Organic Syntheses

A Publication
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for the Preparation
of Organic Compounds

# Working with Hazardous Chemicals

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*These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.*

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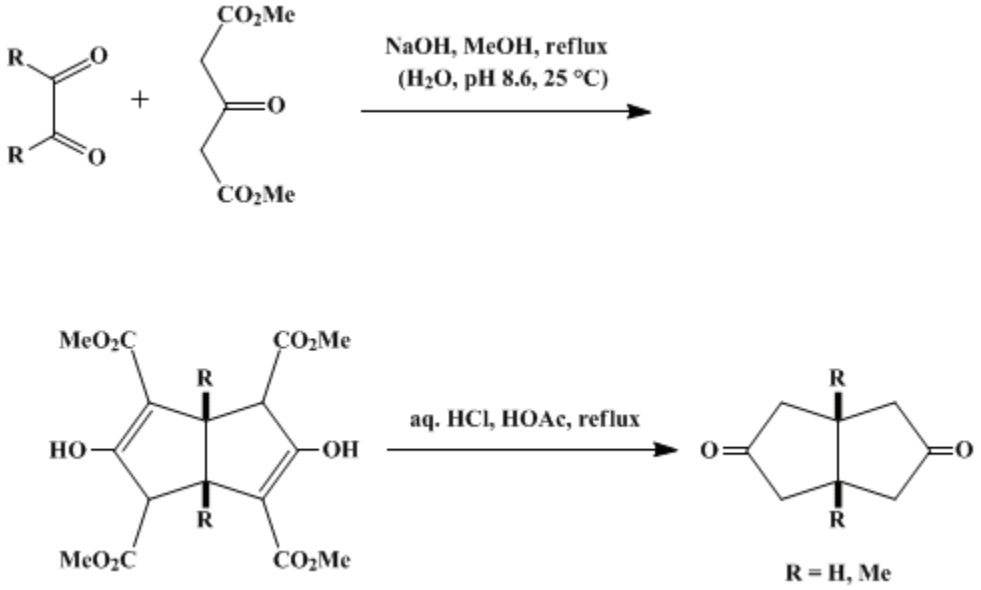
# CONDENSATION OF DIMETHYL 1,3-ACETONEDICARBOXYLATE WITH 1,2-DICARBONYL COMPOUNDS: *cis*-BICYCLO[3.3.0]OCTANE-3,7-DIONES

## [2,5(1*H*,3*H*)-Pentalenedione, tetrahydro-, *cis*-, and 2,5(1*H*,3*H*)-pentalenedione, tetrahydro-, 3a,6a-dimethyl-, *cis*]

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Checked by Todd K. Jones, Scott E. Denmark, S. V. Govindan, and Robert M. Coates.

## 1. Procedure

### I. Specific Procedure for Glyoxal

A. *Tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate*. A 3-L, three-necked, round-bottomed flask is equipped with a thermometer, mechanical stirrer, pressure-equalizing dropping funnel, reflux condenser (Note 1), and a heating mantle. A solution of 64 g (1.60 mol) of sodium hydroxide (Note 2) in 1.15 L of methanol is prepared in the flask, cooled in an ice bath, and stirred as 273 g (1.57 mol) of dimethyl 1,3-acetonedicarboxylate (Note 3) is added dropwise. The resulting slurry is stirred and heated to reflux, at which point the white salt dissolves. The heating mantle is removed, and the solution is stirred rapidly while 128.5 g of aqueous 40% glyoxal (51.4 g, 0.886 mol) (Note 3) and (Note 4) is added at a rate sufficient to maintain the internal temperature at 65° C (Note 5). After the addition is completed (40–60 min, (Note 6)), the mixture is allowed to cool to room temperature and stirred overnight (Note 7). The precipitate is collected by suction filtration, washed with 500 mL of methanol (Note 8), and dried under reduced pressure. The yield of the white to light yellow disodium salt is 197–215 g (58–63%) (Note 9).

A 6-L Erlenmeyer flask equipped with a large magnetic stirring bar (Note 10) is charged with 1 L of chloroform and a solution of the disodium salt (0.46–0.50 mol) in 800 mL of water. The two-phase mixture is stirred rapidly as 2.00 equiv (920–1000 mL, 0.92–1.00 mol) of cold 1 *M* hydrochloric acid is added. The layers are separated and the aqueous phase is extracted with three 500-mL portions of chloroform. The combined organic layers are washed once with saturated sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure by rotary evaporation, keeping the water bath temperature at or below 40°C. Crystallization of the remaining waxy solid from 2 : 1 hexane–ethyl acetate affords 158–171 g (54–59% based on dimethyl 1,3-acetonedicarboxylate) of the

tetraester, mp 97–100°C (Note 11).

B. *cis-Bicyclo[3.3.0]octane-3,7-dione*. A 3-L, three-necked, round-bottomed flask equipped with a heating mantle, two reflux condensers, and a magnetic stirrer (Note 12) is charged with 135 g (0.364 mol) of the tetraester, 66 mL of glacial acetic acid, and 600 mL of 1 *M* hydrochloric acid (Note 13). The mixture is stirred vigorously and heated at reflux for 2.5 hr (Note 14). The solution is cooled in an ice bath and the product is extracted with five 250-mL portions of chloroform. The chloroform extracts are combined, and the solution is concentrated by rotary evaporation (bath temperature at or below 40°C) until most of the acetic acid is removed. The residue is dissolved in 300 mL of fresh chloroform. The solution is washed with 60-mL portions of saturated sodium bicarbonate until the aqueous layer remains basic to litmus paper, dried with anhydrous sodium sulfate, and evaporated cautiously under reduced pressure. The yield is 44–45.5 g (88–90%) of white to light yellow solid, mp 84–85°C (Note 15). The product is sufficiently pure for most purposes; it may be purified by recrystallization from methanol or ethanol and/or by sublimation at 70°C (0.1 mm).

**II. General Procedure Using Aqueous Buffer**

A. *Tetramethyl 3,7-dihydroxy-1,5-dimethylbicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate*. A freshly prepared solution (pH 8.3) of 5.6 g of sodium bicarbonate in 400 mL of water, 70 g (0.40 mol) of dimethyl 1,3-acetonedicarboxylate, and a magnetic stirring bar are placed in a 1-L Erlenmeyer flask. The resulting solution is stirred rapidly as 17.2 g (0.20 mol) of biacetyl (Note 3) is added in one portion. Stirring is continued for 24 hr, during which time white crystals separate. The solid is collected by suction filtration and dried under reduced pressure to afford 60–62 g, mp 155–158°C. The filtrate is cooled in an ice bath, acidified to pH 5 (pHydrion paper) with dilute hydrochloric acid, and extracted with three 100-mL portions of chloroform. The chloroform extracts are combined, washed with saturated sodium chloride, and dried with anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gives another 2–4 g of crude product (Note 16). Recrystallization from hot methanol gives 58–60 g (73–75%) of the tetraester, mp 155–157°C, in two crops (Note 17).

B. *cis-1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione*. A 1-L, one-necked, round-bottomed flask is equipped with a heating mantle, reflux condenser, and a magnetic stirring bar. The flask is charged with 200 mL of 1 *M* hydrochloric acid, 40 mL of glacial acetic acid, and 24 g (0.060 mol) of the tetraester from Section IIA. The mixture is stirred vigorously and heated at reflux for 3–6 hr (Note 18). The solution is cooled in an ice bath and the product is isolated as described in Section IB above. The yield of c white to light yellow solid, mp 219–221°C, is 9.5–9.8 g (95–98%). Recrystallization from a minimum amount of hot ethanol affords 7.5–7.7 g (75–77%) of the diketone, mp 222–225°C, in one crop (Note 19).

## 2. Notes

1. The dropping funnel and the reflux condenser were connected to the same neck using a Claisen adapter.
2. The submitters recommend that a high-purity grade of sodium hydroxide be used. Otherwise insoluble impurities are formed that must be removed by filtration through a sintered-glass Buchner funnel.
3. Dimethyl 1,3-acetonedicarboxylate, aqueous 40% glyoxal, and biacetyl were purchased from Aldrich Chemical Company, Inc. The submitters advise against using glyoxal solution that contains a significant amount of white solid.
4. The submitters report that the yield is decreased by 5% if exactly 0.5 equiv of glyoxal is used. The yield is improved to 75–76% in runs carried out on smaller scale (ca. 0.1 mol of glyoxal).
5. Heating should be resumed if necessary to maintain a temperature of 65°C. The submitters report that lower yields are obtained at lower temperatures (e.g., 37% at 25°C).
6. The submitters caution that the addition time is critical. In one run by the checkers with a 30-min addition time, the yield of the disodium salt was reduced to 49%.
7. Similar yields were obtained by the submitters when the reaction mixture was allowed to cool at room temperature for 2 hr and in an ice bath for another 2 hr.
8. The solid is washed first by allowing methanol to percolate through the filter cake with gentle suction until the brown color is removed. The product is suspended in methanol, filtered, and washed again by

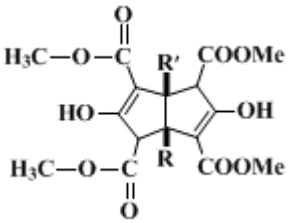
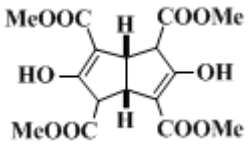
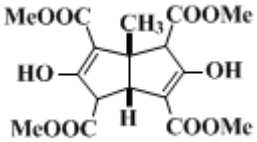
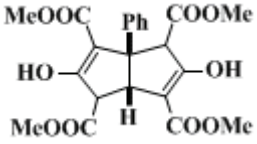
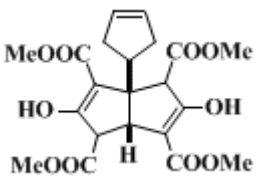
the percolation procedure.
9. The submitters obtained 411–430 g (61–64%) from reactions conducted on twice the scale described using a 2-hr addition time. Elemental analyses by the submitters and checkers indicate a variable degree of hydration ($n$ = 1–2) for the product. The yield and molar quantities of the disodium salt are calculated assuming a monohydrate, $C_{16}H_{16}O_{10}Na_2 \cdot H_2O$. For further characterization of this salt, see [4] [5].
10. The checkers used a mechanical stirrer to achieve more efficient mixing of the layers.
11. The submitters obtained 176–182 g (62–64%) of product, mp 103–105°C, after trituration with a minimum amount of cold methanol. Crystallization was facilitated by scraping the sticky solid with a silver spatula. The reported melting point is 104–107°C.[6] [7] The crude product obtained initially by the checkers was a low-melting solid, mp 70–75°C, that was conveniently transferred and purified by recrystallization from about 1 L of hot 2 : 1 hexane–ethyl acetate. Elemental analyses of the product by the submitters were within ±0.4% of the theoretical value. The spectral properties of the product are as follows: IR ($CHCl_3$) $cm^{-1}$: 3025, 2960, 1740, 1673, 1632, 1450, 1438, 1330, 1250, 1200, 1155, 1058; $^1H$ NMR ($CDCl_3$, 200 MHz) δ: 3.64 (apparent t, 2 H, $J_{app}$ = 2.4, two CH), 3.78 (s, 6 H, two $OCH_3$), 3.81 (s, 6 H, two $OCH_3$), 3.87 (apparent t, 2 H, $J_{app}$ = 2.4, two CH), 10.35 (broad s, 2 H, two enolic OH).
12. The volume of the flask should be at least three times larger than the volume of the solution to avoid losses from excessive foaming caused by rapid evolution of carbon dioxide. The checkers used a mechanical stirrer to facilitate stirring of the initially heterogeneous mixture. Two reflux condensers are recommended for efficient venting of the gas evolved.
13. The submitters point out that the disodium salt may be used directly provided that two additional equivalents of 1 *M* hydrochloric acid are employed. Acetic acid may be omitted to simplify the isolation procedure. In this case the reaction mixture remains heterogeneous throughout.
14. Progress of the reaction can be followed by observing the gas evolved through a bubbler connected to the top of the reflux condensers.
15. The product gave satisfactory elemental analyses. Calcd. for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.42; H, 7.36. The literature melting point is 84–86°C.[6,7] The spectral properties of the product are as follows: IR ($CHCl_3$) $cm^{-1}$: 1738 (C=0), 1405, 1222, 1208, 1175, 792; $^1H$ NMR ($CDCl_3$, 220 MHz) δ: 2.16 (dd, 4 H, $J$ = 4.2, 19.3, $H_A$ of $CH_AH_B$), 2.59 (dd, 4 H, $J$ = 8.5, 19.3, $H_B$ of $CH_AH_B$), 3.04 (m, 2 H, CH); $^{13}C$ NMR ($CDCl_3$) δ: 35.5 (d, CH), 42.6 (t, $CH_2$), 217.2 (s, C=O); mass spectrum (70 eV) *m/e* (relative intensity): 138 ($M^+$, 41), 69 (36), 68 (58), 41 (100), 39 (53).
16. The checkers obtained ca. 19 g of a viscous red oil that on dissolution in ca. 150 mL of methanol deposited 4 g of crude crystalline product.
17. The product gave a satisfactory elemental analysis. Calcd. for $C_{18}H_{22}O_{10}$: C, 54.28; H, 5.53. Found: C, 54.00; H, 5.57. The melting point reported initially (167–169°C after sublimation)[8] is apparently incorrect. The spectral properties of the product are as follows: IR (KBr) $cm^{-1}$: 3539, 1742, 1664, 1425, 1340, 1260, 1235, 1070, 1020; $^1H$ NMR ($CDCl_3$) δ: 1.29 (s, 6 H, two $CH_3$), 3.75 (s, 6 H, two $CO_2CH_3$), 3.87 (s, 6 H, two $CO_2CH_3$), 3.94 (s, 2 H, two CH), 10.62 (br s, 2 H, two OH).
18. The checkers recovered a 1 : 1 mixture of tetraester and diketone from two runs conducted for 2.5 hr. When the reflux time was extended to 6 hr, complete conversion to product was attained. The reaction progress was monitored by gas evolution (Note 14). Some variability of reaction times is probably attributable to differences in stirring efficiency, temperature gradients, and/or particle size of the crystalline starting material.
19. The recrystallized product was analyzed by the checkers. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.45; H, 8.54. The spectral properties of the product are as follows: IR (KBr) $cm^{-1}$: 1736, 1390, 1245, 1210, 1180, 1145, 1070; $^1H$ NMR ($CDCl_3$, 360 MHz) δ: 1.22 (s, 6 H, two $CH_3$), 2.36 and 2.39 (AB q, 8 H, $J$ = 18.5, four $CH_2$).

## 3. Discussion

Bicyclo[3.3.0]octane-3,7-dione has been prepared in five steps from dimethyl malonate and chloral in about 20% overall yield.[6,7] The direct formation of bicyclo[3.3.0]octane-3,7-diones by the 2 : 1 condensation of acetone-1,3-dicarboxylate and 1,2-dicarbonyl compounds was discovered by Weiss and Edwards[8] and is commonly called the Weiss Reaction.[3] The variation described in Section I has been optimized for large-scale preparation of the parent diketone.[4] [5] It is a good example of what Turner[9] has called a "point reaction," as it is very sensitive to experimental details such as temperature and stirring rate. The aqueous buffer procedure given in Part II is a "plateau reaction"[9] and affords a general method for preparing a variety of angularly-substituted bicyclo[3.3.0]octane-3,7-diones (Table I).[10,11,12,13,14,15,16,17]

The parent diketone can also be prepared by the aqueous buffer procedure (Part II), but chromatography is required to purify the product.[15] The mechanism of this novel annulation reaction involves a complex sequence of aldol condensations, dehydrations, and Michael additions,[11,18 19 20,21] the order of which may be pH-dependent.[21] The isolation of γ-hydroxycyclopentenones in certain cases[11,18,19,20] implicates these reactive Michael acceptors as intermediates. A number of other interesting products have been isolated from reaction of glyoxal with acetonedicarboxylate.[21,22 23 24] The various bicyclic diketones prepared by this method have served as starting materials for syntheses of polycyclic compounds[25 26 27 28 29 30 31 32 33 34 35 36 37] and natural products.[38 39 40 41 42 43 44 45] The reaction of dimethyl 1,3-acetonedicarboxylate with cyclic 1,2-diketones is a particularly effective method of propellane synthesis;[8,12,46 47 48] for instance, Ginsburg has used it to prepare a propellanex with a 40-membered ring.[48] Routes have been developed to triquinacene[49] and its derivatives[50 51 52] which employ as the key step the chemistry discussed in this procedure. This general synthesis of bicyclo[3.3.0]octane derivatives has also been extended to selected examples of bicyclo[3.3.1]nonane and bicyclo[3.3.2]decane systems by substituting malondialdehyde[53] and *o*-phthalaldehyde,[54] respectively, for glyoxal. Reviews of recent progress by the Cook group are available.[55 56]

TABLE I
2 : 1 CONDENSATION OF DIMETHYL 1,3-ACETONEDICARBOXYLATE WITH VARIOUS 1,2-DICARBONYL COMPOUNDS

|  |  | Yield (%) | Ref. |
|---|---|---|---|
| | R = R' = H | | |
| Glyoxal |  | 70 | [4,5, 15] |
| | R = H, R' = $CH_3$ | | |
| Pyruvaldehyde |  | 52 | [8] |
| | R = H, R' = Ph | | |
| Phenylglyoxal |  | 66 | [11] |
| | R = H, R' = $C_5H_7$ | | |
| 3-Cyclopentenylglyoxal |  | 90 | [17] |
| | R = H, R' = $C_7H_{11}$ | | |

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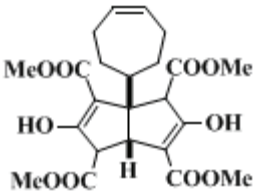
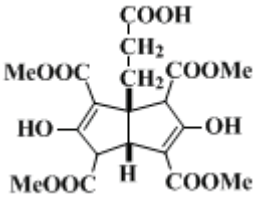
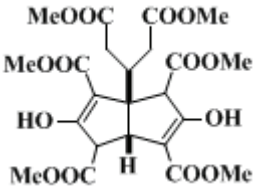
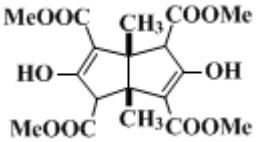
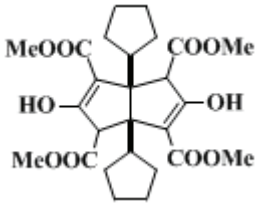
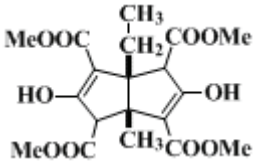
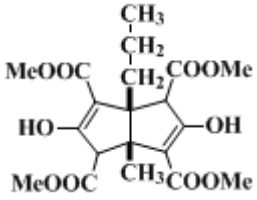
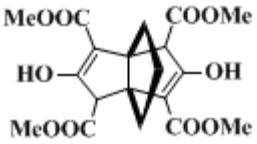
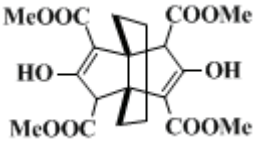
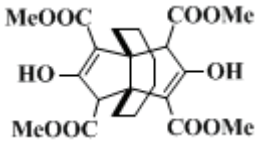
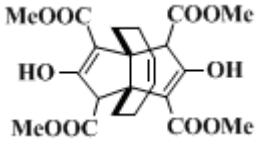
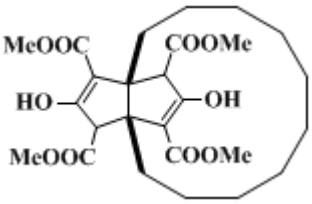
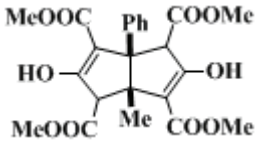
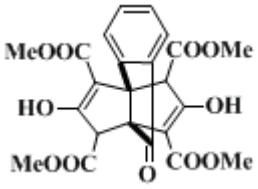
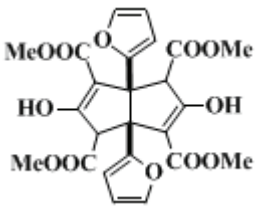
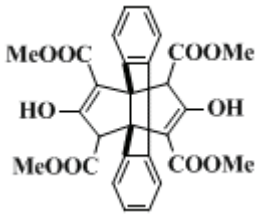
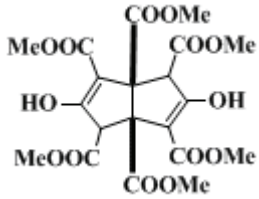
|---|---|---|---|
| 4-Cycloheptenylglyoxal |  <br>R = H, R' = $CH_2CH_2CO_2H$ | 70 | [17] |
| 4,5-Dioxopentanoic Acid |  <br>R = H, R' = $CH(CH_2CO_2CH_3)_2$ | 80 | [10] |
| Dimethyl 3-(dioxo ethyl)glutarate |  <br>R = R' = $CH_3$ | 51 | [18] |
| Biacetyl |  <br>R = R' = $C_5H_9$ | 84 | [8] |
| Bis(cyclopentyl) 1,2-ethanedione |  <br>R = $CH_3$, R' = $CH_2CH_3$ | 12 | [17, 18] |
| 2,3-Pentanedione |  <br>R = $CH_3$, R' = $CH_2CH_2CH_3$ | 70 | [17] |
| 2,3-Hexanedione |  | 64 | [17] |
| Cyclopentane-1,2-dione | R = R' = $(CH_2)_3$ | 45 | [8, 16] |

| | | | |
|---|---|---|---|
| |  <br>R = R' = $(CH_2)_4$ | | |
| Cyclohexane-1,2-dione |  <br>R = R' = $(CH_2)_6$ | 81 | [12] |
| Cyclooctane-1,2-dione |  <br>R = R' = $(CH_2)_2CH{=}CH(CH_2)_2$ | 80 | [13] |
| Cyclooct-5-ene-1,2-dione |  <br>R = R' = $(CH_2)_{10}$ | 87 | [14] |
| Cyclododecane-1,2-dione |  <br>R = $CH_3$, R' = Ph | 94 | [13] |
| 1-Phenyl-1,2-propanedione |  <br>R = R' = $C_7H_4O$ | 68 | [17] |
| Ninhydrin |  <br>R = R' = $C_4H_3O$ | 60 | [11] |
| Furil |  <br>R – R' = 2,2'-biphenyl | 60 | [20] |

| | | | |
|---|---|---|---|
| Phenanthrenequinone |  R = R' = $CO_2CH_3$ | 54 | [17], [20] |
| Dimethyl 2,3-dioxosuccinate |  | 14 | [31] |

## References and Notes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## Appendix
## Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

cis-BICYCLO[3.3.0]OCTANE-3,7-DIONES

2,5(1H,3H)-Pentalenedione, tetrahydro-, cis-, and 2,5(1H,3H)-pentalenedione, tetrahydro-, 3a,6a-dimethyl-, cis

$C_{16}H_{16}O_{10}Na_2 \cdot H_2O$

propellane

triquinacene

o-phthalaldehyde

ethanol (64-17-5)

hydrochloric acid (7647-01-0)

acetic acid (64-19-7)

ethyl acetate (141-78-6)

methanol (67-56-1)

glyoxal (107-22-2)

sodium hydroxide (1310-73-2)

chloroform (67-66-3)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

sodium sulfate (7757-82-6)

carbon dioxide (124-38-9)

Phenylglyoxal (1074-12-0)

phenanthrenequinone (84-11-7)

chloral (75-87-6)

biacetyl (431-03-8)

2,3-Pentanedione (600-14-6)

1-phenyl-1,2-propanedione (579-07-7)

hexane (110-54-3)

Cyclohexane-1,2-dione (765-87-7)

Pyruvaldehyde (78-98-8)

bicyclo[3.3.1]nonane (280-65-9)

ninhydrin (938-24-9)

DIMETHYL 1,3-ACETONEDICARBOXYLATE (1830-54-2)

Bicyclo[3.3.0]octane-3,7-dione

dimethyl malonate (108-59-8)

acetone-1,3-dicarboxylate

3-Cyclopentenylglyoxal

4-Cycloheptenylglyoxal

4,5-Dioxopentanoic Acid

Dimethyl 3-(dioxo ethyl)glutarate

Bis(cyclopentyl) 1,2-ethanedione

2,3-Hexanedione (3848-24-6)

Cyclopentane-1,2-dione

Cyclooctane-1,2-dione

Cyclooct-5-ene-1,2-dione

Cyclododecane-1,2-dione

Dimethyl 2,3-dioxosuccinate

bicyclo[3.3.2]decane (283-50-1)

malondialdehyde (542-78-9)

cis-1,5-Dimethylbicyclo[3.3.0]octane-3,7-dione (21170-10-5)

cis-Bicyclo[3.3.0]octane-3,7-dione (51716-63-3)

Tetramethyl 3,7-dihydroxybicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate (82416-04-4)

Tetramethyl 3,7-dihydroxy-1,5-dimethylbicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate (79150-94-0)