preparative TLC (EtOAc/hexanes, 3:7, three passes) gave 34% of recovered **13** and 36% of the podophyllotoxin derivative **14**;[23] one recycle raised the yield of **13** to 48%.

Desilylation of ether **14** (excess $Et_3N{\cdot}HF$, THF, room temperature, 3 da[24] gave podophyllotoxin (**4**) in 89% yield.[25] Alternatively, ether **14** was reacted with anhydrous HBr[26] (CH_2Cl_2–Et_2O, 0 °C, 8 h). Hydrolysis of the crude 4-epibromo-4′-*O*-demethyl-podophyllotoxin **15** ($CaCO_3$, aqueous Me_2CO, 45 °C, 1 h) gave 47% of white crystalline 4′-*O*-dimethyl-4-epipodophyllotoxin (**3**), mp 244–246 °C (MeOH),[27] identical in all respects with an authentic sample prepared from natural podophyllotoxin.

Our insertion–cyclization strategy and subsequent tactical modifications now make available (±)-podophyllotoxin (**4**) in 12 synthetic steps and 4.5% overall yield from piperonal; aglycon **3** is similarly available in 13 steps and 2.4% overall yield. More convergent variants of our insertion–cyclization scheme in which both the aryltetralin and the γ-lactone are generated in a single operation can be envisioned and are under exploration.

Acknowledgment. Partial support of this work by Grant CA-18846 from the National Cancer Institute (USPHS) and by Sherman Clarke and Elon Huntington Hooker Fellowships to D.P.C. and M.L.K. is gratefully acknowledged.

Registry No. (±)-**3**, 77519-36-9; (±)-**4**, 77519-37-0; (±)-**5**, 77461-23-5; **6**, 51444-50-9; (±)-*cis*-**7**, 77461-24-6; (±)-*trans*-**7**, 77461-25-7; (±)-*cis*-**8**, 77461-26-8; (±)-*trans*-**8**, 77461-27-9; (±)-**9**, 64897-37-6; (±)-**10**, 64897-39-8; (±)-**11**, 64937-82-2; (±)-**12**, 77519-38-1; (±)-**13**, 77461-28-0; (±)-**14**, 77519-39-2; (±)-**15**, 77519-40-5; piperonal, 120-57-0; 3,4,5-trimethoxybenzaldehyde, 86-81-7; diethyl malonate, 105-53-3.

(22) Pyridine hydrochloride was found to give a higher proportion of the trans lactone than was obtained with acetic acid. Use of even more sterically encumbered proton sources, such as collidine hyrochloride, did not result in further improvement of the trans to cis ratio; cf.: Zimmerman, H. E.; Mariano, P. S. *J. Am. Chem. Soc.* **1968**, *90*, 6091 and references therein.

(23) **14**: IR ($CHCl_3$) 1780 cm^{-1}; NMR ($CDCl_3$) δ 6.95 (1 H, s), 6.48 (1 H, s), 6.39 (2 H, s), 5.96 (2 H, s), 4.79 (1 H, d), 4.42–4.66 (2 H, m), 3.8–4.25 (1 H, partially obscured m), 3.82 (3 H, s), 3.72 (6 H, s), 2.70–2.96 (2 H, m), 0.95 (9 H, s), 0.29 (3 H, s), 0.11 (3 H, s); mass spectrum, *m/e* 528 (M^+). Anal. Calcd for $C_{28}H_{36}O_8Si$: C, 63.61; H, 6.86; Si, 5.31. Found: C, 63.55; H, 6.81; Si, 5.26.

(24) Hünig, S.; Wehner, G. *Synthesis* **1975**, 1980.

(25) This material was identical with natural podophyllotoxin.

(26) An analogous procedure was used in ref 3 for preparation of **3** from **4**.

(27) **3**: mp 244–246 °C (MeOH); IR ($CHCl_3$) 3540, 1780 cm^{-1}; NMR ($CDCl_3/Me_2SO$-d_6) δ 6.92 (1 H, d), 6.49 (1 H, s), 6.29 (2 H, s), 6.00 (1 H, s), 5.90 (2 H, s), 4.80 (1 H, d), 4.55 (1 H, d), 4.24–4.46 (2 H, m), 4.24–4.84 (1 H, br s), 3.76 (6 H, s), 3.20–3.48 (1 H, dd), 2.64–2.98 (1 H, m); mass spectrum, *m/e* 400 (M^+). Anal. Calcd for $C_{21}H_{20}O_8$: C, 62.99; H, 5.04. Found: C, 62.83; H, 5.02.

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2,5-Bis(methoxycarbonyl)-4-hydroxycyclopent-2-en-1-one as an Intermediate in Weiss' Glyoxal Reaction. Analogous Chemistry of Malondialdehyde

Summary: Glyoxal and dimethyl 3-oxoglutarate condense at pH <6 to form a reactive intermediate, 2,5-bis(methoxycarbonyl)-4-hydroxycyclopent-2-en-1-one, part of which dimerizes to yield **3** after hydrolysis–decarboxylation. Its structure was proved by single-crystal X-ray crystallography performed on the dimethyl ester. Support for this mechanism comes from studying the analogous reaction of malondialdehyde, which gives 2,6-bis(methoxycarbonyl)phenol at pH 5 but not at pH 8 where phenol formation is usually more rapid. The product at pH 8 is tetramethyl 3,7-dioxobicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylate.

Sir: 4-Hydroxycyclopentenones constitute an exceptionally interesting and important class of organic compounds, considering their role as a structural feature of the naturally occurring pyrethrin insecticides and their synthetic analogues,[1] the pentenomycin antibiotics,[2] and the key intermediates in some syntheses of prostaglandins.[3] We have collected convincing chemical evidence that a simple member of this class, 2,5-bis(methoxycarbonyl)-4-hydroxycyclopent-2-en-1-one (**1**), is the important reactive intermediate formed when dimethyl 3-oxoglutarate and glyoxal are mixed at pH 5. In contrast, at pH 6 the predominant reactive intermediate is 3,5-bis(methoxycarbonyl)-4-oxopent-2-enal (**2**), as proposed by Cook and Weiss.[4] The important new findings are the isolation of the major tetracyclic product **3** at low pH and the demonstration that dimethyl 3-oxoglutarate (**4**) reacts with malondialdehyde by way of intermediates analogous to those it begets with glyoxal. This research clarifies one of the principle mechanistic questions of Weiss' reaction between **4** and glyoxal, viz., which of the proposed possible intermediates[4] is responsible for each of the products.

In 1968 Weiss and Edwards reported[5] that bicyclo[3.3.0]octane-3,7-dione (**5**) was formed in ~15% yield after hydrolysis and decarboxylation of the tetraester **5b** (Scheme I) that collected when **4** and glyoxal were stirred in dilute aqueous solution at pH 5. The endo and exo tetracyclic triketones **6** were later found to accompany **5** in yields of 3.2% and 1.6%, respectively.[6,7] The total yield is substantially increased by buffering the reaction mixture at pH 6 where **7b** can be isolated in 61% yield;[8,9] **7b** gives a 43% yield of **7** upon hydrolysis–decarboxylation.[8] A 12% yield of **5b** is also present at pH 6,[10] as are the usual small amounts of **6**.

A priori, two fundamentally different 1:1 intermediates, **1** and **2**, could be postulated to arise from the interaction of **4** and glyoxal (Scheme I). Either of these might be expected to react further with **4** to give **5b**, which itself could react with **1** or **2** to yield the hexakis(methoxycarbonyl) precursors of **6**.

The isolation of **7b** as the major product at pH 6 im-

(1) Elliott, M.; Jones, N. F. *Chem. Soc. Rev.* **1978**, *7*, 473–505.

(2) Date, T.; Aoe, K.; Kotera, K.; Umino, K. *Chem. Pharm. Bull.* **1974**, *22*, 1963–7.

(3) Bartmann, W. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 337–44.

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(6) Edwards, J. M.; Qureshi, I. H.; Weiss, U.; Akiyama, T.; Silverton, J. V. *J. Org. Chem.* **1973**, *38*, 2919–20.

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(8) Rice, K. C.; Weiss, U.; Akiyama, T.; Highet, R. J.; Lee, T.; Silverton, J. V. *Tetrahedron Lett.* **1975**, 3767–70.

(9) The yield can be improved from the 45% of ref 8 to 61% by adding methanol as a cosolvent, which allows more concentrated solutions of the reactants to be used. In this study we mixed 87.0 g of **4**, 72.5 g of 40% glyoxal, and 250 mL of 50% aqueous methanol containing 3.45 g of monobasic sodium phosphate monohydrate and adjusted the pH to 6 with 17 mL of 10 M NaOH added by drops with vigorous swirling and ice-bath cooling. The product was filtered off after the mixture was stirred for a week at 25 °C.

(10) This yield was measured by quantitative ^{13}C NMR, calibrated with an internal standard (cyclohexane). Gated proton decoupling was used.

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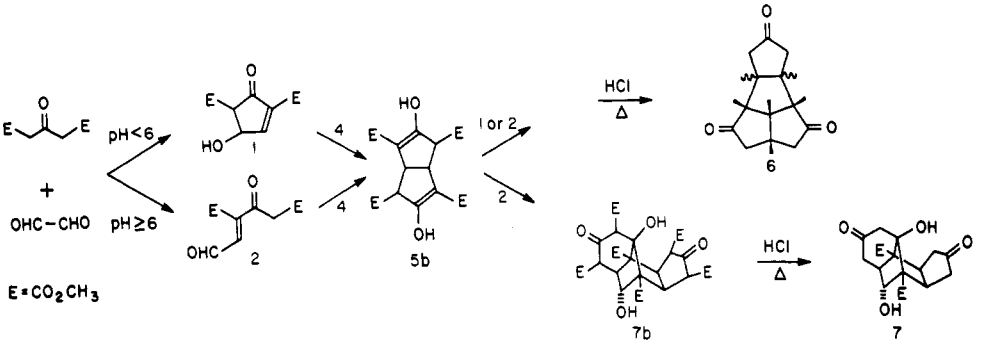
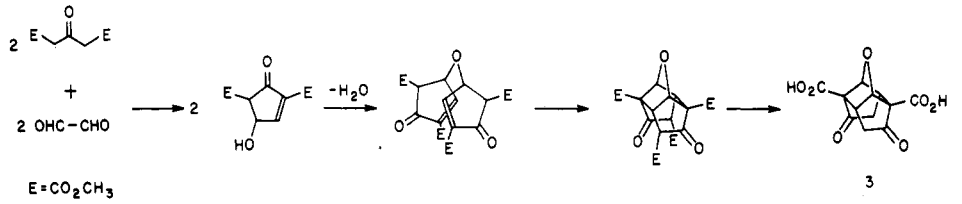
Scheme I



Scheme II



plicates **2** at this pH, since **7b** can be derived in a straightforward manner from **2** and **5b**.[4] We have found that no **7b** is present at pH 5 when equimolar amounts of **4** and glyoxal are allowed to react. Product **7b** is exceedingly insoluble, and even a few percent of it can be isolated easily. With a 2:1 ratio of **4** to glyoxal, which is optimal for **7b**,[8] a 4% yield of it is isolated at pH 5. As **7b** is stable at pH 5, it can be concluded that the amount of **2** at pH 5 is small (~4%). Due to the importance of compounds related to **1** and because of interest in derivatives of **5** and *endo*-**6** as dodecahedrane precursors,[11] we decided to investigate this mechanistic problem in greater depth.

We sought to find a product which would implicate **1** in the same straightforward way that **7** points to **2**. To this end the bicarbonate-soluble fractions (which were not investigated by Weiss and his co-workers) from the decarboxylated reaction mixtures were examined. Crystallization of these fractions from methyl acetate yielded a new product, **3**, which clearly points to the intermediacy of **1** as shown in Scheme II.

The yield of isolated **3** was 11% at pH 5 vs. 5% at pH 6.[12] (At pH 7 it was only 2%.) With a 1:1 reactant ratio at pH 5, no **5b** can be detected by ^{13}C NMR,[10] which shows broad bands at δ 49–59 and 161–175 suggestive of polymer. Molecular weight measurements[13] indicate that the average oligomer contains three or four units of **1**. This material (80% yield) is not precipitated by cupric acetate, as are **4** and **5b**. The "polymer" from 2-(methoxycarbonyl)-cyclopent-2-en-1-one[14] (vide infra) was not characterized. Our evidence strongly suggests that **1** is the predominant intermediate in Weiss' reaction at low pH, where cyclization of an initial aldol is faster than elimination, and **2** is the intermediate at higher pH's where elimination is faster than cyclization. The elimination of water from aldols is known to favor the trans olefin (which cannot cyclize) and is essentially irreversible under acid-catalyzed conditions (pH <7).[15]

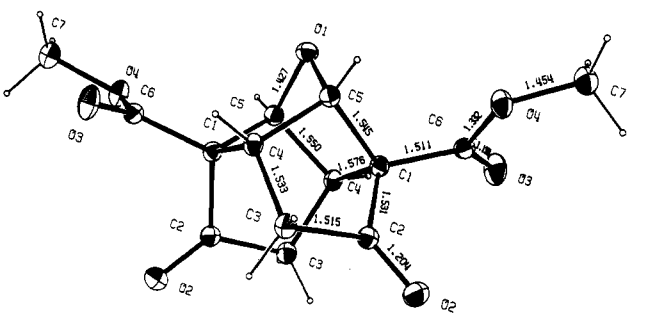
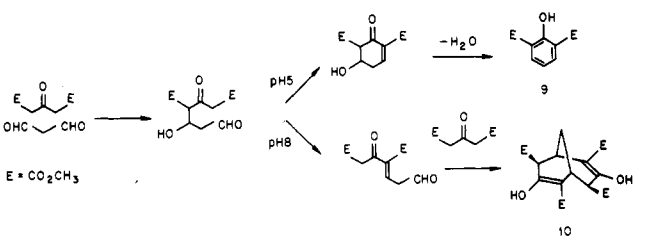


Figure 1. Perspective view of compound **6**, including bond lengths (estimated standard deviations ≤0.003 Å).

Scheme III



The structure of **3** was deduced from its spectral properties and those of its dimethyl ester (**8**, prepared by using diazomethane). In view of its importance to the mechanistic problem, the structure of **8** was confirmed by a single-crystal X-ray diffraction study (*R* factor of 0.041). This is the first report of an X-ray study of the 10-oxahomohypostrophane skeleton, of which one other representative (10-oxahomohypostrophene) is known.[16] The perspective drawing of **8** (Figure 1) shows that the two carbocyclic five-membered rings have nearly perfect classical C(5) envelope conformations[17] (clockwise starting with C(2)–C(3), the torsion angles are 0°, 24.0°, −37.4°, 38.7°, and −24.5°). The flap angle C(4)–C(5)–C(1) is 100.4°, which is identical with the average value in the 7-*tert*-butoxynorbornadiene dimer;[18] it is considerably

(11) Eaton, P. E. *Tetrahedron* **1979**, *35*, 2189–223.
(12) These experiments employed ~0.1 M reactants in 1 M phosphate buffers.
(13) Vapor-phase osmometry established that $\bar{M}_n$ = 747. Gel permeation chromatography using polystyrene standards indicated $\bar{M}_n$ = 429–479 under conditions which gave 195 for **5b** (mol wt 370). The polydispersivity was 1.4–1.8.
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smaller than the value of 107.1° reported for norbornane,[19] reflecting increased strain. The flap angle C(5)–O(1)–C(5′) is also small (97.3°) but not quite as low as the corresponding angle in norbornane (95.3°)[19] or the dimer (95.1°).[18] The presence of this tight angle pinching C(5) and C(5′) causes an elongation of the C(1)–C(4) bond to 1.576 Å; the other bond lengths are more or less normal. The same reflex effect is present in norbornane (1.578 Å)[19] and the dimer (1.568 Å)[18] and appears to be a general phenomenon in bicyclo[2.2.1] systems.

As **1** and **2** cannot interconvert under our conditions,[15] it is not possible to write a plausible mechanism from **2** to **3** or from **1** to **7**. Nonetheless, a second piece of corroborating evidence was desired. Consequently, the reaction of **4** with malondialdehyde was investigated, since it was expected that if 2,6-bis(methoxycarbonyl)-5-hydroxycyclohex-2-en-1-one (the six-membered-ring analogue of **1**) were to form at low pH, it would aromatize to 2,6-bis(methoxycarbonyl)phenol (**9**, Scheme III). In fact, no **9** could be isolated at pH 7–9, which is in itself remarkable considering the high yields of phenols obtained from **4** and many 2-substituted malondialdehydes.[20] The product in this pH range was 2,4,6,8-tetrakis(methoxycarbonyl)bicyclo[3.3.1]nonane-3,7-dione (**10**, 60% yield).[21] In complete confirmation of our prediction, **9** was produced in 41% yield at pH 5, where the yield of **10** was 35%.[22] Treatment of **9** with **4** at pH 8 does not produce any **10**. Although phenol formation is generally more rapid at basic pH's, higher yields have been obtained at pH 5 when the starting material decomposed at higher pH.[23] This is not the case in our system. The striking similarity in the behavior of malondialdehyde to that proposed for glyoxal provides strong support for the intermediacy of **1** at low pH.

Attempts to isolate **1** have thus far failed, which is not surprising in light of the fact that 2-(methoxycarbonyl)-cyclopent-2-en-1-one is stable in dilute solution at −10 °C but polymerizes upon attempted purification.[14] Compound **1** is presumably even more reactive. A 1:1 adduct has been observed spectroscopically upon admixture of **4** and phenylglyoxal, but it was too labile to be isolated.[4] Now that the pH dependence of the condensations of dimethyl 3-oxoglutarate with glyoxal and malondialdehyde is understood, it will be possible to use these previously recondite reactions in a more rational manner for the quick construction of complex natural products and man-made molecules of theoretical interest.

Acknowledgment. The authors express their gratitude to the late Professor R. B. Woodward, under whose aegis part of this work was carried out, and to Dr. U. Weiss (NIH) for his unselfish and energetic assistance. We also thank M. L. M. Schilling, who measured the ^{13}C NMR spectra, and M. Hellman, who determined the molecular weights.

Registry No. **1**, 77589-52-7; **4**, 1830-54-2; **5b**, 68703-09-3; **7b**, 58648-30-9; **8**, 77589-53-8; **10**, 77589-54-9; glyoxal, 107-22-2.

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(21) Satisfactory analytical and spectral data have been obtained for this new compound.
(22) These yields were measured by ^1H NMR; the isolated yield of pure **9** was 10% after a lengthy purification. For the first preparation of **9**, see: Graebe, C.; Kraft, H. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 800.
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Supplementary Material Available: Crystal and refinement data, atomic coordinates, and bond and torsion angles (4 pages). Ordering information is given on any current masthead page.

* S.H.B, Bell Laboratories; W.O.A. and J.V.S., National Heart, Lung, and Blood Institute. The glyoxal chemistry discussed herein has been abstracted from: Bertz, S. H. Doctoral Dissertation, Harvard University, 1978. The malondialdehyde chemistry was presented by S.H.B. at the Third IUPAC Symposium on Organic Synthesis, Madison, WI, June 18, 1980.

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Aporphines. 35. Synthesis of (*R*)-(−)- and (*S*)-(+)-Apomorphine from Thebaine and (+)-Bulbocapnine

Summary: A practical method for the synthesis of (−)-apomorphine and (−)-*N*-*n*-propylnoramorphine from the opioid thebaine is presented. The method is also applicable to the transformation of (+)-bulbocapnine to (+)-apomorphine.

Sir: Apomorphine (APO, **8a**) was first prepared in 1869 by the acid treatment of morphine.[1] The structure of APO was elucidated in 1902,[2] and its absolute configuration was determined to be *R* in 1955.[3] In 1970 the total synthesis of (±)-APO was carried out by a multistep process from isoquinoline and vanillin.[4] (±)-APO was resolved into (−) and (+) enantiomers in 1973,[5] and it was established that dopaminergic activity resides principally in the 6a*R* (levorotatory) isomer. In the century following its first preparation, APO was used in a variety of clincal disorders.[6] With the demonstration in the mid and late 1960's that APO is a dopamine (DA) receptor agonist and evidence that a derangement of DA function may play a role in various neurological, psychiatric, and other disorders, there has been a renewed interest in clinical and pharmacological research with this compound and its more potent *N*-propyl homologue **8b** (NPA).

The actions of (−)-APO at DA-sensitive cells have received further support in studies of the iontophoretic application of APO to striatal neurons,[7] the stimulation of DA-sensitive adenylate cyclase by APO[8,9] and the use of radioactive ligands including ^3H-APO[10] and ^3H-NPA[11] to

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