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Reactions of Dicarbonyl Compounds with Dimethyl β-Ketoglutarate. 4. Formation of 1:1 Adducts[1a]

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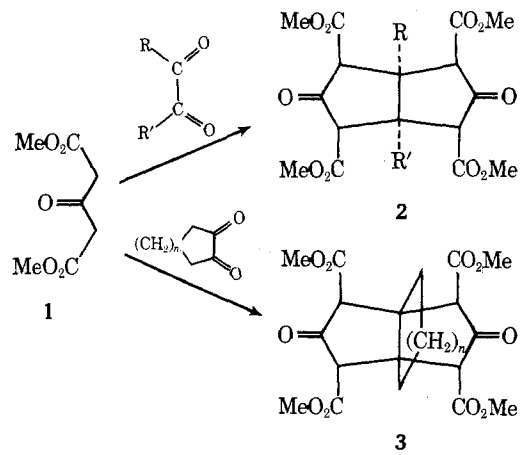
Many aliphatic 1,2-dicarbonyl compounds react at room temperature with dimethyl β-ketoglutarate (1) in aqueous or dilute methanolic solution to furnish 1:2 adducts of type **2**; cyclic 1,2-diketones similarly give the propellane derivatives of type **3**. In contrast, camphorquinone (**14**) and aromatic 1,2-diketones such as benzil (**18**) and phenanthrenequinone (**19**) yield only 1:1 adducts with **1**. The 1,2-glycol (**17**) resulting from simple aldolization followed by hemiketal formation, was isolated in the case of **14**, whereas 4-hydroxycyclopent-2-enones **20** and **23** were obtained in the case of the two fully aromatic dicarbonyl compounds. Ninhydrin gave only the 1:2 adduct (**31**) when reacted with **1**, while phenylglyoxal (**27**) yielded both a stable 1:2 adduct of type **2** and a very unstable 1:1 adduct (not isolated). The significance of these findings for the interpretation of the course of such reactions is discussed.

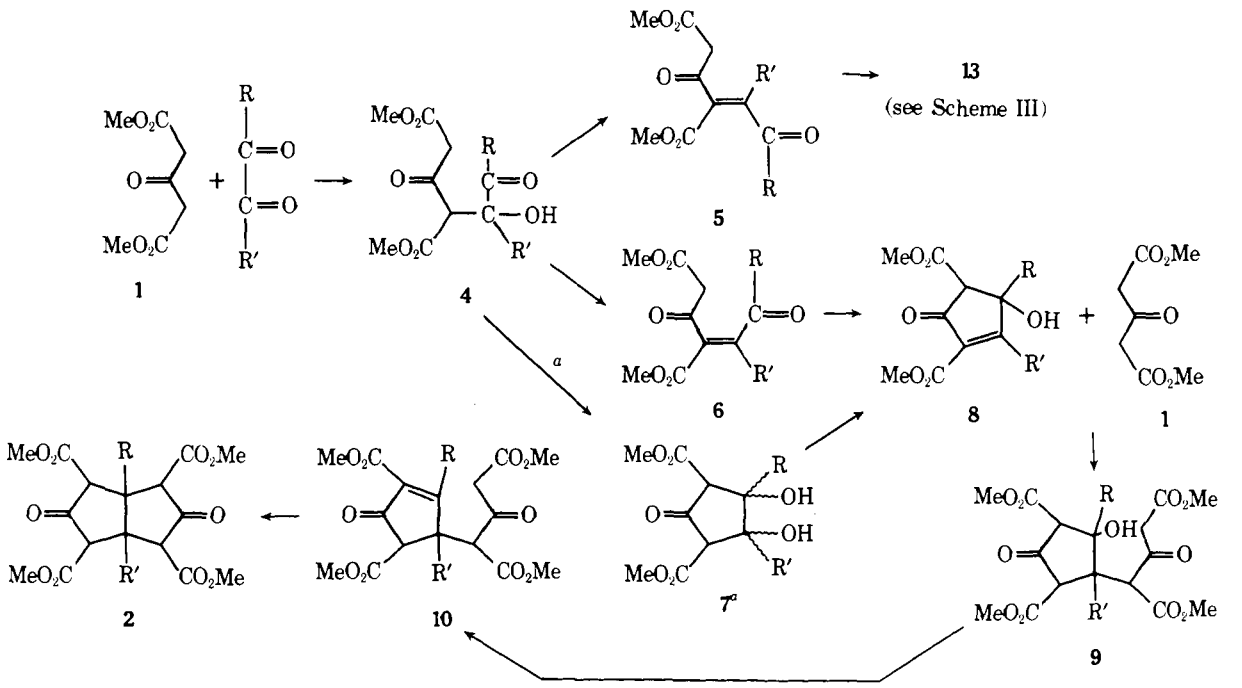
Dimethyl β-ketoglutarate (**1**) has been found[3] to react with aliphatic 1,2-dicarbonyl compounds in aqueous or aqueous/methanolic[4] solution at neutral or slightly acidic pH to provide β-keto esters (**2**)[5] derived from bicyclo[3.3.0]octane-3,7-dione. Alicyclic 1,2-diones in similar fashion yield esters (**3**) of [*n*.3.3]propellanediones.[3,4] From the reaction of **1** with glyoxal, more complex products (see below) have been isolated[3,6] in addition to **2**, R = R′ = H.



It seemed probable a priori that the 1:2 adducts **2** and **3** would be formed stepwise by reaction of one molecule each of **1** and the 1,2-dicarbonyl compound to yield a primary 1:1 adduct, capable of adding a second molecule of **1** to furnish the β-keto esters **2** and **3** actually isolated. A plausible sequence, shown in Scheme I, can be formulated, which is consistent with all information available to date. Simple aldolization of **1** and the dicarbonyl compound in equimolar amounts would generate the adducts **4**, **5**, or **6**. Of these, **4** and **6** could easily be converted to the 4-hydroxycyclopent-2-enone **8**. Michael addition of a second molecule of **1** to **8** would furnish the intermediate **9** which, as a β-hydroxy ketone, would readily eliminate water to form the α,β-unsaturated ketone **10**. A second Michael addition (intramolecular) would then lead to the product **2**.[7] This sequence also can be readily extended to provide an explanation for the origin of the more complex β-keto esters **11**, **12**, and **13** which are obtained from glyoxal[3,6] (see Scheme II). The endo[6a] and exo[6b] isomers **11** and **12** can be assumed to arise through reaction of **2** (R = R′ = H) with intermediate **8** in a sequence of reactions which is perfectly analogous to formation of **2** itself from **8** and **1** via intermediates **9** and **10**. In addition, the hexacarbomethoxy derivative **13**[6c] could similarly originate from **2** by reaction with the α,β-unsaturated aldehyde **5** (R = R′ = H), the *E* isomer of **6**. The formation of the entire series of compounds can thus be explained in a uniform and consistent manner through a sequence of aldolizations and Michael additions.

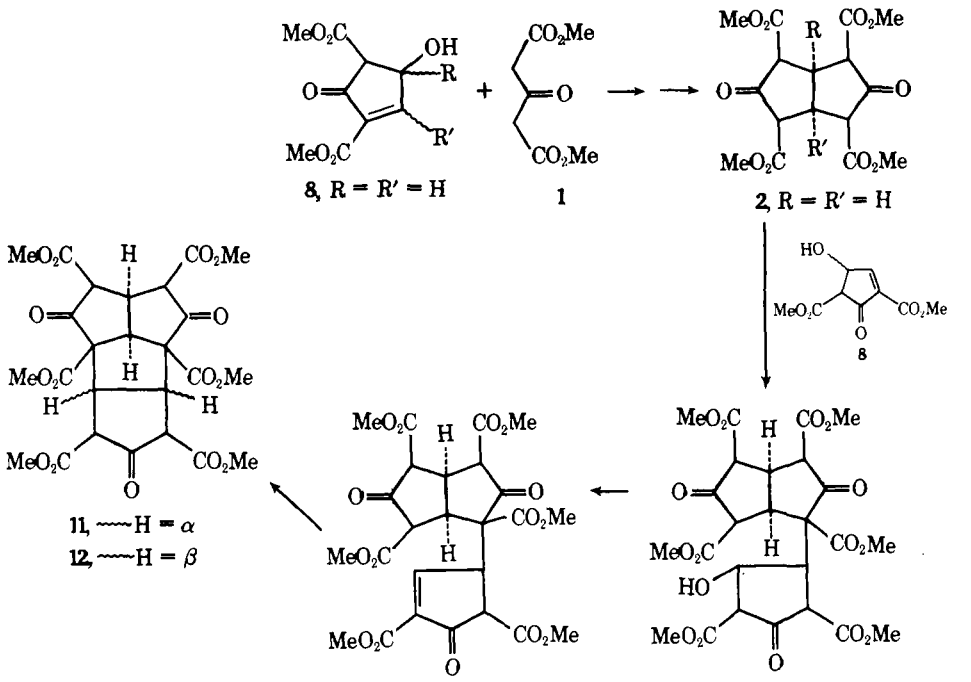
Since all the reactions outlined in Schemes I, II, and III are undoubtedly reversible, there would seem to be little hope for direct experimental verification. However, use of suitable 1,2-dicarbonyl compounds has now permitted the actual isolation of a 1:1 adduct (**17**, see below) derived from the monoaldolization product **4**, and of several 4-hydroxycyclopent-2-enones of type **8**. Several substances related to this latter type[8,9] have been isolated by Japp and his associates long before our work (see below). While none of these compounds can qualify as an actual intermediate in the formation

Scheme I



[a] The sequence 4 → 7 → 8 is plausible but at present highly conjectural; we have so far not encountered any diol of type 7.

Scheme II

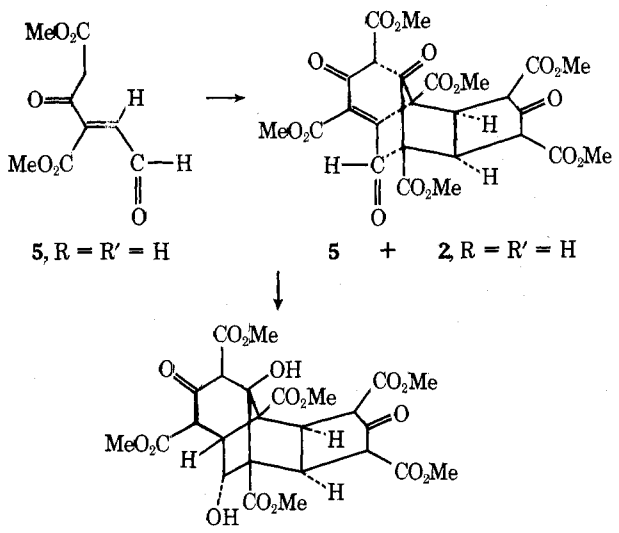


of substances of type **2**, **3**, **11**, **12**, or **13**, their isolation lends definite support to our interpretation of the course of the reactions illustrated in Schemes I–III.

Initial attempts to demonstrate the intermediate formation of 1:1 adducts of type **4**, **5**, **6**, or **8** in reactions of **1** with aliphatic or alicyclic 1,2-diketones were uniformly unsuccessful. For instance, when the reaction was carried out with a tenfold excess of the 1,2-dicarbonyl compound, cyclododecane-1,2-dione, in a citrate/phosphate buffer (pH 6.8) in the presence of methanol, the only product isolated or observed by TLC was the 1:2 adduct (**3**, n = 10).[4] Moreover, reaction of cyclododecane-1,2-dione (tenfold excess) and **1** with sodium methoxide in methanol similarly provided only the 1:2 adduct (**3**, n = 10).[4]

It seemed likely, however, that a 1,2-dicarbonyl compound with bulky groups adjacent to the keto functions might react to give a 1:1 intermediate unable, for steric reasons, to add a second molecule of **1** (step 8 → 9 in Scheme I). Camphorquinone (**14**) appeared to be a suitable α-diketone for this purpose. Reaction of **14** at room temperature with 1 equiv of **1** in citrate/phosphate buffer (pH 6.8)[10] for 1 week furnished a new compound which was obtained in pure, crystalline form by column chromatography in 20% yield, mp 138–140 °C. The empirical formula $C_{17}H_{24}O_7$, established by microanalysis and mass spectrometry (mol wt calcd and found 340), showed that the substance was a simple 1:1 adduct of **14** ($C_{10}C_{14}O_2$) and **1** ($C_7H_{10}O_5$). On heating with sodium methoxide in methanol, the adduct reverted to **14** and **1**, indicating that no rear-

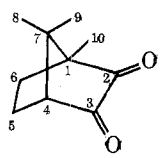
Scheme III



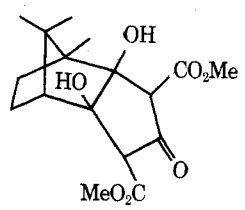
5, R = R′ = H 5 + 2, R = R′ = H

13

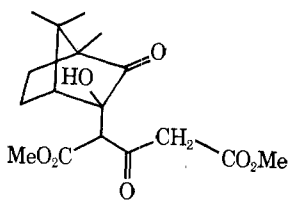
rangement had taken place during the formation of the C_{17} compound. These data are compatible with an aldol-type structure analogous to intermediates **4** or **7** in Scheme I, i.e., with formulas such as **15, 16,** or **17.**



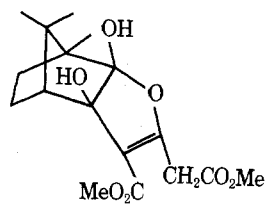
14



15



16



17

Spectroscopic findings excluded the possibility of structure **15.** The symmetry of such a 1,2-glycol, formed through aldolization of *both* carbonyls of **14,** would cause hydroxyl signals to appear at very similar chemical shifts in the NMR spectrum. In fact, the 220-MHz spectrum of the adduct exhibited two signals (singlets, 1 H each) but at very *different* locations (δ 3.35 and 4.48), indicative of a nonsymmetrical structure. The ^{13}C NMR spectrum (see below) is likewise quite incompatible with **15,** as are the ir and uv spectra.

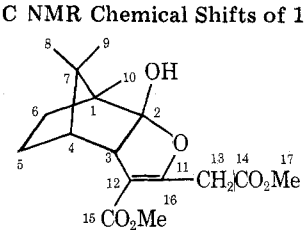
However, it would also be difficult to reconcile the various spectroscopic data with formula **16.** While the presence of *two* hydroxyl signals in the NMR spectrum could be rationalized as being due to enolization of the β-keto ester grouping,[5] the occurrence of a pair of doublets (1 H each) with J = 17.5 Hz, centered at δ 3.56 and 3.92, points clearly to a methylene group with nonequivalent protons, subject to geminal coupling.[11] These findings, and other spectroscopic observations to be discussed, however, can be readily accommodated by formula **17,** the hemiketal of the enol form of **16.** Here, the adjacent carbomethoxy group would interfere somewhat with the rotation of the side chain methylene group; this fact, together with influences from the endo protons of the methylenes of the norbornane system, would create the observed nonequivalence.

Formula **17** also finds strong support from the ir spectrum, which shows hydroxyl stretching bands at 3480 and 3410 cm^{-1}, a band at 1740 cm^{-1} (nonconjugated ester group), and, significantly, bands at 1695 and 1630 cm^{-1}. These latter two absorptions agree well with those reported for other compounds containing the chromophore $MeO_2C-C=C-O$; the iridoids genipin (ν 1695, 1630 cm^{-1})[12] and daphylloside (ν 1700, 1635 cm^{-1})[12] and the indole alkaloids mayumbine[13a] and serpentinine[13b] are pertinent examples.

The uv of **17** (λ_{max} 250.8 nm) is likewise compatible with the spectra of iridoids carrying a carbomethoxy group at C-4 (cf. inter alia, genipin and verbenalin, 240 nm, loganin, 237 nm, and daphylloside, 235 nm).[14] The plausible assumption can be made that the difference in size of the unsaturated heterocyclic ring, six membered in the iridoids, five membered in **17,** is responsible for the bathochromic shift of ~10 nm in the latter case.

Additional support for structure **17** can be obtained from examination of the ^{13}C NMR spectrum (see Table I). Signals from all 17 carbon atoms can be identified, but the spectrum definitely does not contain any resonance ascribable to a free carbonyl in a five-membered ring; this fact eliminates structures **15** and **16.** In contrast, the assignments of the observed signals are entirely compatible with formula **17.** The spectrum

Table I. ^{13}C NMR Chemical Shifts of 1:1 Adduct 17



17

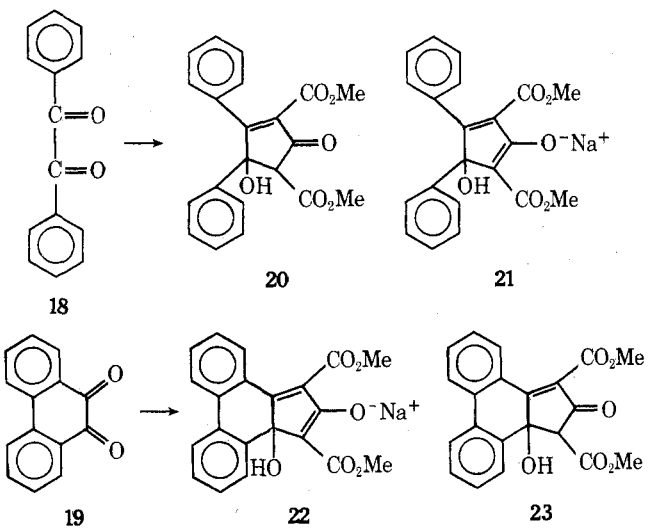
ppm[a]	Sford[b]	Carbon atom		ppm[a]	Sford[b]	Carbon atom	
168.3	s	14	a[c]	52.3	q	16	d[c]
165.2	s	15	a	51.3		17	d
162.9	s	11	a	49.7	s	1	c
117.3	s	12	b	34.6	t	13	
109.2	s	2	b	29.6	t	5	e
86.9	s	3		24.9	t	6	e
54.7	d	4		22.1	q	9	f
53.1	s	7	c	21.5	q	8	f
				9.8	q	10	f

[a] Measured from $(CH_3)_4Si$ standard. [b] Multiplicites observed on angle frequency off-resonance decoupling. [c] Assignments within lettered groups may be interchanged.

contains signals from two fully substituted vinylic carbon atoms [C-11, 162.852 ppm; C-12, 117.259 ppm (see Table I)], one of which is deshielded due to the bond to an oxygen atom. Furthermore, the resonances from two fully substituted carbon atoms are located downfield; one of these is bound to hydroxyl (C-3), while the other is attached to two oxygen atoms (C-2). The formulation of **17** with the stereochemistry shown is based on analogous reactions of **14** with lithium aluminum hydride[15] and Grignard reagents.[16] The assignment[17] was further corroborated by the lanthanide-induced shifts of the "carbon-bound" methyl functions of **17**, which are similar to ones described in analogous systems recently reported by Burgstahler.[18]

As mentioned previously, reaction of cyclododecane-1,2-dione with **1** in methanolic sodium methoxide gave the propellanedione (**3**, $n = 10$)[4] as the only isolable product, although traces of another compound were observed by TLC. However, reaction of **14** with **1** under the same conditions yielded exclusively the 1:1 adduct **17**.

In contrast to the behavior of the aliphatic and alicyclic 1,2-dicarbonyl compounds, fully aromatic α-diketones (Ar–CO–CO–Ar) such as benzil (**18**) and phenanthrenequinone

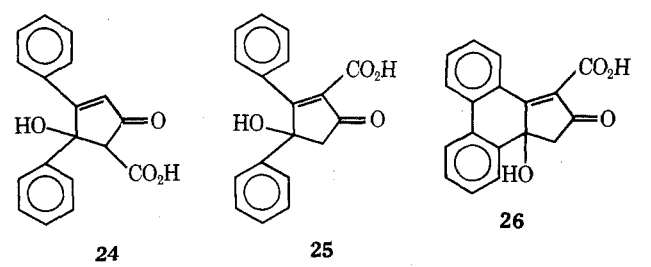


18 20 21

19 22 23

(**19**) failed to react with **1** in aqueous methanol (buffer added, either pH 6.8 or 8.4). In more strongly alkaline media, 1:1 adducts **20** and **23** of the type **8** were readily obtained.

Some related 4-hydroxycyclopent-2-enones have been prepared in the 1890's during the classical studies of Japp and co-workers. Japp and Lander, e.g., reported that they obtained the dicarboxylic acid corresponding to **20** by reaction of benzil (**18**) with free β-ketoglutaric acid in alcoholic KOH.[8] In addition, the acid[8] **24**[8,19] was reported by Japp and co-workers



24 25 26

to result from loss of CO_2 from the diacid of **20**; however, this structure has recently been revised to **25**.[1] In similar experiments, Japp and Klingemann[20] reported that the reaction of **19** and acetoacetic acid yielded the 1:1 adduct **26**; this was later reinvestigated by Cope and MacDowell and the structure of **26** was confirmed.[21]

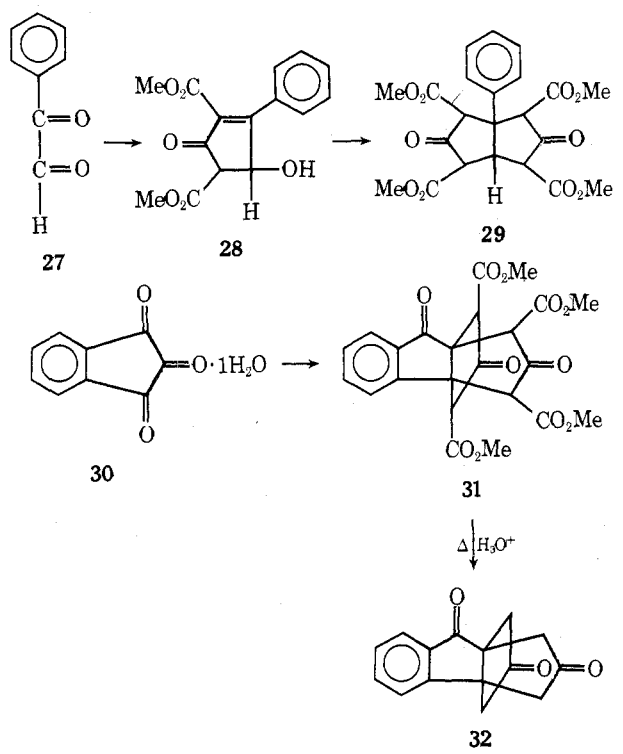
We had previously obtained the 4-hydroxycyclopent-2-enone **20** by reaction of **18** and **1** in alcoholic KOH[4] under conditions similar to those described in the literature.[9a-c] When this same procedure was employed in the reaction of **19** and **1**, a compound (M^+ at *m/e* 364) corresponding to the alcohol **23** was isolated. However, it was contaminated with impurities of high molecular weight and was not obtained completely pure. In the course of the investigation of the reactions of **18** and **1**, we had carried out this condensation in methanolic sodium methoxide, from which yellow crystals precipitated in 50% yield. The same compound (mp 227–235 °C dec) was obtained by stirring the cyclopent-2-enone **20** with sodium methoxide in either methanol or ethanol. This new compound is therefore **21**, the sodium enolate of **20**. Spectroscopic data were in agreement with this assignment; treatment of the salt **21** with cold, dilute hydrochloric acid (0.1 N) converted it back to **20**. Reaction of **20** with potassium methylate in methanol at room temperature did not produce an analogous enolate; however, heating the solution and subsequent removal of most of the solvent produced a yellow, crystalline potassium salt in amounts too small for study. While our work was in progress a brief mention of a similar sodium compound generated by Harris and co-workers appeared and confirmed our assignment.[22]

Alkali enolates, often colored, have been obtained repeatedly from cyclic β-keto esters related to **2**; cf. e.g., the red mono- and yellow disodium enolates of a derivative of **2** (R = R′ = H) which were discovered by Vossen[23] and studied more recently by Yates et al.[24] Because the enolate salts crystallize rapidly from methanol, it was felt that reaction of **19** with **1** in methanolic sodium methoxide would generate the methanol-insoluble salt **22**, so that further reaction would be stopped. Production of high molecular weight impurities found in ethanolic potassium hydroxide would thus be held to a minimum. This was found to be the case. The sodium enolate **22** precipitated in 68% yield as red-orange crystals (mp 263–270 °C) when **19** and **1** were stirred for 4 h in methanolic sodium methoxide. Acidification with cold hydrochloric acid (0.1 N) furnished the pure 4-hydroxycyclopent-2-enone **23** as a yellow powder (mp 175 °C dec).

The tendency of **18** and **19** to provide 1:1 adducts with **1** and related compounds (e.g., the corresponding free acid)[1] appears to be quite typical of fully aromatic (Ar–CO–CO–Ar) α-dicarbonyl compounds, although strongly alkaline conditions seem to be required. This behavior contrasts with that of aliphatic and alicyclic 1,2-diones which furnish 1:2 adducts in weakly acidic,[3,4,6] neutral,[6] weakly alkaline, or strongly alkaline media.[4,25] The formation of the 1:1 adduct **17** from **14** is the exception rather than the rule and is undoubtedly due to steric factors.

Surprisingly, compounds (Ar–CO–CO–R) in which the 1,2-dicarbonyl system is bound to only one aromatic ring seem not to occupy an intermediate position but to resemble their aliphatic or alicyclic congeners more than **18** or **19**. Two such compounds have been studied to date: phenylglyoxal (**27**) and ninhydrin (**30**).

Reaction of **27** with **1** in bicarbonate buffer (pH 8.4) at room temperature for 60 h produced a yellow solution, which furnished a copious precipitate when it was acidified to pH 1 with sulfuric acid (6 M). Recrystallization from methanol gave the pure 1:2 adduct [**29** (**2**, R = C_6H_5; R′ = H)], mp 147–148 °C. The yield of recrystallized product was 65%. The same reaction was carried out in citrate/phosphate buffer (pH 6.8) for 3 days and furnished an oil which was extracted into chloroform. Column chromatography on silica gel gave a 27% yield of **29**; however, both TLC and mass spectrometry revealed the presence of another, more polar substance in the crude oil. The molecular weight (mass spectrometry) of this product, *m/e* 290, is that expected for the 1:1 adduct **28**, and the fragment corresponding to the loss of methanol ($M^+ - 32$), typical of these β-keto esters,[4] was present. Unfortunately, this com-



pound proved to be very elusive; all attempts at isolation so far yielded only **29** or material of higher molecular weight. The lability of **28** can be understood by assuming reversion to **27** and **1** by retroaldolization, or loss of the second molecule of water to give the unstable cyclopentadienone. In the first case, the compounds formed would recombine to give **29**, while dimerization of the intermediate cyclopentadienone would lead to products of high molecular weight.

In the case of ninhydrin (**30**), only the 1:2 adduct, the propellane derivative (**31**, mp 95–98 °C) has been observed; it was converted readily into the trione (**32**, mp 172.5–174 °C) by acid hydrolysis.[26]

It would seem plausible that the fully aromatic α-diketones do not add a second molecule of glutarate **1**, for the enone system is stabilized by overlap with the π bonds of the phenyl ring; however, this effect would also be expected to occur in the monoaromatic cases (Ar–CO–CO–R), but apparently does not. Work is in progress at present to explain the difference in reactivity of these closely related systems.

Experimental Section

Microanalyses were performed on an F & M Scientific Corp. Carbon, Hydrogen, Nitrogen Analyzer Model 185; some analyses were also performed at the National Institutes of Health, Bethesda, Md. Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. Nuclear magnetic resonance spectra were recorded on Varian T-60 and 220 MHz spectrometers. Infrared spectra were taken on a Beckman Acculab-1 instrument. The ultraviolet spectra were recorded on a Cary 17 spectrophotometer, and mass spectra on Finnigan 1015 and AEI MS-902 instruments.

Analytical TLC plates used were E. Merck Brinkmann uv active silica gel on plastic. The citrate/phosphate buffer (pH 6.8) was prepared by dissolving disodium hydrogen phosphate heptahydrate (11.67 g) and citric acid (3.68 g) in water (900.00 ml). The bicarbonate buffer (pH 8.4) was prepared by dissolving $NaHCO_3$ (1.40 g) in water (100.00 ml). Camphorquinone, benzil, phenanthrenequinone, phenylglyoxal, ninhydrin, and dimethyl β-ketoglutarate were purchased from Aldrich Chemical Co.

Reaction of Camphorquinone (14) with Dimethyl β-Ketoglutarate (1) to Produce the 1:1 Adduct (17). Camphorquinone (**14**, 5 g, 0.030 mol) was dissolved in methanol (70 ml). Citrate/phosphate buffer (pH 6.8) was added until the solution became turbid, whereupon small amounts of methanol were added to clarify the solution. To this solution, dimethyl β-ketoglutarate (**1**, 10.5 g, 0.060 mol) was added and the liquid stirred at room temperature for 1 week. It was next extracted with ether (5 × 100 ml); and the combined extracts were washed with water and dried (Na_2SO_4). Removal of solvent at reduced pressure afforded 8.1 g of a solid shown by TLC to consist of **17** and starting materials. The adduct **17** was isolated by column chromatography (silica gel) using petroleum ether (bp 30–60 °C)/benzene as eluent. Recrystallization from methanol furnished white needles (2.1 g, 20%) of mp 138–140 °C: uv λ_{max} (MeOH) 250.8 nm; R_f 0.19 (10% ethyl acetate in benzene); ir (KBr) 3480 and 3410 (OH absorptions), 1740 (saturated ester), 1687 (conjugated ester), and 1630 cm^{-1} (>C=C<); NMR ($CDCl_3$) δ 0.94 (3 H, s), 1.0 (3 H, s), 1.28 (3 H, s), 1.30–1.70 (4 H, broad multiplet), 2.1 (1 H, d, J = 4 Hz), 3.35 (1 H, s, OH) 3.56 (1 H, d, J = 17.5 Hz), 3.71 and 3.73 (6 H, 2 OCH_3 singlets), 3.92 (1 H, d, J = 17.5 Hz), and 4.48 (1 H, s, OH). The singlets at δ 3.35 and 4.48 disappeared on treatment with D_2O. Mass spectrum (electron impact): m/e at 340 (5.5), 322 (5.5 $M^+ - 18$), 310 (30.3, $M^+ - 30$), 308 (10, $M^+ - 32$), 291 (36), 280 (100), 275 (17.2), 252 (38), 249 (56).

Anal. Calcd for $C_{17}H_{24}O_7$: C, 60.00; H, 7.10. Found: C, 60.14; H, 7.18.

Retroaldolization of 17 by Treatment with Base. The hemiketal (1 g) was dissolved in methanol (25 ml) and sodium methoxide (100 mg) was added. The solution was heated gently for 0.5 h. TLC showed the presence of two compounds with R_f values identical with those of **14** and **1**. These two compounds were separated by preparative TLC (silica gel) and were identified by comparison of their mass spectra with those of authentic samples.

Reaction of Benzil (18) and Dimethyl β-Ketoglutarate (1) in Sodium Methoxide and Methanol. Sodium Enolate (21) of Alcohol 20. Benzil (**18**, 2.1 g, 0.010 mol) was dissolved in methanol (125 ml) and sodium methoxide (1.0 g, 0.020 mol) was added. To the resulting solution, dimethyl β-ketoglutarate (**1**, 1.74 g, 0.0100 mol) was added and the mixture was stirred at room temperature for 24 h. Yellow crystals (**21**, 2.0 g, 50%) were filtered from the solution. They were identical with the product obtained by treating **20** with sodium methoxide in methanol or ethanol: mp 227–235 °C dec; ir (KBr) 3500 (s, OH), 3600–3300 (broad OH), 1695 (C=O), 1655 (C=C), and 1005 cm^{-1} (C–O); NMR (pyridine-d_5) δ 3.7 (6 H, s, 2 OCH_3) and 7.0–8.0 (10 H, broad multiplet). Tests indicated the presence of sodium in the salt.

Treatment of the enolate salt **21** with cold aqueous hydrochloric acid (0.1 N) yielded the 4-hydroxycyclopent-2-enone **20** whose properties were identical with those reported previously by several groups.[4,9]

Reaction of Benzil (18) with Dimethyl β-Ketoglutarate in Potassium Methoxide/Methanol. Reaction of benzil (**18**) with **1** in the same proportions as before but with potassium methoxide (0.02 mol) in place of sodium methoxide yielded no crystals on stirring at room temperature. After heating for several hours, followed by evaporation of most of the solvent, a yellow, crystalline potassium salt of **20** was isolated in very low yield. Acidification of this solid gave the previously characterized alcohol **20**.

Reaction of Phenanthrenequinone (19) with Dimethyl β-Ketoglutarate (1) in Sodium Methoxide and Methanol to Provide the Sodium Enolate (22) of 23. Phenanthrenequinone (**19**, 1.0 g, 0.0048 mol) was suspended in methanol (50 ml). Dimethyl β-ketoglutarate (**1**, 0.84 g, 0.0048 mol) and sodium methoxide (0.52 g, 0.0095 mol) were added to the mixture in that order. The phenanthrenequinone dissolved gradually, and red-orange crystals of **22** (1.3 g, 68%) precipitated from the solution during 4 h. They were filtered off and dried: mp 263–270 °C dec; ir (KBr) 3600–3350 (broad OH peak), 1705 (C=O, intense), 860 (s), 840 (s), and 825 cm^{-1} (s); NMR (Me_2SO-d_6) δ 3.60 (3 H, s, OCH_3), 3.64 (3 H, s, OCH_3), 7.1–8.3 (8 H, aromatic multiplet). Tests for sodium were positive.

The red-orange crystals (**22**) were treated with cold aqueous hydrochloric acid (0.1 N). The red color disappeared and a yellow powder (**23**) precipitated from the solution: mp 175 °C dec; ir (KBr) 3440 (sharp, OH), 1750 (C=O, ester), 1725 (cyclopentenone), 1710 (unsaturated ester), 760 (s), and 732 cm^{-1} (s); NMR (Me_2SO-d_6) δ 3.70 (3 H, s, OCH_3), 3.76 (3 H, s, OCH_3), 4.8 (1 H, s), 6.45 (1 H, s, OH), 7.10–8.30 (8 h, broad multiplet). The peak at δ 6.45 disappeared on treatment with D_2O. Mass spectrum: m/e 364 (80, M^+), 348 (30), 346 (15), 332 (50), 316 (90), 305 (50), 273 (95), 257 (100).

Anal. Calcd for $C_{21}H_{16}O_6$: C, 69.20; H, 4.39. Found: C, 69.21; H, 4.52.

Reaction of Phenanthrenequinone (19) with Dimethyl β-Ketoglutarate (1) and Potassium Hydroxide in Ethanol to Furnish 4-Hydroxycyclopentenone (23). Phenanthrenequinone (**19**, 0.7 g, 0.0033 mol) was placed in ethanol (25 ml) and dimethyl β-ketoglutarate (**1**, 0.64 g 0.0036 mol) was added. To the slurry, potassium hydroxide (0.1 g) was added and the reaction mixture was stirred for

24 h. A yellow solid was filtered from the reaction; its ir spectrum was very similar to that of product **23**. The mass spectrum indicated the presence of the alcohol (M^+, 364); however, other products with mass numbers in the 500–600 region were present. The yellow solid **23** had the same R_f as that of the alcohol **23** obtained by acidification of the red-orange salt **22** above.

Tetramethyl 1-Phenylbicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate (29). Phenylglyoxal monohydrate (**27**, 2.50 g, 0.0164 mol) was dissolved in aqueous sodium bicarbonate (100 ml, pH 8.4). After the solution was stirred for 2 min, dimethyl β-ketoglutarate (**1**, 5.71 g, 0.0328 mol) was added in one portion, whereupon the solution immediately turned yellow. After stirring for 60 h, the reaction was acidified to pH 1 with aqueous sulfuric acid (6 N); a pink solid precipitated from the solution. This solid was recrystallized from methanol to furnish white crystals of **29** (4.79 g, 65.6%): mp 147–148 °C; ir (KBr) 3015 (C–H, aromatic) and 1740 cm^{-1} (broad ester carbonyl); NMR ($CDCl_3$) δ 3.50–3.80 (14 H, 4 overlapping singlets of unequal intensity), 4.36 (1 H, s), 7.28 (5 H, s, aromatic), 10.02 (1 H, s, enol proton), and 10.82 (1 H, s, enol proton). The signals at δ 10.02 and 10.82 disappeared on treatment with D_2O. Mass spectrum: *m/e* 446 (13, M^+), 414 (57, $M^+ - 32$), 383 (36), 382 [100, $M^+ - (2 \times 32)$], 351 (36), 350 [100, $M^+ - (3 \times 32)$], 323 (46), 322 (29), 318 (26), 292 (46), 282 (24), 276 (38).

Anal. Calcd for $C_{22}H_{22}O_{10}$: C, 59.18; H, 4.97. Found: C, 58.93; H, 4.94.

Preparation of Tetramethyl 1-Phenylbicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate (29) at pH 6.8. Phenylgloxal monohydrate (**27**, 2.50 g, 0.0164 mol) was dissolved in citrate/phosphate buffer (70 ml, pH 6.8). Dimethyl β-ketoglutarate (**1**, 5.71 g, 0.0328 mol) was added all in one portion to the solution. After 3 days, an oil had formed at the bottom of the flask. The mixture was extracted with chloroform (3 × 60 ml). The organic layer was dried (Na_2SO_4) and the solvent removed under reduced pressure to yield an oil which was shown by TLC to be composed of two compounds (R_f 0.10 and 0.86; 2:98 acetic acid/ethyl acetate). This oil (6.25 g) was purified by column chromatography (gradient elution with benzene/ethyl acetate) and yielded a white, crystalline solid (**29**, 2.00 g, 27%) identical in all respects with the 1:2 adduct (**29**) from the previous experiment. The R_f of the 1:2 adduct was 0.86, while the compound of R_f 0.10 has tentatively been assigned structure **28**. The molecular ion of the 1:1 adduct (M^+, 290) was observed in the mass spectrum of the crude oil. In addition a peak at *m/e* 258 could be attributed[4] to the loss of methanol from the parent ion (290) of the 1:1 adduct (**28**). Neither the peak at *m/e* 290 nor the one at *m/e* 258 was found in the spectrum of the 1:2 adduct **27** or the starting materials. Many attempts to isolate the 1:1 adduct **28** were made; however, only decomposition products and **29** were obtained.

Tetramethyl Benzo[3,4]tricyclo[3.3.3.0^{1,5}]undeca-2,7,10-trione-6,8,9,11-tetracarboxylate (31). Dimethyl β-ketoglutarate (**1**, 3.90 g, 0.022 mol) was added to aqueous sodium bicarbonate solution (100 ml, pH 8.4) and the resulting mixture was stirred until the glutarate dissolved. Ninhydrin monohydrate (**30**, 2.00 g, 0.0110 mol) was added to the reaction in one portion and the mixture was stirred for 72 h. The reaction was then acidified to pH 1 with aqueous sulfuric acid (6 M). A white solid precipitated from the solution, which was crystallized from methanol to furnish a 59.2% yield of **31** (2.13 g): mp 95–98 °C; ir (KBr) 2955, 1750–1720 (broad carbonyl), and 1665 cm^{-1} (enol form of β-keto ester); NMR ($CDCl_3$) δ 3.27 (3 H, m), 3.50 (12 H, overlapping singlets), 7.20–7.67 (4 H, m, aromatic protons), and 8.58 (2 H, broad band, enolic protons); mass spectrum *m/e* 472 (2, M^+), 440 (6), 414 (7), 408 (2), 382 (13), 340 (13), 323 (13), 280 (26), 82 (100).

Anal. Calcd for $C_{23}H_{20}O_{11}$: C, 58.48; H, 4.27. Found: C, 58.76; H, 4.22. High-resolution mass spectrum, calcd for $C_{23}H_{20}O_{11}$, 472.1005; found, 472.1027.

Benzo[3,4]tricyclo[3.3.3.0^{1,5}]undeca-2,7,10-trione (32). The tetracarbomethoxy propellanetrione (**31**, 4.5 g, 0.0095 mol) was added to a mixture of glacial acetic acid (55 ml), concentrated hydrochloric acid (40 ml), and water (20 ml). The mixture was refluxed for 10 h and a portion of the excess acid was removed under reduced pressure. The resulting solution was made alkaline with sodium hydroxide/sodium bicarbonate solution and extracted with chloroform (3 × 100 ml). The organic layer was washed with water and dried over sodium sulfate and the solvent removed under reduced pressure to furnish an oil, which crystallized after dissolution in methanol to furnish yellow crystals (**32**, 1.47 g, 70%): mp 172.5–174 °C; ir (KBr) 3060 (aromatic C–H), 1735 (cyclopentanone carbonyl), and 1700 cm^{-1} (conjugated carbonyl); NMR ($CDCl_3$) δ 2.62 (2 H, d, J = 20 Hz), 2.83 (4 H, s) 3.05 (2 H, d, J = 20 Hz), and 7.23–7.93 (4 H, m, aromatic protons). One of the peaks of the AB quartet overlapped with the singlet at δ 2.83. Mass spectrum: *m/e* 240 (26, M^+), 212 (19), 199 (24), 198 (100), 184 (10), 171 (16), 170 (81), 156 (26).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.67; H, 5.17.

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Registry No.—**1**, 1830-54-2; **14**, 465-29-2; **17**, 60428-14-0; **18**, 134-81-6; **19**, 84-11-7; **20**, 16691-78-4; **21**, 60428-15-1; **22**, 60428-16-2; **23**, 60428-17-3; **27**, 1074-12-0; **29**, 60428-18-4; **30**, 938-24-9; **31**, 60428-19-5; **32**, 60428-20-8.

References and Notes

(1) (a) J. Oehldrich and J. M. Cook, *Can. J. Chem.*, in press. Part 3 in this series. (b) Undergraduate research participants.
(2) This paper also constitutes part 6 in the series "Reactions of Dimethyl β-Ketoglutarate with 1,2-Dicarbonyl Compounds", by U. Weiss and coworkers. Part 5: K. C. Rice and U. Weiss, in press.
(3) U. Weiss and J. M. Edwards, *Tetrahedron Lett.*, 4885 (1968).
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(5) For convenience, these esters are written in the keto form; actually, P. Camps [*Tetrahedron Lett.*, 4067 (1974)] has shown that **2** (R = R′ = H) exists as one of the possible dienols in chloroform solution.
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(7) This sequence could easily be formulated with fewer steps, if it were assumed that intermediate **8** lost a second molecule of water to give the corresponding cyclopentadienone, which could produce **2** directly by double Michael addition of another molecule of **1**. However, such cyclopentadienones (other than those stabilized by aromatic rings, see below), if formed at all under the mild conditions of our reaction, would undoubtedly dimerize at once by Diels–Alder reactions, yielding the corresponding endocarbonyl cyclohexenes. These dimerizations have been studied by C. F. H. Allen, *Chem. Rev.*, **37**, 709 (1945). No compounds of this type have been encountered in any part of our work.
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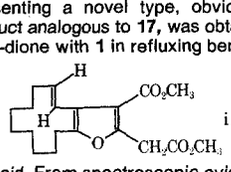
(26) A 1:1 adduct representing a novel type, obviously derived from a monoaldolization product analogous to **17**, was obtained through reaction of cyclododecane-1,2-dione with **1** in refluxing benzene in the presence



i

of *p*-toluenesulfonic acid. From spectroscopic evidence, this adduct has a furanoid structure and appears to be i. It will be discussed elsewhere: O. Campos and J. M. Cook, manuscript in preparation.