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REACTION OF DIMETHYL SODIO-3-KETOGLUTARATE WITH GLYOXAL AND SUBSTITUTED GLYOXALS

FIRST EXPEDITIOUS PREPARATION OF BICYCLO[3.3.0]OCTANE-3,7-DIONE; SYNTHESIS AND CRYSTAL STRUCTURE OF 5,7-DIHYDROXY-4-METHOXYCARBONYL-3-PHENYL-1-INDANONE

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Abstract—A simple and efficient two-step preparation of bicyclo[3.3.0]octane-3,7-dione starting from the sodium enolate of dimethyl 3-ketoglutarate and glyoxal is described. This is an unprecedented case in which a condensation reaction of glyoxal is more successful under vigorous conditions (refluxing methanol) than under much milder ones (buffered water at ambient temperature). The major product (after hydrolysis-decarboxylation) from the analogous sequence with phenylglyoxal is 5,7-dihydroxy-4-methoxycarbonyl-3-phenyl-1-indanone, the result of a Dieckmann reaction in addition to the Michael and aldol reactions. Only the latter two occur in aqueous buffers, where the product after hydrolysis-decarboxylation is 1-phenylbicyclo[3.3.0]octane-3,7-dione. The X-ray crystal structure of the indanone reveals a novel hydrogen bonding phenomenon.

Bicyclo[3.3.0]octane-3,7-dione[1] (**1**) was first prepared by Vossen and Schroeter in the course of their attempt to synthesize "Ladenburg benzene" (prismane).[2] In spite of the inconvenience of their route, which proceeded by way of "Vossen's Red Salt" (Fig. 1a), it remained the sole source of **1** for structural[3] and synthetic[4] investigations until Weiss' study of the condensation of dimethyl 3-ketoglutarate (**2**) with 1,2-dicarbonyl compounds more than half a century later.[5] In Weiss' original procedure[5a] **1** and glyoxal were simply stirred in dilute aqueous solution (pH 5) to obtain a 15% yield of tetramethyl bicyclo[3.3.0]octane-3,7-dione-2,4,6,8-tetracarboxylate (**3**). From **3**, **1** was prepared by hydrolysis-decarboxylation following Vossen's procedure.[2,3c] Although the yield of **3** was low, Weiss' one-step synthesis was valuable because the overall yield from Vossen's route (18%) was only slightly higher after four steps.

We have discovered that by adding the glyoxal to the preformed sodium enolate of **2** dissolved in refluxing methanol, a 60–70% overall yield of **1** can be obtained reliably on a large scale, also by way of **3**. Compounds **1** and **3** are valuable starting materials in view of the current interest in polyquinane chemistry[6] in general and carbocyclic prostacyclins[7] in particular. The key intermediate in our route is a new "White Salt", **4**, the *bis*-enolate of **3**, which can be isolated in one of two epimeric forms depending upon the reaction conditions. The treatment of **4** with phenylselenylbromide produces the *bis*-phenylselenyl derivative **5**, which is reported as part of the structure proof and which also has considerable synthetic potential as a polyquinane intermediate.

While under Weiss' conditions phenylglyoxal gives the expected 1-phenylbicyclo[3.3.0]octane-3,7-dione (**6**) after hydrolysis and decarboxylation, under our conditions it engenders an interesting new compound, 5,7-dihydroxy-4-methoxycarbonyl-3-phenyl-1-indanone (**7**), which exhibits novel hydrogen bonding properties. An intramolecular *H* bond is replaced by an intermolecular one upon going from solution to the solid state. Compound **7** is the first product of **2** and a glyoxal that is not rationalizable solely on the basis of the aldol and Michael reactions, a Dieckmann reaction being perforce involved, thus adding another dimension to the condensation of **1** with glyoxals.

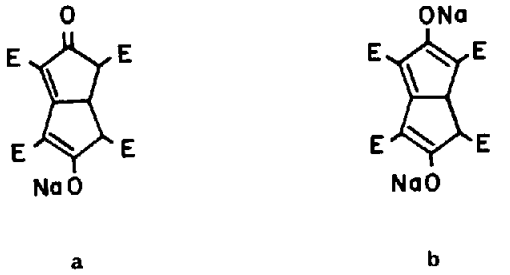

Fig. 1. (a) Vossen's Red Salt; (b) Vossen's Yellow Salt. E = CO_2CH_3.

RESULTS AND DISCUSSION

The addition of **2** to a cold solution of sodium hydroxide in methanol results in a thick white precipitate of sodio-**2**, which can be isolated in 89% yield and stored indefinitely. The ^{1}H-NMR spectrum of this substance confirms the structure drawn for it in Scheme 1. In dimethyl sulfoxide-d_6 (DMSO-d_6) four singlets are observed at δ2.95, 3.38, 3.57, and 4.32 with relative areas of 2, 3, 3, and 1, respectively. Addition of a drop of D_2O immediately causes the outer two peaks to be substantially diminished and a new singlet to appear at δ3.48, which is in the range for water in DMSO, indicating exchange with the heavy water.

It was necessary to prove the structure of sodio-**2** because, surprisingly, it had not previously been isolated. Willstätter and Pfannenstiel[8a] were unable to prepare it by the method they used to obtain pure potassio-**2**, namely treatment of **2** with potassium in ether. The

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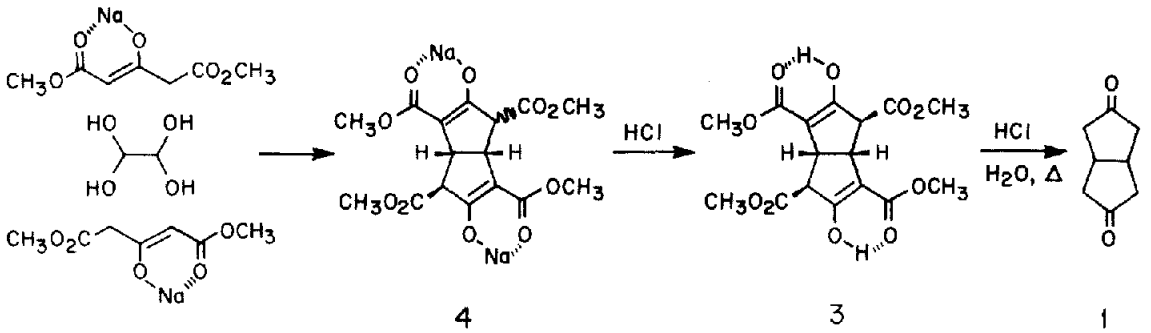


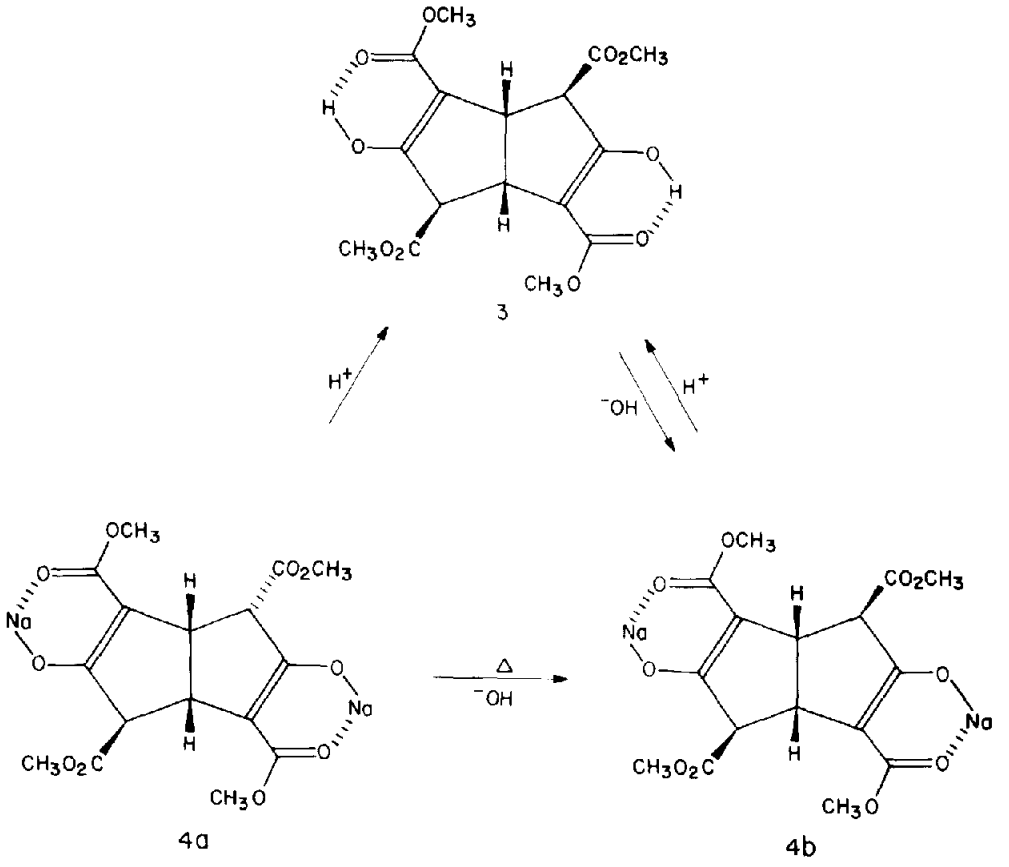
Scheme 1

acyloin reaction[9] may have occurred when **2** was treated with sodium in ether, as they report that the product contained two atoms of sodium per molecule. Presumably, they would have been able to identify the product had it simply been the disodium salt of **2**; as the dipotassium salt of diethyl 3-ketoglutarate had been known for some time.[8b] Our procedure for sodio-**2** is a modification of that of Dünschmann and von Pechmann[8b] for diethyl potassio-3-ketoglutarate. For some reason, when von Pechmann and Wolmann[8c] later attempted to make diethyl sodio-3-ketoglutarate, they used sodium in ether. With one or two equivalents of sodium, only 10–15% of 2,3,5,6-tetraethoxycarbonylhydroquinone was isolated after treatment of the reaction mixture with iodine. In contrast, procedures which employed sodium in alcoholic solvents generally gave good yields of isolated products.[8d–f] In view of the chequered history of sodio-**2**, we were concerned to prove both the existence of pure sodio-**2** in the solid state by analysis and IR spectroscopy (see the experimental section) and its structure in solution by NMR. A thorough search of *Chemical Abstracts* failed to uncover any other preparations of sodio-**2**.

For the reaction with glyoxal, the sodio-**2** need not be isolated; the glyoxal simply can be added to the preformed methanolic suspension (solution at elevated temperatures). The product isolated under these conditions is the *bis*-enolate **4**, also a stable compound, storable for months in the freezer. The precursor of "Vossen's Red Salt" was a "Yellow Salt", the structure of which was proposed[2,3c] to be the *bis*-enolate shown in Fig. 1(b). Our "White Salt" can be protonated to **3**, or it can be protonated, hydrolyzed, and decarboxylated in a single step to **1**. Unexpectedly, the yield of **4** improved with increasing temperature; on a 0.1 mol scale[10] it was 37% at 25°, 69% at 40°, and 76% at 65° (refluxing methanol). In view of the notorious sensitivity of glyoxal to alkali,[11] especially at elevated temperatures,[12] the success of this stratagem is attributable to the fact that the sodio-**2** condenses with glyoxal in an aldol reaction much faster than it induces a 1,2-hydride shift.[11] Moreover, the precipitation of **4** probably drives the desired reaction to completion faster than the formation of side-products. Such a driving force can be a crucial factor under alkaline conditions in protic solvents, where the aldol reaction is reversible.[13] The removal of **4** from the solution also obviates those by-products observed in aqueous buffers[5b–d] which are the result of the further reaction of **3** with a 1:1 intermediate[8e,14] from **2** and glyoxal. As much methanol as necessary may be used to wash the crude **4** free of the resinous materials which invariably form in reactions with glyoxal,[12] permitting the product to be isolated in analytically pure form without significant loss. This is a substantial advantage of **4** over the product from buffered solutions. While the yield from the Weiss procedure has been optimized to *ca* 70%,[15] chromatography is necessary to attain the same level of purity that we achieve so handily.

White salt **4** can exist in two epimeric forms. If the reaction is carried out at room temperature and the mixture is filtered after a short time, **4a** (Scheme 2) can be isolated. In refluxing methanol the product is **4b**. Between these extremes the product is a mixture of the two epimers. The *endo*-disposition of one of the methoxycarbonyl groups of **4a** is established by spectroscopic evidence. Two bands due to the carbonyl stretching modes of the free ester groups are present in the infrared spectrum of **4a** at 1740 and 1720 cm^{-1}, which are replaced by a single band at 1710 cm^{-1} in the spectrum of **4b**. Singlets of equal intensity attributable to these ester groups are present at δ3.30 and δ3.71 in the ^{1}H-NMR spectrum of **4a**. A third singlet at δ3.55, the area of which equals the sum of the previous two, may be assigned to the chelating ester groups. These peaks are replaced by two of equal intensity at δ3.57 and δ3.72 in the case of **4b**, indicating that the *endo*-ester group of **4a** is responsible for the δ3.30 peak. The ^{13}C-NMR spectrum of **4a** has one more peak than that of **4b** (see the experimental section for chemical shifts), presumably due to the carbon atom bearing the *endo*-ester group. Upon treatment with acid, both **4a** and **4b** are converted into **3**. The *exo*-stereochemistry of the non-hydrogen bonded ester groups in the tetraethyl analogue of **3** has already been established by P. Camps;[3d] his analysis applies to the ^{1}H-NMR spectrum of **3** as well. The treatment of **3** with two equivalents of sodium hydride also yields **4b**; thus **4a** is the kinetic product, and **4b** is the thermodynamically favored one.

The analysis of Camps[3d] also proves that the double bonds of **3** are related by C_2-symmetry and not C_s-symmetry. The ^{1}H NMR spectrum of **4b** did not lend itself to such an analysis, due to the partial obscuration of some of the methine resonances by the ester peaks. Therefore it was treated with phenylselenylbromide to give the C_2-product **5** (Scheme 3), the structure of which was established by the fact that its ^{1}H-NMR spectrum contains a sharp singlet at δ2.85 for the bridgehead methine protons. The spectrum of the alternative C_s-structure would contain an AB pattern[16] instead. As a synthetic reaction, the introduction of phenylselenyl provides a versatile, easily removed control element which fixes the *endo*-stereochemistry of the ester



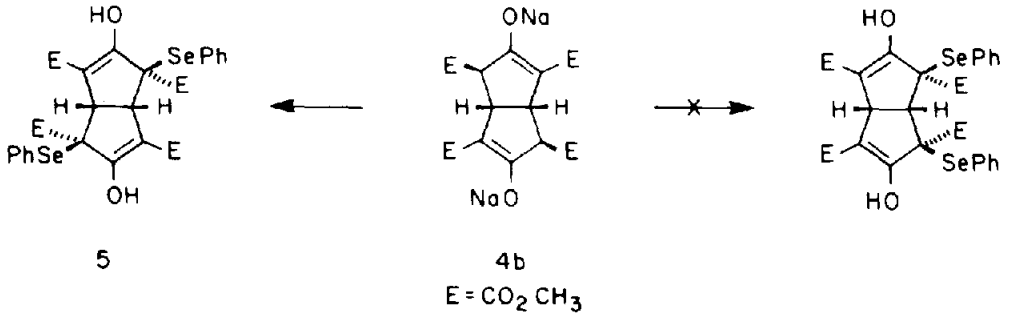
Scheme 2

group.[17] It also enables specificity to be realized by blocking further functionalization at the sites to which it is attached and directing reaction to the other β-keto-ester groups.[18]

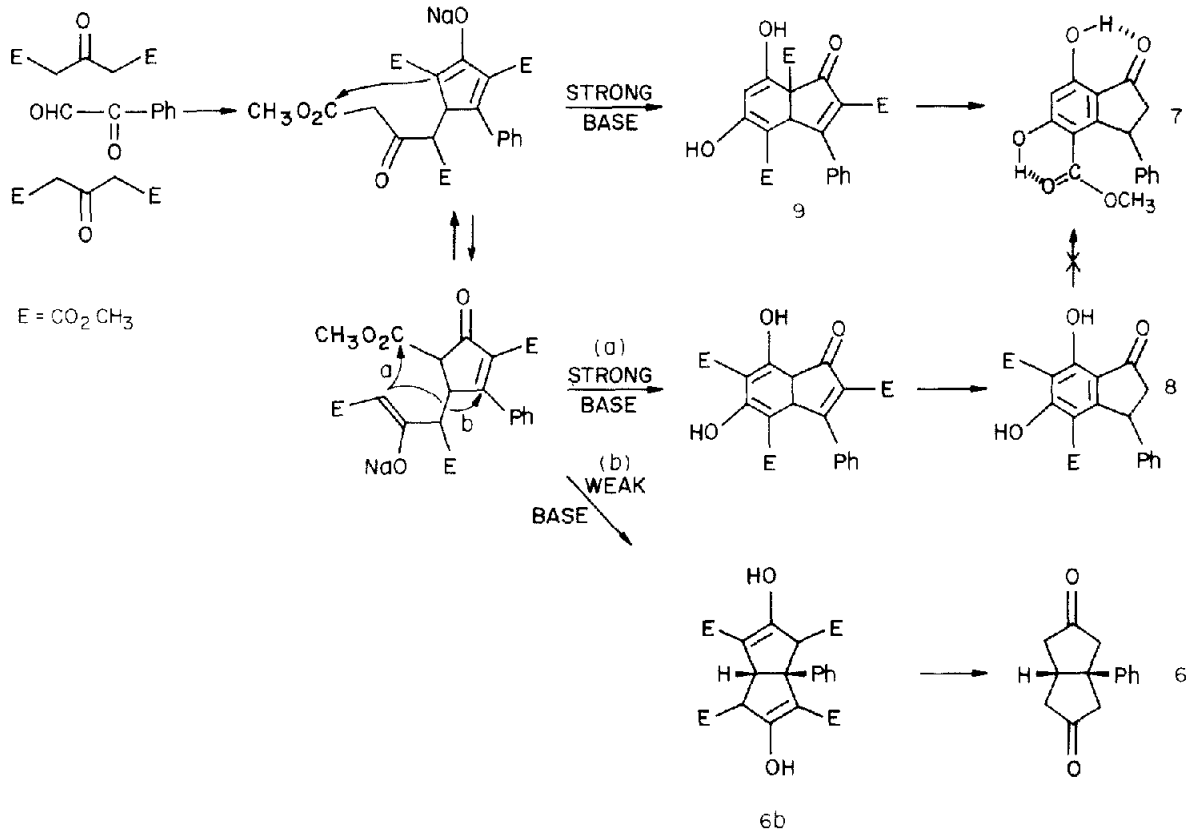
Under our experimental conditions, substituted glyoxals gave derivatives of **1** in yields lower than those obtained in aqueous solution. For example, 1-methylbicyclo[3.3.0]octane-3,7-dione was isolated in 30% yield by our procedure *vs* 52% by that of Weiss and Edwards.[5a] Under our conditions, phenylglyoxal only yielded 2% of 1-phenylbicyclo[3.3.0]octane-3,7-dione, **6**, from hydrolysis-decarboxylation of the 2,4,6,8-tetramethoxycarbonyl derivative, **6b** (Scheme IV), which has been isolated in 66% yield from an aqueous buffer.[8c] Thus our procedure using sodio-**2** compliments those using **2** in aqueous buffers, and taken together they make **1** and **3** and their 1-methyl and 1-phenyl derivatives abundantly available.[19] However, neither mesoxaldehydic acid[20a] nor its ethyl ester[20b] condensed with **2** under either set of conditions; only hydroxymalonate was isolated. In this case the 1,2-hydride shift appears unavoidable.

The major product of hot methanolic sodio-**2** and phenylglyoxal was resorcinolic phenylindanone **7** (Scheme IV) after acid-catalyzed hydrolysis and decarboxylation. Although the yield of **7** is modest (11% from phenylglyoxal after two steps), this is a new compound not available by another route. Its appearance is attributable to the Dieckmann reaction, which does not occur in aqueous buffers.[21] The "abnormal Michael reaction", due to the intervention of the Dieckmann reaction, is known to take place under conditions similar to ours.[22]

The structure of the product from phenylglyoxal was



Scheme 3



Scheme 4

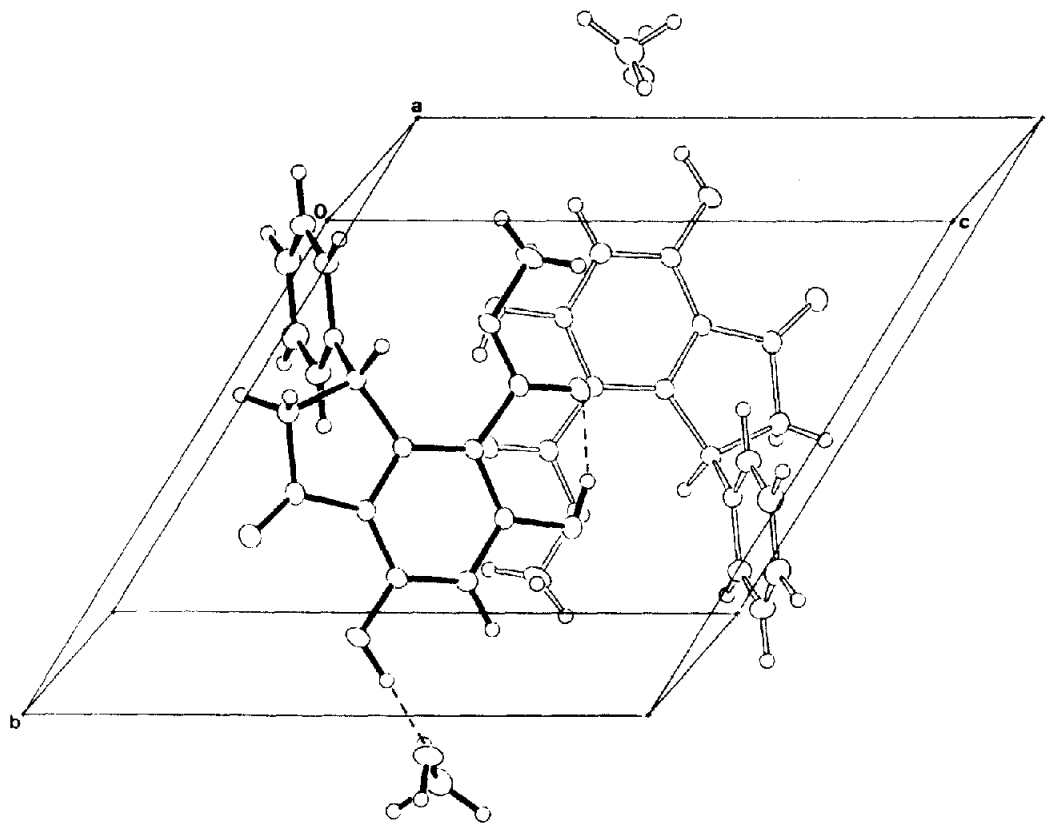


Fig. 2. Crystal packing in the unit cell of 7.

determined to be **7** (and not its isomer with the ester group in the 6-position, i.e. between the hydroxyl groups) by single-crystal X-ray diffraction, which also revealed a surprising hydrogen bonding phenomenon. The compound crystallized from methanol as a 1:1 solvate with two molecules of **7** per unit cell (Fig. 2). From the values of the torsion angles (Fig. 3) and the bond lengths and angles (Tables 1 and 2), it can be concluded that the indanone ring system is nearly planar and that extensive conjugation exists from the indanone carbonyl through the ester group. The five-membered ring has an envelope conformation,[23] although the degree of puckering is small.

The O(11)···H-O(14) bond (Table 3) is a typical intramolecular *H* bond.[24] The presence of an intermolecular O(15)-H···O(23) bond to a solvate molecule instead of an intramolecular *H* bond between O(15) and O(16), which is present in solution (*vide infra*), constitutes a unique case in which an intramolecular *H* bond has been broken and replaced by an intermolecular one upon going to the solid state. Dimethyl 3,6-dichloro-2,5-dihydroxyterephthalate can exist in two forms with different intramolecular *H* bonds,[25a] and 14-hydroxymorphinone has two crystalline modifications, which have different intermolecular *H* bonds.[25b] In the crystal structure of perdeuterated violuric acid monohydrate,[25c] a bifurcated *H* bond to a water molecule is present. Although a small percentage of intramolecular *H* bonding between O(15) and O(16) could remain undetected by the X-ray method,[26a] the position of the methanolic *O*, which can be located accurately, precludes any bifurcated *H* bonding. The O(15)···O(16) distance is 2.88 Å, significantly greater than the O(15)···O(23) distance, 2.59 Å. Since the O···O distance is the dominant factor in determining the strength of *H* bonds between oxygen atoms,[27] an intramolecular *H* bond between O(15) and O(16) would be weaker than the intermolecular one actually present. The O(15)-H···O(23) angle (175°) is close to the ideal linear configuration.[26b] The observed

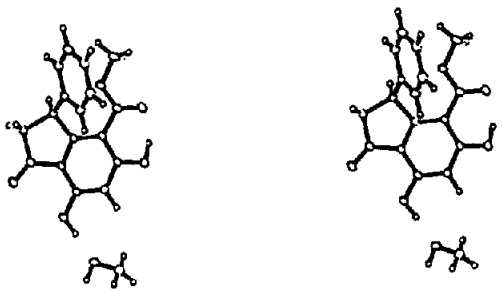


Fig. 4. Stereo-pair.

angles and distances represent the best compromise between *H* bonding forces and crystal packing forces.[25]

In solution both *H* bonds are intramolecular, as vouchsafed by the ^{1}H-NMR spectrum. The singlets at δ10.0 and δ12.0 in chloroform-*d* are independent of concentration; in contrast, the chemical shift of the hydroxyl proton of phenol varies from δ4.0 to δ7.5.[28] The chemical shifts of **7** are at the opposite ends of the range for phenolic protons with carbonyl groups in the *ortho*-position.[28] Based upon the inverse dependence of magnetic shielding on the O···O distance,[27] the upfield resonance is assigned to the *H* between O(15) and O(16) and the downfield one to the *H* between O(11) and O(14). The implicit assumption that the O···O distances in solution have the same order as the corresponding ones in the solid state is good in view of the rigidity imposed upon **7** by its planar, conjugated framework.

A small amount (4%) of compound **8**, the result of an alternative mode of Dieckmann cyclization, was also isolated from the reaction mixture that yielded **7**. Its structure was assigned on the basis of the similarity between its spectral data (see experimental section) and that of **7**. Remarkably, when **8** was subjected a second time to the decarboxylation conditions, no **7** was detectable. Therefore, it must be concluded that **8** is not an

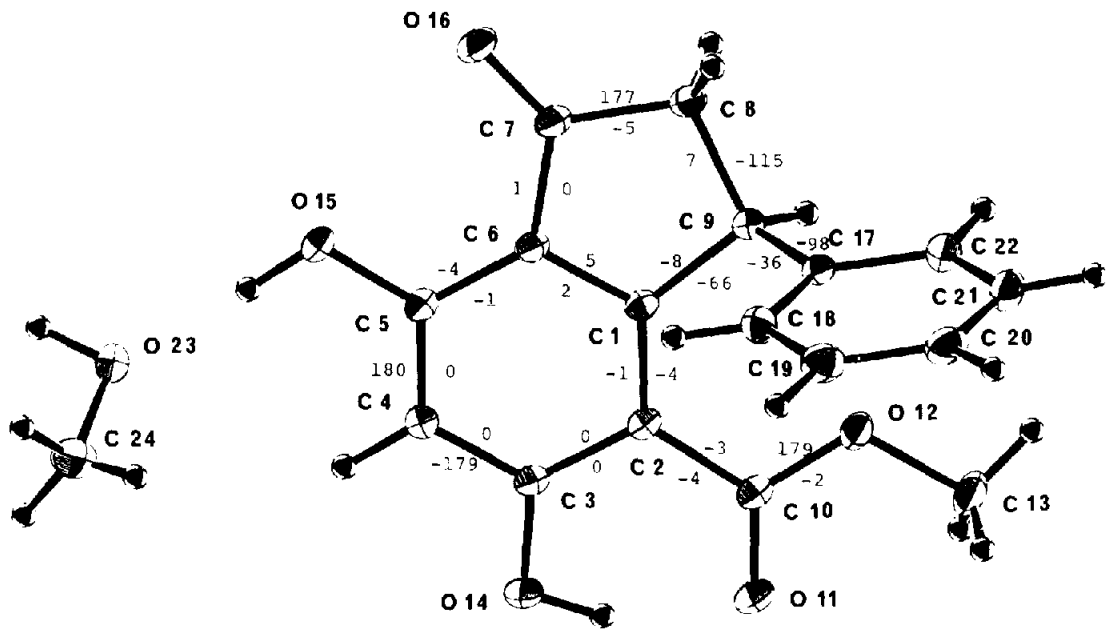


Fig. 3. Perspective view of **7** with torsion angles.

Table 1. Bond lengths (Å)

C(1)-C(2)	1.402±0.004		
C(1)-C(6)	1.390	C(8)-C(9)	1.551
C(1)-C(9)	1.526	C(9)-C(17)	1.517
C(2)-C(3)	1.411	C(10)-O(11)	1.227
C(2)-C(10)	1.465	C(10)-O(12)	1.313
C(3)-C(4)	1.389	O(12)-C(13)	1.453
C(3)-O(14)	1.349	C(17)-C(18)	1.381
C(4)-C(5)	1.385	C(17)-C(22)	1.388
C(5)-C(6)	1.401	C(18)-C(19)	1.388
C(5)-O(15)	1.341	C(19)-C(20)	1.375
C(6)-C(7)	1.466	C(20)-C(21)	1.380
C(7)-C(8)	1.509	O(21)-C(22)	1.392
C(7)-O(16)	1.217	O(23)-C(24)	1.411

Table 2. Bond angles (degrees)

C(2)-C(1)-C(6)	120.5±0.4	C(8)-C(7)-O(16)	124.7
C(2)-C(1)-C(9)	128.5	C(7)-C(8)-C(9)	106.5
C(6)-C(1)-C(9)	111.0	C(1)-C(9)-C(8)	103.6
C(1)-C(2)-C(3)	117.0	C(1)-C(9)-C(17)	113.0
C(1)-C(2)-C(10)	124.9	C(8)-C(9)-C(17)	111.3
C(3)-C(2)-C(10)	118.0	C(2)-C(10)-O(11)	123.4
C(2)-C(3)-C(4)	122.5	C(2)-C(10)-O(12)	114.6
C(2)-C(3)-O(14)	122.0	O(11)-C(10)-O(12)	122.0
C(4)-C(3)-O(14)	115.5	C(10)-O(12)-C(13)	117.6
C(3)-C(4)-C(5)	119.6	C(9)-C(17)-C(18)	121.1
C(4)-C(5)-C(6)	118.9	C(9)-C(17)-C(22)	120.5
C(4)-C(5)-O(15)	122.6	C(18)-C(17)-C(22)	118.3
C(6)-C(5)-O(15)	118.5	C(17)-C(18)-C(19)	121.3
C(1)-C(6)-C(5)	121.4	C(18)-C(19)-C(20)	120.1
C(1)-C(6)-C(7)	110.4	C(19)-C(20)-C(21)	119.3
C(5)-C(6)-C(7)	128.2	C(20)-C(21)-C(22)	120.7
C(6)-C(7)-C(8)	108.0	C(17)-C(22)-C(21)	120.3
C(6)-C(7)-O(16)	127.3		

Table 3. Hydrogen bond data

O(14)···O(11)	2.54Å	O(15)···O(23)	2.59Å
O(14)-H	0.92Å	O(15)-H	0.96Å
H···O(11)	1.69Å	H···O(23)	1.63Å
O(14)-H···O(11)	155°	O(15)-H···O(23)	175°

intermediate in the formation of **7**, which must derive solely from **9** by a combination of double bond migration, ester hydrolysis and decarboxylation. The interesting chemistry learned from **7** and **8** illustrates the importance of isolating new compounds, even though the yields may not be impressive.

CONCLUSION

Considering the historical[3,4] and the recent[6,7] interest in **1** and its derivatives as synthetic intermediates, it may be expected that this preparation will find wide application. It may also inspire the further development of glyoxal chemistry, as it relaxes longstanding taboos against using base and heat to promote condensations with glyoxal.[11,12] Product **7** represents the first observation of a Dieckmann reaction in the condensation of **1** with 1,2-dicarbonyl compounds, which broadens this path for the rapid construction of complex molecules.[29]

Table 4. Crystal data

Molecular formula:	$C_{17}H_{14}O_5 \cdot CH_3OH$
Molecular weight:	330.3
Crystal system:	triclinic
Space group:	$P\bar{1}$ (no. 2)
Crystal size:	0.5 × 0.3 × 0.15mm
Cell parameters:	
a	= 8.150(1) Å
b	= 10.694(2) Å
c	= 11.432(2) Å
α	= 121.32(1)°
β	= 78.35(1)°
γ	= 107.74(1)°
V	= 809.5Å^3
Z	= 2
D_x	= 1.355 g cm^{-3}

EXPERIMENTAL

General Information. Melting points were determined in sealed capillaries using a Thomas Hoover apparatus and have been corrected. Elemental analyses were performed by Scandinavian Microanalytical Laboratories (Herlev, Denmark) or Galbraith Laboratories (Knoxville, Tennessee). NMR spectra were obtained with a Brüker WH-90 or with Varian T-60, CFT-80, or XL-100 spectrometers; IR spectra with Perkin–Elmer 137, 457A, or 597 spectrophotometers; and mass spectra with an AEI/MS9. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Other solvents and reagents were the best commercial grade available and were used without further purification.

Dimethyl sodio-3-ketoglutarate (Sodio-2). A 4.00-g (0.10 mol) quantity of NaOH (Mallinckrodt AR) was dissolved in 100 mL of methanol in a 250 mL Erlenmeyer flask with the aid of vigorous magnetic stirring. The clear solution was cooled to ice bath temperature and 17.4 g (0.10 mol) of dimethyl 3-ketoglutarate was added by drops. Toward the end of the addition a thick white precipitate formed. The reaction mixture was agitated for 30 min more and then keep in a freezer (−20°) for 2 hr. Filtering and drying in vacuum over phosphorus pentoxide yielded 14.4 g (73%) of white solid. Found: C, 42.91; H, 4.56; Na, 11.52. $C_7H_9O_5Na$ requires: C, 42.87; H, 4.63; Na, 11.72%. IR (KBr): 3440, 3000, 2960, 1720, 1670, 1540, 1340, 1230, 1190, 1170, 1150, 1050, 900, 770. ^{1}H-NMR (DMSO-d_6): δ2.95 (s, 2H), 3.38 (s, 3H), 3.57 (s, 3H), 4.32 (s, 1H). The spectrum was not changed by passing the solution through powdered molecular sieves layered on a wad of glass wool in a Pasteur pipette, which had been heated in a Bunsen burner flame and cooled under nitrogen just before use. Addition of one drop of D_2O to the sample reduced the outer two peaks to 30% of their former intensity and caused a new peak to appear at δ3.48, the intensity of which equalled the sum of that which disappeared. The spectrum was recorded <5 min after the D_2O was added.

An additional 3.1 g (16%) of product was gleaned by evaporation of the filtrate, trituration of the resulting solid with 5 mL of methanol, and filtration with the aid of three 10 mL portions of ether.

White salts **4a** *and* **4b**. A solution of 5.64 g (141 mmol) of NaOH in 100 mL of methanol was clarified by filtration through sintered glass and 20.0 mL (23.9 g, 136 mmol) of dimethyl 3-ketoglutarate was added to it in a 250 mL three-neck flask fitted with a reflux condenser, a dropping funnel, and a nitrogen inlet.

The reaction mixture was heated to reflux, which caused the initially formed precipitate to dissolve; and 10.0 mL (89 mmol) of 40% glyoxal was added in drops over 20 min. Precipitation of a white solid began midway through the addition. After another 10 min at reflux, the reaction mixture was allowed to cool to room temperature (2–4 hr). It was filtered and the filter deposit was washed with 100 mL of methanol, which was allowed to percolate down through the solid under gentle vacuum. The amount of light yellow **4b** dried to constant weight in vacuum was 22.4 g (76%). IR(KBr): 3410, 2920, 1710, 1660, 1520, 1440, 1275, 1240, 1185, 1155, 1035, 780, 725. ^{1}H-NMR (D_2O)[30]: δ3.28 (m, 2H), 3.57 (s, 6H), 3.63 (m, 2H), 3.72 (s, 6H). ^{13}C-NMR (D_2O)[30]: δ44.5, 48.8, 49.7, 67.8, 97.5, 169.9, 182.8, 187.0.

Starting with isolated sodio-2 (see previous section), the yield was the same as with sodio-2 generated *in situ*, when the rest of the experiment was performed in the same way. The yield was 75% when the above procedure was carried out on twice this scale.[10] Using 10% more glyoxal lowered the yield to 53%; using 20% less lowered it to 70%. Increasing the amount of base by 30% decreased the yield to 41%. When this procedure was repeated at 40°, it decreased to 69%.

When the temperature was maintained at 25° (water bath) and the reaction mixture was filtered after 1 hr, the yield dropped to 37% of **4a**. IR (KBr): 3350, 2900, 1740, 1720, 1640, 1520, 1440, 1290, 1240, 1190, 1160, 1040, 780, 730. ^{1}H-NMR (D_2O)[30]: δ3.20 (m, 2H), 3.30 (s, 3H), 3.55 (s, 6H), 3.65 (m, 2H), 3.71 (s, 3H).^{13}C-NMR (D_2O)[30]: δ44.1, 48.8, 50.0, 52.3, 66.5, 96.8, 169.5, 177.3, 182.6. The product decomposes at ~250° without melting. Found: C, 45.00; H, 4.52. $C_{16}H_{16}Na_2O_{10}\cdot H_2O$ requires: C, 44.45; H, 4.20; Na, 10.64. Recrystallization from methanol/water (~3:1, 50% recovery) gave a white crystalline solid. Found: C, 45.00; H, 4.41; Na, 10.50%.

Tetramethyl bicyclo[3.3.0]*octane*-3,7-*dione*-2,4,6,8-*tetracarboxylate* (**3**). A 4.145-g (9.58 mmol) portion of **4a** dissolved in 25 mL of deionized water was titrated with 19.40 mL of 1.000 *M* HCl to a potentiometric endpoint. The equivalent weight is therefore 214 (216 is calculated for $4\cdot H_2O$). Filtration of the precipitate and drying in vacuum gave 3.14 g (89%) of white solid, m.p. 101–103° (lit[3c] 104–107.5°). Found: C, 51.88; H, 4.98. Calc. for $C_{16}H_{18}O_{10}$: C, 51.89; H, 4.90%. IR (KBr): 3600-2700, 2930, 1745, 1675, 1635, 1440, 1260, 1170, 1060, 1020, 1000, 795. ^{1}H-NMR ($CDCl_3$): δ3.64 (t, *J* = 2.5 Hz, 2H), 3.78 (s, 6H), 3.80 (s, 6H), 3.88 (t, *J* = 2.5 Hz, 2H), 10.3 (broad s, 2H). ^{13}C-NMR ($CDCl_3$): δ43.7, 51.4, 52.3, 55.2, 103.6, 168.7, 170.2, 170.5. MS (190°, 70 eV) *m/e*(%): 369(20), 339(28), 338(77), 307(34), 306(100), 279(25), 278(15), 275(17), 274(50), 247(42), 246(18), 232(17).

Bicyclo[3.3.0]*octane*-3,7-*dione* (**1**). A 176-g (0.407 mol) quantity of **4b** was added to 600 mL of 3*M* HCl in a two liter three-neck flask fitted with three reflux condensers and equipped with a heating mantle. After vigorously refluxing for 3 hr, the reaction mixture no longer evolved gas, which was monitored with a bubbler. It was allowed to cool and then extracted with five 200-mL portions of dichloromethane, each of which was counter-extracted with 50-mL portions of saturated bicarbonate to remove yellow-colored material. When evaporated individually, the organic layers yielded 32.50 g, 11.06 g, 3.33 g, 1.01 g, and 0.17 g; extraction of the combined bicarbonate layers with dichloromethane gave an additional 3.04 g, for a total of 51.1 g (91%). Purification by recrystallization from ethanol and sublimation at 70°/0.1 torr gave 48.7 g, m.p. 85–86° (Lit.[3c] 84–86°). Found C, 69.58; H, 7.29. Calc. for $C_8H_{10}O_2$: C, 69.54; H, 7.30%. IR (KBr): 2920, 2870, 1730, 1395, 1290, 1230, 1180, 1145, 915, 795. ^{1}H-NMR ($CDCl_3$): δ2.15 (dd, *J* = 5.5, 19 Hz, 4H), 2.61 (dd, *J* = 8.7, 19 Hz, 4H), 3.08 (m, 2H). ^{13}C-NMR ($CDCl_3$): δ36.3, 43.5, 217.5. MS (100°, 70 eV) *m/e*(%): 139(10), 138(100), 110(10), 95(11), 69(39), 68(65), 67(10), 42(10), 41(65), 39(18). The properties of **1** were identical with those of an authentic sample prepared by Vossen's route.[2,3c]

Tetramethyl 2,6-bis(phenylselenyl)bicyclo[3.3.0]*octane*-3,7-*dione*-2,4,6,8-*tetracarboxylate* (**5**). A 370-mg (1.0 mmol) quantity of **2** was added in small portions over 5 min to 84 mg of 57% NaH/mineral oil (washed off with THF), which was suspended in 10 mL of dry THF under nitrogen. The IR spectrum of a sample of the resulting precipitate was identical with that of **4b**.

A solution of phenylselenylbromide, prepared by adding 160 mg (1.0 mmol) of bromine to 310 mg (1.0 mmol) of diphenyl diselenide dissolved in 4 mL of dry THF, was added by drops to the magnetically stirred THF suspension of **4b**. After 5 min the reaction mixture was poured into 10 mL of water and extracted with two 50-mL portions of ether, which were combined, dried over magnesium sulfate, filtered, and evaporated down to 912 mg of brown oil. Trituration with hot methanol yielded 470 mg (70%) of an off-white solid, m.p. 167–169°. Further recrystallization from methanol gave the analytical sample, m.p. 182–184°. Found: C, 49.55; H, 3.83; Se, 23.31. $C_{28}H_{26}O_{10}Se_2$ requires: C, 49.43; H, 3.85; Se, 23.21%. IR (KBr): 3340, 2920, 1730, 1710, 1640, 1440, 1305, 1235, 1125, 1080, 1055, 770, 753, 690. ^{1}H-NMR ($CDCl_3$): δ2.85 (s, 2H), 3.62 (s, 6H), 3.67 (s, 6H), 7.4 (m, 10H), 10.3 (broad s, 2H).

5,7-Dihydroxy-4-methoxycarbonyl-3-phenylindanone (**7**). A solution of 1.37 g (34.2 mmol) of NaOH in 25 mL of methanol was prepared in a 50 mL three-neck flask fitted with a mechanical stirrer, a dropping funnel, and a reflux condenser capped with a drying tube. Dimethyl 3-ketoglutarate (5.00 mL, 5.9 g, 34 mmol) was added, then phenylglyoxal monohydrate (2.60 g, 17.1 mmol, dissolved in 10 mL methanol) was added over 30 min to the refluxing solution. No solid formed during the next 40 hr of reflux; therefore, the solvent was evaporated and the residue (4.52 g) was hydrolyzed and decarboxylated by refluxing it in 10 mL of 20% HCl for 45 min. The red oil that separated was extracted into dichloromethane and, after drying and evaporation, chromatographed on a 2.7 × 42 cm column containing 100 g of activity I silica gel. Elution with dichloromethane gave 635 mg of **7**, m.p. 133–136°, in column volumes 3.6–8.9 (1 C.V. = 170 mL). Sublimation at 100°/0.3 torr yielded 523 mg of white solid, m.p. 137.5–138.5°. Recrystallization from ethanol brought the product to a constant m.p. 139.5–140°. Another sublimation gave the analytical sample, also used for spectral study. Found: C, 68.47; H, 4.80. $C_{17}H_{14}O_5$ requires: C, 68.45; H, 4.73%. MS (130°, 70 eV) *m/e*(%): 299(13), 298(62), 266(20), 265(100), 238(15), 224(9), 210(9), 181(5), 152(5), 69(5). ^{1}H-NMR ($CDCl_3$): δ 2.52 (dd, *J* = 2.1, 19.2 Hz, 1H), 3.20 (dd, *J* = 7.8, 19.2 Hz, 1H), 3.57 (s, 3H), 4.92 (ddd, *J* = 0.4, 2.1, 7.8 Hz, 1H), 6.43 (d, *J* = 0.4 Hz, 1H), 6.9 (m, 2H), 7.3 (m, 3H), 10.0 (s, 1H), 12.0 (s, 1H). ^{13}C-NMR ($CDCl_3$): δ46.3(d), 46.9(t), 51.5(q), 102.9(d), 104.0(s), 118.0(s), 126.2(d), 126.5(d), 128.6(d), 144.4(s), 161.5(s), 162.3(s), 169.6(s), 171.1(s), 206.7(s). UV (EtOH) $\lambda_{max}(\epsilon)$: 247(35,200), 259(30,600), 335(1500). IR(KBr): 3280, 3180, 2970, 2910, 1665, 1610, 1600, 1445, 1335, 1240, 1170, 1120, 945, 850, 825, 765, 697.

1-Phenylbicyclo[3.3.0]*octane*-3,7-*dione* (**6**). The residue from the sublimation and the filtrates from the recrystallizations of **7** were combined and purified by preparative TLC on four 20 × 20 cm, 0.5 mm silica gel plates developed twice with 3.5% ethanol/chloroform to obtain 1 - phenylbicyclo[3.3.0]octane - 3,7 - dione at R_f = 0.64–0.81. Sublimation at 110°/0.1 torr gave 67 mg (2%), m.p. 103–104°. Recrystallization from methanol gave colorless plates, m.p. 106.5–107°. Found: C, 78.14; H, 6.56. $C_{14}H_{14}O_2$ requires: C, 78.48; H, 6.59%. Its physical properties were identical with those of an authentic sample prepared by hydrolysis-decarboxylation of the 2,4,6,8-tetramethoxycarbonyl derivative,[8c] provided by J. M. Cook.

5,7 - Dihydroxy - 4,6 - dimethoxycarbonyl - 3 - phenylindanone (**8**). A 580-mg portion of the crude red oil from the preparation of **7** was chromatographed on 50 g of activity I silica gel eluted with 12 column volumes (C.V.) of dichloromethane and 35 C.V. of 0.5% methanol/dichloromethane to give 100 mg of impure product from C.V. 20–22. Two recrystallizations from methanol followed by sublimation at 150°/0.2 torr gave 39 mg of **8**, m.p. 153–153.5°. Found: C, 64.37; H, 4.70. $C_{19}H_{16}O_7$ requires: C, 64.04; H 4.53%. MS (170°, 70 eV) *m/e*(%): 356(22), 325(25), 324(75), 294 (11), 293(64), 292(100), 266(12), 265(10), 264(21), 236(24), 225(10), 208(14), 180(10), 152(20), 139(12), 92(11), 91(21), 77(10), 76(11), 44(12), 43(10), 40(12). UV (EtOH) $\lambda_{max}(\epsilon)$: 248(34,500), 251(34,400), 253(34,100), 256(33,800), 258(33,600), 321(2800), 339(3300). IR (KBr): 3500–2300, 1735, 1665, 1635, 1600, 1440, 1340, 1245, 1230, 1215, 985, 828, 697. ^{1}H-NMR ($CDCl_3$): δ2.55 (dd, *J* = 2.4, 19.2 Hz, 1H), 3.25 (dd, *J* = 8.1, 19.2 Hz, 1H), 3.58 (s, 3H), 4.01 (s, 3H), 4.95 (dd, *J* = 2.4, 8.1 Hz, 1H), 6.9 (m, 2H), 7.2 (m, 3H), 11.5 (s, 1H), 13.0

(s, 1H). ^{13}C-NMR ($CDCl_3$): δ45.9, 46.9, 51.9, 52.9, 105.7, 105.9, 117.6, 126.7, 127.0, 129.0, 143.8, 162.2, 163.8, 167.2, 168.9, 169.4, 205.5.

Attempted decarboxylation of **8**. A 34-mg quantity of **8** was refluxed in 5 mL of 20% HCl for 30 min under nitrogen. Extraction with dichloromethane gave 33 mg of white solid, the ^{1}H-NMR spectrum of which was identical with that of the starting material. The recovered material was refluxed for 30 min in 2.5 mL of 20% HCl to which 2.5 mL of dioxane had been added. Extraction with dichloromethane yielded 20 mg of product, the ^{1}H-NMR spectrum of which showed no **7**. Refluxing this material in 5 mL of conc. HCl for 1 hr followed by dichloromethane extraction produced 21 mg of solid which contained 10% of **7**, measured using its δ6.43 ^{1}H-NMR peak.

X-ray crystallography of **7**. X-ray intensity data for the Mo Kα radiation were collected with a PICKER FACS-I automatic four-circle diffractometer using a θ-2θ scan technique. A total of 3129 reflections having 2θ in the range 2°–55° were recorded, of which 2785 were unique; 2606 which had $I > 2\sigma(I)$ were used for the least-squares refinement. The structure was solved by direct methods using the program MULTAN 77.[31] The positions of all non-hydrogen atoms were revealed by the E-map corresponding to the solution with the highest combined figure of merit. Structure factor calculation and Fourier synthesis produced two additional electron density peaks corresponding to the carbon and oxygen atoms of methanol. The positional and thermal parameters of the 24 non-hydrogen atoms were subjected to several cycles of block-diagonal least-squares refinement. The 18 hydrogen atoms were located on an electron density difference map after R had reached 0.081. Inclusion of their positional and thermal parameters in the least-squares refinement lowered R to 0.044.

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Supplementary material—Structural factors and positional and thermal parameters are available upon request.

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