. *J. Org. Chem.* **1983**, *48*, 139.
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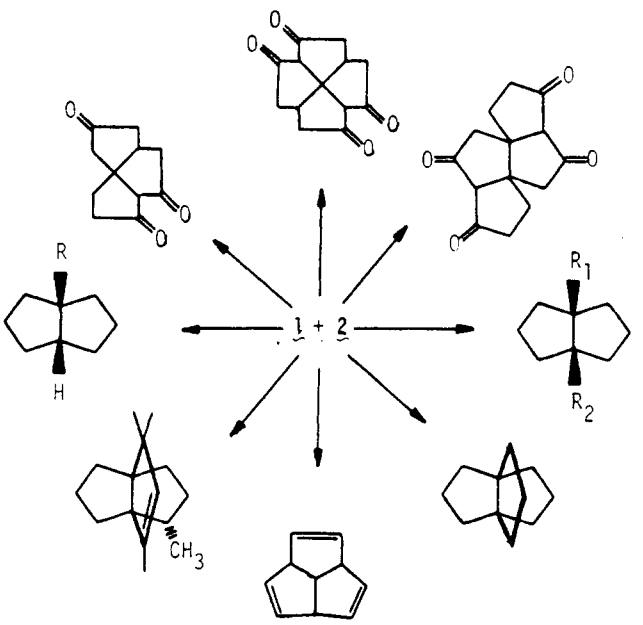
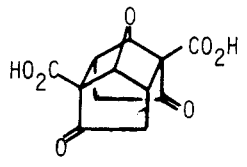
(8) (a) Coates, R. M.; Shah, S. K.; Mason, R. W. *J. Am. Chem. Soc.* **1979**, *101*, 6765. Han, Y.-K.; Paquette, L. *J. Org. Chem.* **1979**, *44*, 3731. (b) Dauben, W. G.; Walker, D. M. *Ibid.* **1981**, *46*, 1103.
(9) Yang-Lan, S.; Mueller-Johnson, M.; Oehldrich, J.; Wichman, D.; Weiss, U.; Cook, J. M. *J. Org. Chem.* **1976**, *41*, 4053.
(10) Bertz, S. H.; Adams, W. O.; Silverton, J. V. *J. Org. Chem.* **1981**, *46*, 2828.

0022-3263/84/1949-0561$01.50/0

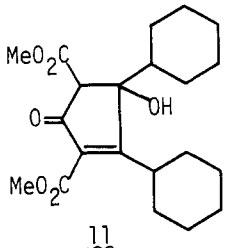
Scheme I



pentenone **5** is again found to be the key intermediate along the reaction path toward **8**.[9] It had not been possible until now, however, to establish such a role for **5** by experiment. There is a good deal of indirect evidence that suggests this role for the 4-hydroxycyclopentenone; for instance; compound **5** (R = R′ = H) is unquestionably present in the reaction between **1** and glyoxal **2** (R = R′ = H), since a small amount of the heterocyclic cage compound **10** can be isolated from the reaction mixture after hydrolysis.[3,10] Formation of **10** must undoubtedly begin with a Michael-type addition of one molecule of **5** to the conjugated enone system of another molecule of **5**, subsequent intramolecular Michael additions would produce the complete carbon oxygen skeleton of **10**.



10



11

In addition, several 4-hydroxycyclopentenones of type **5** have been isolated from reactions of **1** with benzil and with phenanthrenequinone,[9] but neither of these materials could be converted into a 1:2 adduct. Their possible role as true intermediates in the formation of the [3.3.0] system, consequently, remained in question. It was earlier proposed[9] that the failure to convert the 1:1 adduct **5** (R = R′ = Ph) into the *cis*-bicyclooctane-3,7-dione system was due primarily to electronic effects. However, recently it has been shown that biscyclohexane-1,2-dione formed with **1** a 1:1 adduct, which also could not be converted into the 1:2 species even under strongly alkaline conditions.[11] The failure of **11** to add another molecule of **1** owes its origin to steric constraints, moreover, biscyclopentene-1,2-dione, under analogous conditions, gave both a crystalline 1:2 adduct **8** (R = R′ = 3-cyclopentyl) and a 1:1 adduct **5** (R = R′ = 3-cyclopentenyl) that was too unstable to be fully characterized.[12] It was clear that the borderline between isolation of a 1:1 intermediate and a 1:2 adduct **8** (R = R′ = 3-cyclopentenyl) was generally the difference in molecular volume occupied by the two cyclopentane units in **5** (R = R′ = cyclopentane), in contrast to the alicyclic groups present in the biscyclohexane derivative **11**.

It is not surprising that 4-hydroxycyclopent-2-en-1-one intermediates related to **5** have not been isolated, for Marx et al.[13] demonstrated that 2-(methoxycarbonyl)cyclopent-2-en-1-one was stable only in dilute solution at −10 °C and polymerized on attempted isolation. It was decided, therefore, to choose a 1,2-dicarbonyl compound for this sequence with a size similar to a cyclopentene unit, however, one in which electronic effects could be employed to influence the stability of the 4-hydroxycyclopentenone via π-orbital overlap. Furil (**12**), a compound that seemed ideal for this purpose, failed to react with **1** in aqueous media buffered to either pH 6.8 or 8.3.[14] Under more vigorous conditions of methanolic sodium hydroxide, however, the condensation of 1 mol of **12** with 2 mol of **1** produced the *cis*-bicyclo[3.3.0]octane-3,7-dione **13** in 60% yield. This material was further converted into **14** by acid-catalyzed hydrolysis, as illustrated in Scheme III. However, when **1** and **12** were allowed to react under the same conditions in 1:1 stoichiometry, a compound was obtained that was homogeneous on TLC but proved difficult to isolate. A pure material was obtained by column chromatography (SiO_2, ethyl acetate/hexane) at rapid flow rate, although most of the material decomposed on the column. This product isolated in 56% yield by flash chromatography was fully characterized as the 1:1 adduct 4-hydroxycyclopent-2-en-1-one **15**. Moreover, examination of the NMR spectrum of a sample of **15**, previous to purification, clearly indicated that this adduct had initially been present in >80% yield; decomposition had occurred on chromatography, as alluded to above.

With pure **15** available, it remained to determine if this was a true intermediate on the reaction path toward **13**. To this end, a methanolic solution of sodium hydroxide and **1** was heated to 68 °C, analogous to the conditions of Bertz,[3] and the 1:1 adduct **15** was added as a solid to the mixture that resulted. After the solution was heated for 8 h, followed by the usual workup,[3,9,11] the 1:2 adduct **13** was isolated as the exclusive product. If on the other hand the 1:1 adduct **15** was heated in methanolic sodium hydroxide in the absence of **1**, neither **1** or **12** nor the 1:2 adduct **13** could be found in the reaction mixture; consequently, **15** was clearly not reverting to **1** and **12** during this process. The effect of a strongly alkaline medium on the reaction of **1** with dicarbonyl compounds such as **12** is somewhat different than that observed by Bertz under mildly alkaline conditions[10] and serves to illustrate the sensitivity of this condensation to the conditions of pH, a fact repeatedly observed in our laboratories over the last few years.[2,4,9,15]

The experiments with **12** provide the first clear evidence that the reaction sequence proposed earlier[9] is essentially correct and that 1:1 adducts of type **5** are indeed key intermediates. While the set of experiments described here are conceptually simple, their origin rests firmly on previous work directed toward determining the scope of the

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(12) Avasthi, K.; Kubiak, G.; Cook, J. M., unpublished results.

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(14) It is felt that **12** is inert under these conditions because of low solubility and low reactivity in this medium.

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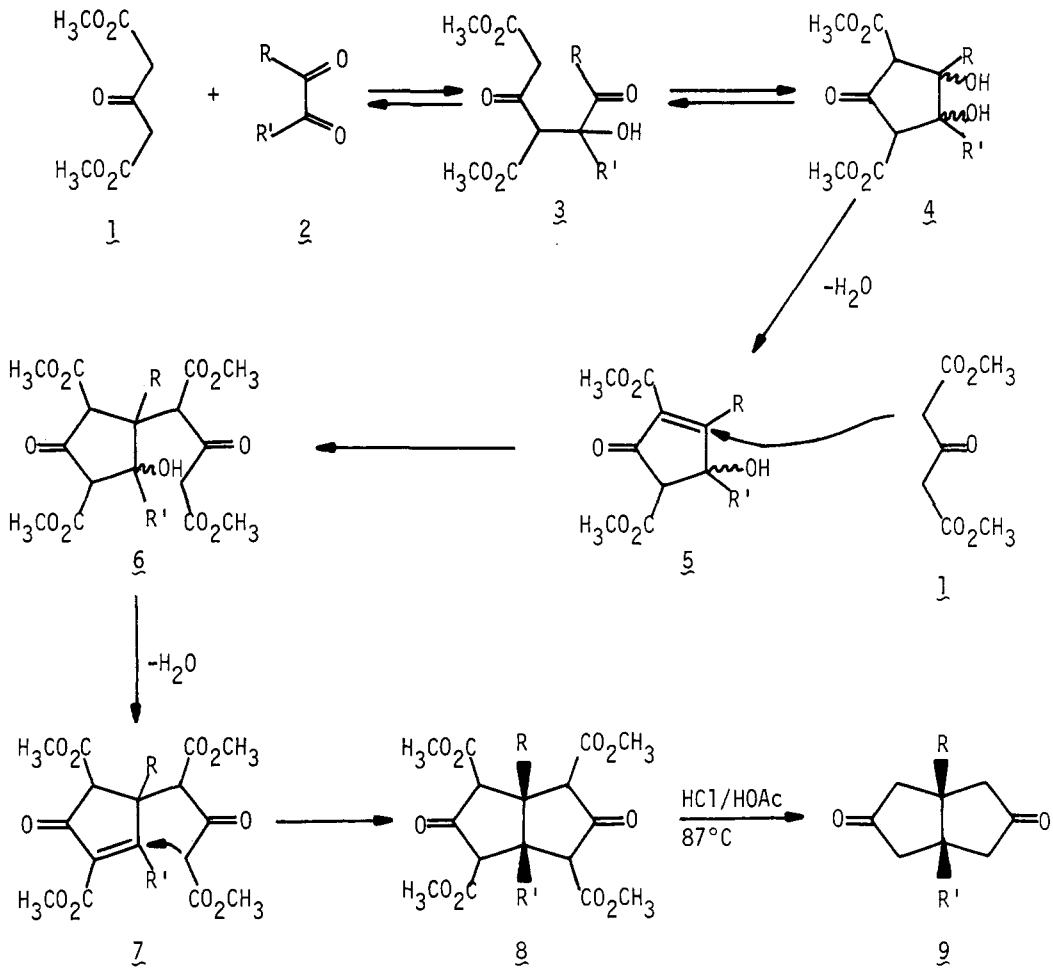
Scheme II



reaction of 1 with 2.[2,4,9,11] Furthermore, isolation of a pure 1:1 adduct capable of reacting with a second molecule of 1 suggests the possibility of expanding the scope of this reaction by substitution of another Michael addend in place of 1. Experiments toward this end are in progress.

Experimental Section

Microanalysis were performed on an F and M Scientific Corp Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. Low-resolution NMR spectra were recorded on a Varian EM-360 spectrometer, while the high-resolution spectra were run on a Bruker 250-MHz multiple-probe instrument. Chemical ionization (CI) mass spectra and electron impact (EI) mass spectra were obtained on either a Finnigan GC/MS or a Hewlett Packard 5855 gas chromatograph–mass spectrometer. Dimethyl 3-ketoglutarate (1) and furil (12) were purchased from Aldrich Chemical Co.

1,5-Bis(2-furyl)-2,4,6,8-tetracarbomethoxy-*cis*-bicyclo-[3.3.0]octane-3,7-dione (13). Dimethyl 3-ketoglutarate (1, 3.6 g, 0.02 mol) was added to a solution of methanol (75 mL) and sodium hydroxide (0.84 g, 0.02 mol). The mixture was heated to 60 °C (oil bath), and furil (12, 2.0 g, 0.01 mol) was added. The mixture was held at 60 °C for 8 h and then cooled to room temperature. The solution was filtered to provide the bis sodium salt of the 1:2 adduct 13 (mp >300 °C). This salt was dissolved in ice water (30 mL) and brought to acidic pH (10% aqueous HCl) to provide 13 as a tan solid: 2.87 g, 52% yield; mp 232–233 °C; IR (KBr) 3400–2800 (br), 1750–1650 (br), and 1630 cm^{-1}; NMR (Me_2SO-d_6) δ 3.23 (6 H, s), 3.54 (6 H, s), 4.47 (2 H, s), 6.00–6.10 (4 H, m), 7.25 (2 H, m), 10.69 (2 H, s); CI mass spectrum (CH_4), m/e (relative intensity) 503 (P + 1, 7.7), 471 (42), 439 (100); high-resolution mass spectrum calcd for $C_{24}H_{22}O_{12}$, 502.1111, found 502.1125.

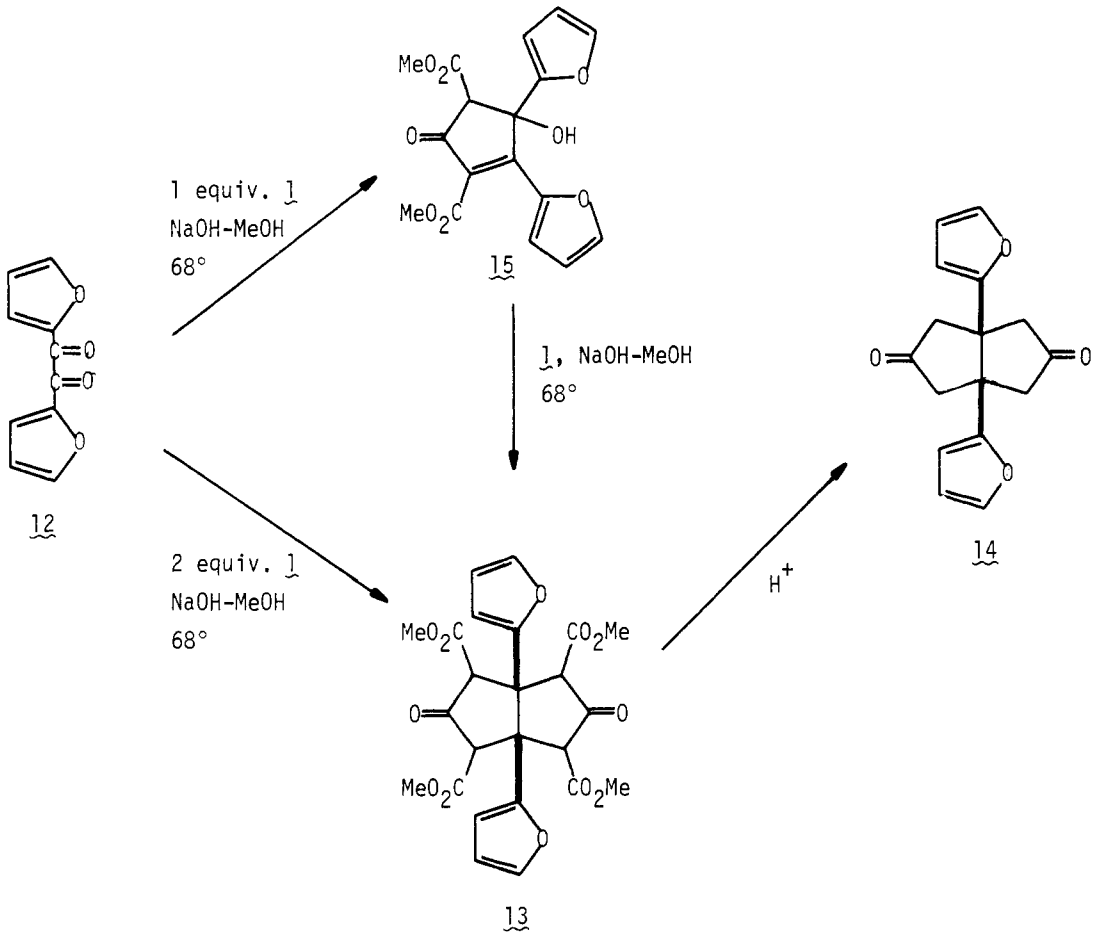
2,5-Dicarbomethoxy-3,4-bis(1-furyl)-4-hydroxycyclopent-2-enone (15). Dimethyl 3-ketoglutarate (1, 4.5 g, 0.028 mol) was added to a solution of sodium methoxide [prepared in situ: 0.75 g, 0.028 mol of Na in dry CH_3OH (100 mL)] and allowed to stir for 15 min. Furil (12, 5.0 g, 0.026 mol) was then added, and the resulting dark brown solution was stirred at room temperature for 18 h. This solution was filtered to yield the Na salt of 15 as a yellow-orange colored solid: mp >300 °C dec. This salt was dissolved in ice water (100 mL), added to $CHCl_3$ (100 mL), and brought to acidic pH at 0 °C with ice-cold aqueous HCl (10%). The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure at room temperature to provide 15 as a dark viscous oil. This oil was purified via flash chromatography (60% EtOAc/hexane) to furnish 15 as a clear yellow oil which solidified when triturated with small portions of ethyl ether; crystalline 15 (3.3 g) was obtained in this fashion.

The original methanol filtrate was concentrated at room temperature under reduced pressure to yield a dark oil. This oil was treated in an analogous fashion to the orange-yellow solid discussed above to provide additional quantities of 15 (1.8 g). The combined yield of the 1:1 adduct 15 (5.1 g) was 56%. An analytically pure sample was obtained by recrystallization of 15 from CH_2Cl_2/hexane: mp 115–116 °C; IR (KBr) 3390 (s), 3150 (m), 2950 (m), 2900 (m), 1750 (s), 1710 (s), 1621 (s) 1460 (s); ^1H NMR ($CDCl_3$, 250 MHz) δ 3.77 (s, 3 H), 3.89 (s, 3 H), 3.94 (s, 1 H), 5.04 (1 H, D_2O exchangeable), 6.31–6.50 (2 m, 3 H total), 7.12–7.58 (3 m, 3 H total); mass spectrum (CI, CH_4), m/e (relative intensity) 347 (M + 1, 23), 329 (M + 1–H_2O, 100), 315 (M + 1 – CH_3OH, 38), 289 (7), 257 (14); high-resolution mass spectrum, calculated for $C_{17}H_{14}O_8$ 346.0688, found 346.0704.

Anal. Calcd for $C_{17}H_{14}O_8$: C, 58.96; H, 4.08. Found: C, 58.69; H, 3.95.

1,5-Bis(2-furyl)-*cis*-bicyclo[3.3.0]octane-3,7-dione (4). The tetramethyl ester 13 (2.0 g, 4.0 mmol) was added to a solution of HCl (15 mL, 10%) and glacial acetic acid (45 mL). The mixture

Scheme III



was heated rapidly (20 min) to 87 °C and held between 87 and 90 °C for 7 h, after which the solution was allowed to stir at room temperature overnight. The solution was then cooled, filtered, and diluted with $CHCl_3$ (500 mL). Ice was added and the pH was adjusted to ~8 with solid Na_2CO_3. Water (100 mL) was added to the mixture and the phases were separated. The aqueous layer was then extracted with $CHCl_3$ (3 × 100 mL), and the combined organic fractions were dried (Na_2SO_4) after which the solvent was removed under reduced pressure to yield **14** (0.92 g, 85%). An analytically pure sample was obtained by recrystallization of **14** from EtOAc/hexane: mp 175–176 °C; IR (KBr) 3464 (w), 3128 (m), 2978 (w), 1742 (s), 1509 (s); ^1H NMR ($CDCl_3$) δ 2.50 (4 H, d, J = 18 Hz) 3.20, (4 H, d, J = 18 Hz), 5.90 (1 H, d), 6.20 (2 H, m), 7.30 (2 H, m); ^{13}C NMR ($CDCl_3$) δ 47.63, 51.80, 105.62, 109.90, 141.94, 154.94, 213.48.

Anal. Calcd for $C_{16}H_{14}O_4$: C, 71.10; H, 5.20: Found: C, 70.70; H, 5.20.

Conversion of 1:1 Adduct 15 into the 1:2 Adduct 13. Dimethyl 3-ketoglutarate (**1**, 0.015 g, 0.087 mmol) was added to dry methanol (3 mL) containing sodium hydroxide (4 mg, 0.087 mmol). The solution was heated to 60 °C (oil bath) and the 1:1 adduct **15** (30 mg, 0.087 mmol) was added. The mixture was held at this temperature with stirring for 8 h. The reaction mixture was next cooled in an ice bath and acidified (1% aqueous HCl). At this point the colored solution became clear and a white solid precipitated (26 mg). The compound **13** proved to be identical with the 1:2 adduct **13** previously prepared from furil as evidenced by comparison of the TLC, mixed melting point, and CI mass spectral data of the two materials.

Treatment of 15 with Strong Alkali. To a solution of methanol (15 mL) and sodium hydroxide (0.02 g, 0.6 mmol) held at 60 °C (oil bath) was added the 1:1 adduct **15** (100 mg, 0.3 mmol). The mixture was stirred at 60 °C and was periodically monitored by TLC. The mixture was held at this temperature for 48 h and then worked up as previously described. TLC indicated the presence of 1:1 adduct **15** along with baseline material. Examination of the crude product by TLC, NMR, and CI mass spectrometry indicated that none of the glutarate **1**, furil (**12**), or the 1:2 adduct **13** were present.

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Registry No. **1**, 1830-54-2; **12**, 492-94-4; **13**, 88131-23-1; **14**, 88131-24-2; **15**, 16344-55-1.

Noncoupling Synthesis of Tetrathiafulvalenes

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Interest in the chemistry and physics of tetrathiafulvalene derivatives (**1**, X = S, TTF; X = Se, TSeF) continues strong[1] with the discovery of a wealth of novel organic solid-state phenomena, including superconductivity,[2,3] unusual magnetic orderings, and phase transitions.

(1) For a recent summary of work in this area, see: *Mol. Cryst. Liq. Cryst.*, **79**, 1–362 (1982).

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