Reaction of Dimethyl 3-Ketoglutarate with 1,2-Dicarbonyl Compounds. 5.[1] Simple Synthesis of Derivatives of 2,3,3a,4,5,9b-Hexahydro-1*H*-benz[*e*]indene from Dimethyl 3-Ketoglutarate and Glyoxal

Kenner C. Rice and Ulrich Weiss*

Laboratory of Chemical Physics, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Maryland 20014

J. V. Silverton and G. John Shaw

Laboratory of Chemistry, National Heart, Lung and Blood Institute, Bethesda, Maryland 20014

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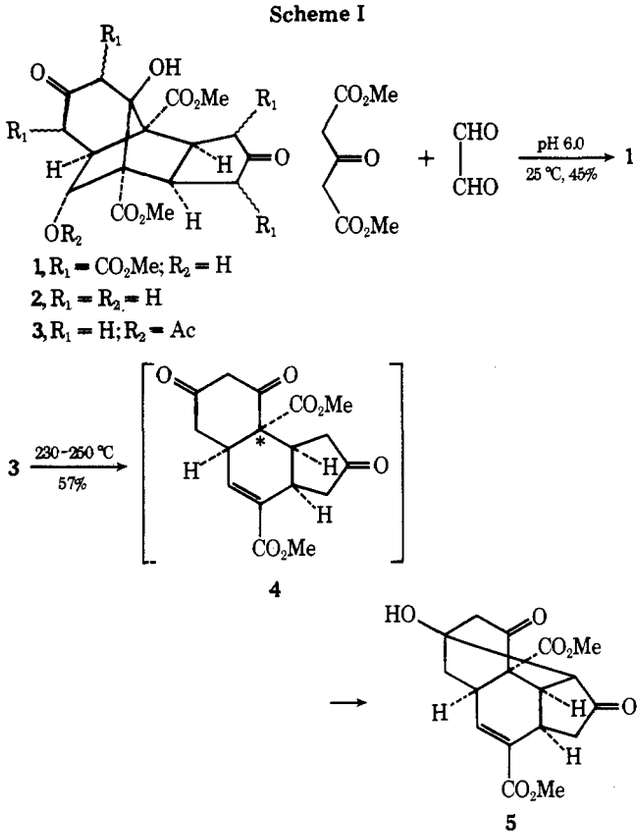
Treatment of either of the tetracyclic aldols **3** or **5** (themselves readily available in three simple steps from dimethyl 3-ketoglutarate and glyoxal) with excess sodium methoxide in boiling methanol gives the 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indene derivative **6a** in good yield. The structure of this compound was assigned on the basis of spectral data; the resulting assignment was confirmed by x-ray crystallographic analysis of the dimethyl ether **8** of **6a**. The unexpected aromatization involved in the formation of **6a** seems to proceed with a 1,3 shift of a quaternary carbomethoxy group, presumably by way of an intermediate cyclobutanone. Further transformations of **6a** are described.

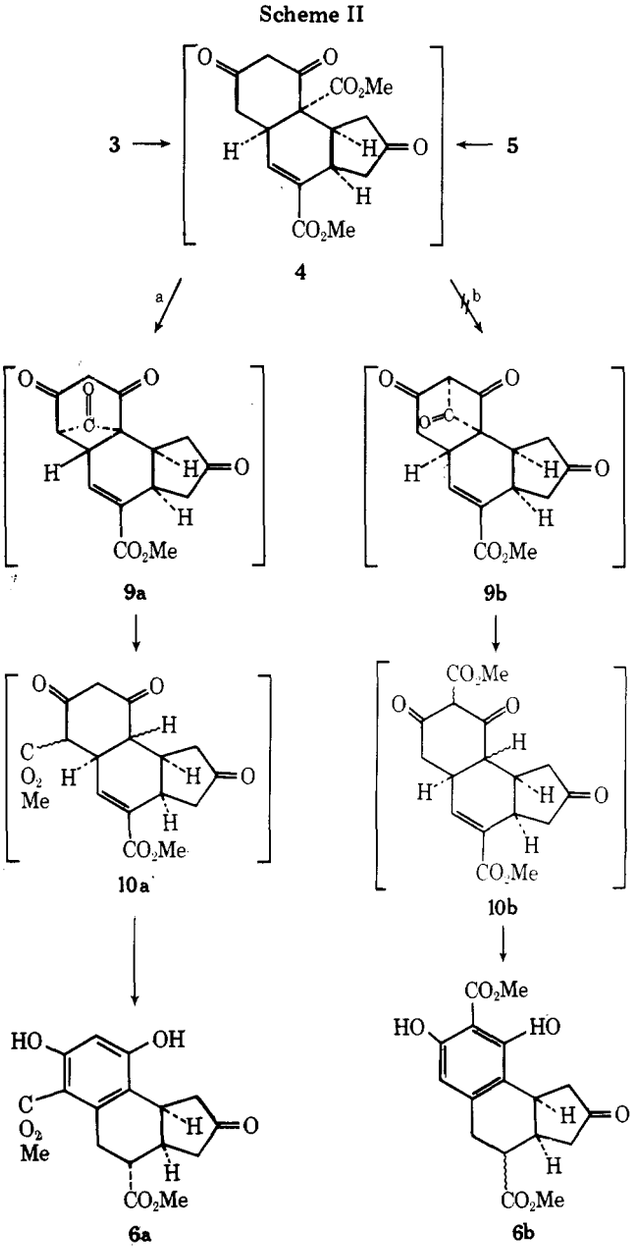
In the preceding communication[1] of our series concerning certain biomimetic-type reactions, we have described (Scheme I)[2] the ready formation of the tetracyclic aldol (**2**) by partial

Scheme I

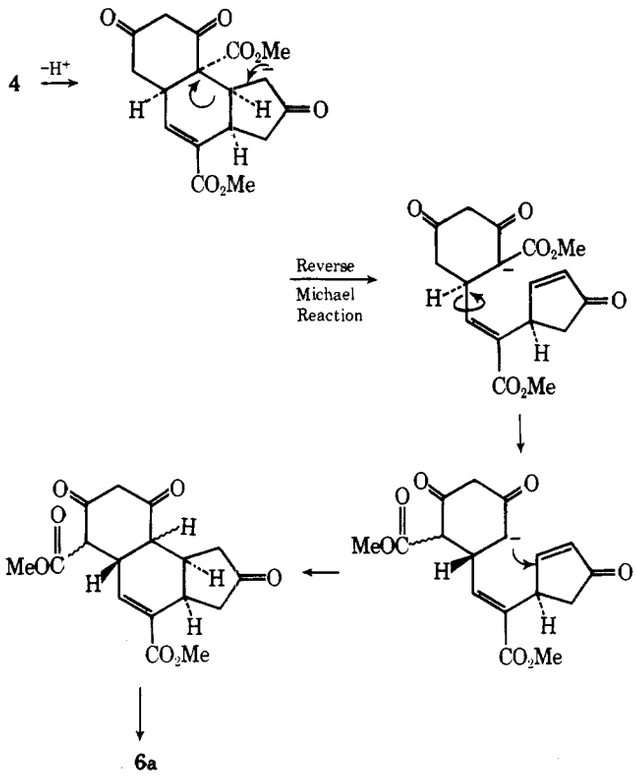


acid hydrolysis and decarboxylation of the corresponding hexacarbomethoxy derivative (**1**), which itself is formed in 45% yield by simply stirring a solution of dimethyl 3-ketoglutarate and glyoxal at room temperature in aqueous solution buffered to pH 6.0. Pyrolysis of **3**, the monoacetate of **2**, was shown to give **5**, obviously arising through intramolecular aldolization of a primary thermolysis product **4**. We now wish to describe the facile synthesis of derivatives of 2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indene through an unexpected base-catalyzed aromatization of **3** or **5** which involves an apparent 1,3 shift of a carbomethoxy group.

Scheme II



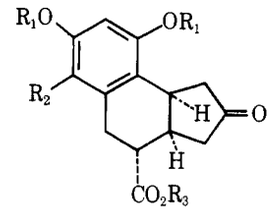
Scheme III



Action of sodium methoxide (10 equiv) in refluxing methanol upon either **3** or **5** converted both compounds, in about 60% yield, into a new substance, **6a**, isomeric with **5**, which gave a diacetate **7** and a dimethyl ether **8**. The formation of these two derivatives, a singlet, 1 H, at δ 6.38 in the NMR spectrum of **6a**, and other spectral data suggested a diphenolic structure with a single free position on the aromatic ring. Conversion of **3**, **4**, or **5** to a benzenoid compound *isomeric* with **5** can obviously take place only if the quaternary nature of the carbon marked by an asterisk is altered. A priori, two possibilities for such a change can be formulated. The one which we prefer is illustrated in Scheme II. As shown there, it could yield either one of two isomeric aromatic compounds, **6a** and **6b**; it will be shown below that **6a** is the one actually obtained. In both cases, dealdolization of **5** to **4** by the NaOMe is assumed. Internal, base-promoted acylation of **4** can next produce two different cyclobutanone intermediates, **9a** or **9b**. The four-membered rings in these intermediates would then undergo cleavage as indicated, to give **10a** or **10b**, respectively. Their conversion to the aromatic structures, **6a** and **6b**, by enolization, extraction of the doubly allylic proton at the ring juncture by the base,[3] and shift of the double bond into the ring seems reasonable; the aromaticity of the resulting structure provides a powerful driving force. The apparent shift of the carbomethoxy group[4] by way of an intermediate cyclobutanone has its exact precedent in the sequence[5] generally accepted[4] to occur in the so-called "abnormal Michael reactions", e.g., the addition of diethyl ethylmalonate to ethyl crotonate,[6] which takes place in the presence of excess NaOMe under conditions very similar to ours.

This mechanism of the aromatization reaction provides a satisfactory interpretation of the observed facts, and it is based on well-established precedent. However, an alternative possibility has been pointed out to us by Professor R. Morrin Acheson, Oxford, after completion of this work; it is shown in Scheme III. Evidently, this sequence can only yield **6a**. We are not aware of a practicable way of deciding conclusively between the mechanisms given in Schemes II and III. We prefer the former on account of its similarity to the anomalous Michael reaction, and because of the negative outcome of a test of the alternative, which was suggested by Professor W. B. Whalley, London, and kindly carried out in his laboratory. It is based on the assumption that the ionic intermediate involved in this sequence might become stabilized not only by the intramolecular Michael reaction shown, but also by Michael addition of an active external nucleophile added in excess. However, addition of nitromethane, dimethyl malonate, or thiophenol had no detectable influence upon the course of the reaction or the yield of the aromatization product.

Except for the ^{1}H NMR spectrum, the spectroscopic properties of the aromatic compound are compatible with either structure **6a** or **6b**. Decision in favor of the former is



6a, R_1 = H; R_2 = CO_2Me; R_3 = Me
7, R_1 = Ac; R_2 = CO_2Me; R_3 = Me
8, R_1 = R_3 = Me; R_2 = CO_2Me
11, R_1 = R_3 = H; R_2 = CO_2H
12, R_1 = R_2 = R_3 = H
13, R_1 = R_3 = Me; R_2 = H

based on the presence, in the ^{1}H NMR spectrum, of two signals from the phenolic hydroxyls (D_2O-exchangeable singlets, 1 H each) with widely different chemical shifts: δ 6.79 and 11.60, respectively. These δ values prove that only *one* of the two hydroxyls, the one giving rise to the signal at δ 11.60, is adjacent to the aromatic carbomethoxy group and hydrogen-bonded to it. This situation prevails in **6a**, while in **6b** both hydroxyls would be bonded, and should produce coinciding or closely adjacent signals at much lower field than δ 6.79. Our findings on model compounds prove the correctness of this interpretation: methyl 2,6-dihydroxybenzoate, δ 9.78 (D_2O-exchangeable singlet, 2 H); methyl 2,4-dihydroxybenzoate, δ 6.55 and 11.28 (D_2O-exchangeable singlets, 1 H each).

The free acid (**11**) corresponding to **6a** should lose CO_2 with great ease to give the resorcinol (**12**), readily recognizable as such by the characteristic NMR signals for two aromatic protons in meta relationship. Saponification of **6a** with aqueous sodium hydroxide, followed by acidification of the warm solution with hydrochloric acid, gave **12** directly. The compound showed the expected AB system, with the signals centered at δ 6.18 and 6.30, J = 2.3 Hz. Treatment of **12** with dimethyl sulfate and K_2CO_3 in acetone gave **13**.

The structural assignment for each new compound reported in this work was strongly confirmed by the corresponding ^{13}C NMR spectrum; all spectra were fully consistent with the assignments formulated. These spectra, together with those of a number of closely related compounds previously described,[1,7-9] will be discussed elsewhere.

The NMR spectra of **6a**, **7**, **8**, **12**, and **13** were too complex for complete analysis and provided no evidence concerning the configuration of the carbomethoxy group on the alicyclic ring in **6a**, **7**, **8**, and **13**, or the carboxyl group in **12**. In order to settle this point, and to provide unequivocal confirmation of the structure of **6a**, an x-ray crystallographic analysis of the well-crystallized dimethyl ether **8** was undertaken. This analysis proves that **6a** has indeed the structure assigned by us, and that the orientation of the carbomethoxy group is cis to the hydrogens at the ring juncture.

The x-ray crystallographic data are summarized in Table I. The molecule in its crystal conformation is shown in Figure

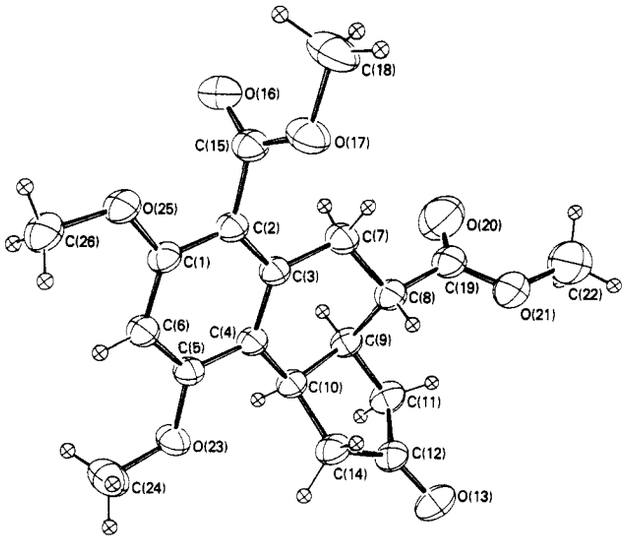


Figure 1. The molecule 8 in its crystal conformation. The heavier atoms are drawn with 40% probability ellipsoids and the hydrogen atoms are arbitrary spheres.

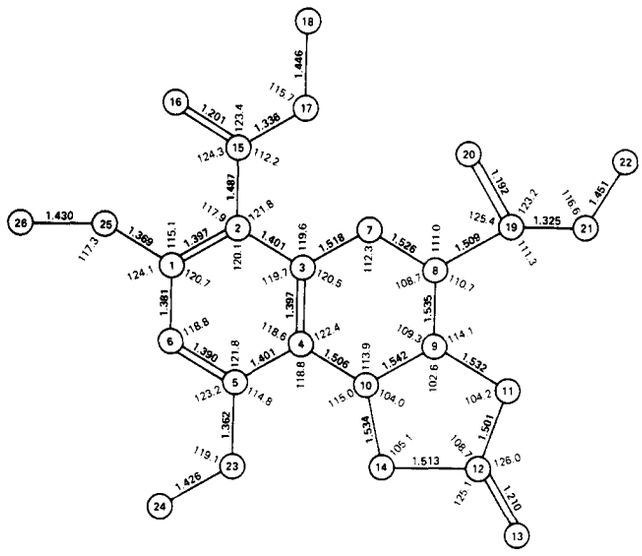


Figure 2. The bond lengths and angles of 8. Esd's of bond lengths range from 0.002 to 0.003 Å for atoms in the nucleus and are less than or equal to 0.005 Å for substituted atoms. Esd's of angles are less than or equal to 0.2°.

Table I. Crystal and Refinement Data

Mol formula	$C_{19}H_{22}O_7$	Space group	$P\bar{1}$ (no. 2)
Formula weight	362.38	Habit	Prismatic
		Crystal size	0.4 × 0.25 × 0.18 mm³
Cell parameters[a]		X-radiation	Cu Kα[b]
		λ	1.5418 Å
		Diffractometer	Nonius CAD-4
a	9.558 (1) Å	Reflections	3584 (793 unobsd 1σ)
b	10.336 (2) Å		
c	10.662 (1) Å	Max sin θ/λ	0.616 Å^{-1}
α	109.78 (1)°	Function minimized	$\Sigma w\Delta^2$
β	106.28 (1)°		
γ	98.76 (1)°	Weighting	Peterson and Levy[13]
V	915.11 Å³	R-factor (obsd refs. only)	0.045
Z	2		
D_x	1.315 g cm^{-3}		
D_m	1.32 (1) g cm^{-3}		

[a] From LS refinement of $\pm\theta$ data. [b] Graphite monochromator.

1 (ORTEP[10] drawing); the bond lengths and angles are given in Figure 2. Molecular dimensions do not present any surprises, and the intermolecular distances are all consistent with van der Waals contacts. The ring junctions are all cis, as may be seen from the pattern of torsion angles.[11] A full table of torsion angles has been deposited as supplementary material. The conformation of the substituted cyclopentanone ring has Altona, Geise, and Romers[12] parameters $\Delta = 44.8°$ and $\varphi_m = 39.2°$. This conformation therefore lies between the half-chair ($\Delta = 36°$) and the envelope ($\Delta = 72°$) and, as might be expected for a cyclopentanone ring, it is somewhat flatter than that of a cyclopentane ring in a steroid ($\varphi_m \approx 45°$).

Experimental Section

Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation, Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, Bethesda, Md. Melting points are uncorrected and were taken on a Kofler hot stage. Mass spectra were determined using a Hitachi Perkin-Elmer RMN-6E spectrometer; infrared spectra were obtained with a Perkin-Elmer 257 instrument. The ^{1}H NMR spectra were recorded using a Varian HR-220 instrument with tetramethylsilane as the internal reference. Ultraviolet spectra were measured using a Cary 14 or Beckman DB-G spectrophotometer.

Reaction of 3 with NaOMe. Preparation of 6a. To a solution of Na (6.9 g, 300 mmol) in MeOH (450 mL) was added 3[1] (12.0 g, 30 mmol). The solution was heated under reflux for 3 h (N_2), cooled, acidified with HCl gas, and filtered. The filtrate was evaporated in vacuo, and the residue was dissolved in hot dioxane (200 mL), treated with Norite, filtered, and evaporated. The residue was crystallized from MeOH–H_2O (90:10) to give **6a** (6.4 g, 64%), mp 206–209 °C. Recrystallization from 95% EtOH gave pure material: mp 210–212 °C; M$^+$ *m/e* 334; IR (KBr), 3370, 1730, 1650, and 1600 cm^{-1}; UV λ_{max}(EtOH) 304 nm (ϵ 5100), 263 (10 300), 215 (16 600); NMR ($DCCl_3$) δ 1.92–2.12 (m, 1 H), 2.27–2.84 (m, 4 H), 3.01–3.23 (m, 2 H), 3.42–3.56 (m, 1 H), 3.57–3.74 (m, 1 H), 3.78 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 6.38 (s, 1 H, ArH), 6.79 (s, 1 H, exchanges with D_2O, OH), and 11.60 (s, 1 H, exchanges with D_2O, OH).

Anal. Calcd for $C_{17}H_{18}O_7$: C, 61.07; H, 5.43. Found: C, 60.88; H, 5.23.

Diacetate of 6a (7). Acetylation of **6a** with excess Ac_2O in pyridine at 25 °C (24 h) gave, after workup and recrystallization from 2-propanol, pure **7** (83%): mp 147–149 °C; M$^+$ *m/e* 418; IR (KBr) 1720, 1660, and 1600 cm^{-1}; UV λ_{max}(EtOH) 275 nm (ϵ 930), 225 (5900, shoulder), and 210 (16 500); NMR ($DCCl_3$) δ 2.09 (dd, 1 H, J = 18.0 and 11.0 Hz), 2.26 (s, 3 H, CH_3CO), 2.32 (s, 3 H, CH_3CO), 2.30–2.67 (m, 3 H), 2.71–2.88 (m, 2 H), 3.05–3.14 (m, 2 H), 3.50–3.66 (m, 1 H), 3.74 (s, 3 H, CH_3O), 3.88 (s, 3 H, CH_3O), and 6.97 (s, 1 H, ArH).

Anal. Calcd for $C_{21}H_{22}O_9$: C, 60.28; H, 5.30. Found: C, 60.19; H, 5.49.

Dimethyl Ether of 6a (8). A mixture of **6a** (300 mg, 0.9 mmol), anhydrous K_2CO_3 (1.0 g, 7.24 mmol), Me_2SO_4 (504 mg, 4.0 mmol), and dry acetone (25 mL) was refluxed while stirring for 3.5 h. The inorganic material was filtered off and washed with acetone, and the filtrate was evaporated. The residue was dissolved in $HCCl_3$ (30 mL) and the solution washed with water, dried, and evaporated to give **8** (334 mg, 100%), mp 175–177 °C. Recrystallization from 2-propanol gave pure **8**: mp 176–178 °C; M$^+$ *m/e* 362; IR ($HCCl_3$) 1736, 1718 (shoulder), and 1600 cm^{-1}; UV λ_{max}(EtOH) 286 nm (ϵ 3400), 250 (5150, shoulder), 213 (16 500); NMR ($DCCl_3$) δ 1.76–2.02 (1 H, 5 lines), 2.21 and 2.34 (1 H, 2 lines), 2.45–2.80 (3 H, complex), 2.86–3.02 (3 H, complex), 3.59–3.70 (1 H, complex), 3.73 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), and 6.39 (s, 1 H, ArH).

Anal. Calcd for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 63.19; H, 5.96.

Alkaline Hydrolysis of 6a and Decarboxylation to 12. To a refluxing solution of NaOH (3.0 g, 75 mmol) in H_2O (30 mL), which had been purged with N_2 for 0.5 h, was added **6** (2.5 g, 7.48 mmol). Reflux under N_2 was continued for 2.5 h; the solution was then cooled to 50 °C and acidified to pH 1.0 with 37% HCl (CO_2 evolution). After cooling to 5 °C, the solution was filtered and the solid washed with H_2O and dried in air to give the monohydrate of **12**, mp 277–278 °C dec. Recrystallization was carried out by dissolving the solid in the minimum amount of 95% EtOH, treating with Norite, filtering, and adding two volumes of H_2O. Air drying gave pure **12** H_2O: mp 282–284 °C; M^+ *m/e* 262; IR (KBr) 3255, 1735, 1710, 1615, and 1600 cm^{-1}; UV λ_{max}(EtOH) 280 nm (ϵ 2200), 223 (8500, shoulder), and 210 (14 000). The NMR spectrum (acetone-d_6) of a sample that had been dried under high vacuum overnight (100 °C) showed absorptions at δ 1.95 (dd, 1 H, J = 17.0 and 11.0 Hz), 2.18–3.05 (m, 7 H), 3.52–3.82 (m, 1 H), 5.55 (s, broad, 1 H), 6.18 and 6.30 (AB system, J_{AB} = 2.3 Hz, meta ArH), and 3.46 (s, broad, 2 H).

Anal. Calcd for $C_{14}H_{14}O_5 \cdot H_2O$: C, 62.66; H, 6.02. Found: C, 62.60; H, 5.70.

Methylation of 12 to 13. To a solution of dimethyl sulfate (1.52 g, 12.0 mmol) in acetone (20 mL) were added **12** (800 mg, 3.05 mmol) and anhydrous K_2CO_3 (1.66 g, 12.0 mmol). The solution was refluxed during 5 h with stirring, cooled, filtered, and evaporated to give **13**. Two recrystallizations from 2-propanol gave pure material: mp 107–109 °C; M^+ *m/e* 304; IR ($HCCl_3$) 1740, 1730, 1610, and 1590 cm^{-1}; UV λ_{max}(EtOH) 280 nm (ϵ 2100), 224 (8460, shoulder), and 209 nm (14 300); NMR ($DCCl_3$) δ 1.91 (dd, 1 H, J = 17.5 and 12.0 Hz), 2.29 (d, 1 H, J = 17.5 Hz), 2.45–3.07 (m, 6 H), 3.50–3.68 (m, 1 H), 3.75 (s, 3 H, OCH_3), 3.78 (s, 6 H, 2 OCH_3), 6.26 and 6.32 (AB system, J_{AB} = 2.4 Hz, meta ArH).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.14; H, 6.72.

X-Ray Crystallography. Preliminary experimental techniques and data collection methods were standard for this laboratory and have been described previously.[14] Details are given in Table I. As the crystal system was triclinic, there was a possible ambiguity as to the space group, but since the compound is racemic and there were two molecules in the unit cell, $P\bar{1}$ was assumed and appears confirmed by the successful refinement. Programs used for most computations were from the XRAY72 system,[15] but the structure was solved using MULTAN.[16]

All but two of the heavier atoms were visible in the E map. The missing atoms, including hydrogen, were found by a sequence of least-squares refinements and difference maps and the structure was finally refined using a partitioned full-matrix least squares approach with anisotropic thermal parameters for the heavier atoms, to an R factor of 4.5%. Final parameters are given in Tables II and III. (See paragraph at end of paper concerning supplementary material.)

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Registry No.—**3**, 58648-32-1; **6a**, 62562-54-3; **7**, 62562-55-4; **8**, 62562-56-5; **12**, 62562-57-6; **13**, 62562-58-7; dimethyl 3-ketoglutarate, 1830-54-2; glyoxal, 107-22-2.

Supplementary Material Available. Tables of final parameters and torsion angles (3 pages). Ordering information is given on any current masthead page.

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1,3-Butadiene-2,3-dicarboxylic Acid Derivatives from Cyclohexene-1,2-dicarboxylic Acid Analogues

R. Lynn Cobb* and John E. Mahan

Phillips Petroleum Company, Bartlesville, Oklahoma 74004

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Vapor-phase pyrolysis of dimethyl cyclohexene-1,2-dicarboxylate (**1**), and of cyclohexene-1,2-dicarbonitrile (**3**), at 700–800 °C and a few hundredths of a second contact time gave dimethyl 1,3-butadiene-2,3-dicarboxylate (**4**) and 1,3-butadiene-2,3-dicarbonitrile (**12**) in about 50 and 90% (ultimate) yields, respectively. Similar pyrolysis of *N*-methylcyclohexene-1,2-dicarboximide (**2**) gave a polymeric product, apparently arising from (labile) *N*-methyl-1,3-butadiene-2,3-dicarboximide (**8**). Evidence for the formation of **8** was obtained by isolation of its dimer *N,N'*-dimethyl-4-vinylcyclohexene-α,1,2,4-tetracarboxdiimide (**9**), and by trapping it with *N*-methylmaleimide, producing *N,N'*-dimethylcyclohexene-1,2,4,5-tetracarboxdiimide (**10**).

Derivatives of 1,3-butadiene-2,3-dicarboxylic acid are difficult to prepare; consequently, their chemistry has not been well studied. Esters of this type have been prepared by pyrolysis of dimethyl cyclohexene-1,2-dicarboxylate (**1**),[1] dimethyl 2,3-diacetoxy-2,3-dimethylsuccinate,[2] and diethyl 2,3-bis(1-piperidinomethyl)succinate dihydrochloride,[3] while the dinitrile has been prepared by pyrolysis of 2,3-diacetoxy-2,3-dimethylsuccinonitrile.[2,4,5] Because the method has not been well documented, and because of the potential value of these compounds, we have reinvestigated some of these pyrolytic syntheses. Very recently, the thermal rearrangement of derivatives of cyclobutene-1,2-dicarbonitrile has been shown to provide ready access to dienes of this type.[6,7]

Although the retro-Diels–Alder cleavage of cyclohexenes