Tetramethyl 3,7-Dihydroxybicyclo[3.3.1]nona-2,6-diene-2,4,6,8-tetracarboxylate: A Useful Companion to Meerwein's Ester. Topological Analysis of Bicyclo[3.3.1]nonane Synthesis[1]

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The pH dependence of the condensation of dimethyl 3-oxoglutarate and malondialdehyde to produce 2,6-bis(methoxycarbonyl)phenol and tetramethyl 3,7-dihydroxybicyclo[3.3.1]nona-2,6-diene-2,4,6,8-tetracarboxylate has been studied in detail: the yield of the former is maximal at pH 4.5, the latter at pH 7.5. The hydrolysis–decarboxylation of the latter provides a convenient route to bicyclo[3.3.1]nonane-3,7-dione. The mechanism proposed for this reaction of malondialdehyde is also relevant to the chemistry of glyoxal and dimethyl 3-oxoglutarate. The retrosynthetic analysis of the bicyclo[3.3.1]nonane skeleton is considered from a topological perspective.

While studying the reactions of 2,4,6-heptanetrione and dimethyl 3-oxoglutarate (**1**) with 1,3-dicarbonyl compounds such as 2,4-pentanedione (which give substituted phenols under mild, buffered conditions),[2] we were surprised when the white solid that precipitated in good yield upon treating **1** with malondialdehyde (**2**) turned out to be tetramethyl 3,7-dihydroxybicyclo[3.3.1]nona-2,6-diene-2,4,6,8-tetracarboxylate (**3**), the bis(enol) of tetramethyl 3,7-dioxobicyclo[3.3.1]nonane-2,4,6,8-tetracarboxylate. This result is analogous to the Weiss reaction of **1** with glyoxal yielding tetramethyl 3,7-dioxobicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate[3] (also completely enolized) and represents a departure from the usual course of the reaction of **1** with 1,3-dicarbonyl compounds.[4] During this work, it came to our attention that the prototype of this reaction had also been discovered independently by two other individuals: D. E. Jackman[5] at the Woodward Institute (CIBA-GEIGY) and R. D. Sands,[6] who published a note on his results shortly after our preliminary communication.[7] Hydrolysis–decarboxylation of **3** makes bicyclo[3.3.1]nonane-3,7-dione (**4**) readily available via simple procedures from inexpensive starting materials. By lowering the pH from 8 to 5, it was possible to isolate 2,6-bis(methoxycarbonyl)phenol (**5**). In this paper we detail the pH dependence of the reaction of **1** and **2**, summarize our experiments optimizing the yields of **3** and **4**, and present our proof of structure **3**. The various approaches to the bicyclo[3.3.1]nonane system are analyzed from a topological point of view.

Results

Malondialdehyde was prepared by the acidic hydrolysis of 1,1,3,3-tetramethoxypropane (**6**). The reaction was monitored by periodically extracting a sample of the reaction mixture with chloroform-*d* and recording its ^{1}H NMR spectrum. In this way it was found that the best results were obtained by using 1 equiv of 2 M HCl at room temperature for 1–2 h. Under these conditions, the yield of **2** was 75–78%, measured by adding 1 equiv of base (to neutralize the HCl) and titrating the resulting solution to a potentiometric endpoint. The equivalence point was taken to be pH 10, the pH of a solution of sodiomalondialdehyde prepared by the literature method.[8] The ^{1}H NMR spectrum of the major product from the hydrolysis of **6** was different from the ^{1}H NMR spectrum of the sole product prepared by acidification of sodio-**2**. The former (see Experimental Section for spectral parameters) fits (*E*)-3-hydroxy-2-propenal, whereas the latter fits the symmetrically H-bonded *Z*-isomer. About 20% of the *Z*-isomer was also formed during the hydrolysis of **6** under our conditions.

Previous hydrolysis conditions involved stirring a mixture of **6** and 0.06 equiv of 0.3 M HCl at 50–55 °C "until it was homogeneous" (71% yield)[8] or a mixture of **6** and 1 equiv of 4 M HBr at room temperature for 5–10 min (48% yield).[9] Under our conditions, the mixture became homogeneous within 10 min, but the ^{1}H NMR measurements showed that the amount of **2** had not reached its maximum until 1 h had elapsed. Normally the solutions yellowed; however, if the hydrolysis was allowed to proceed too long (>2 h), they turned red, and a brown tar was eventually deposited. Although a good yield of **3** could be obtained from the **2** prepared at 50 °C,[8] making the conditions milder results in a more reproducible "plateau" reaction rather than a "point" reaction.[10]

The condensation of **1** with **2** was found to be mainly dependent upon four variables: the pH, the reactant ratio, the scale of the reaction, and the temperature. Each of these variables was optimized independently while holding the others constant. Although in one set of experiments conducted at pH 8, the yield of **3** using **2** prepared as above was nearly the same as the yield starting from sodio-**2**[8] (64% vs. 67% on a 0.05-mol scale), the ^{1}H NMR spectra of the crude extracts of the reaction mixtures from sodio-**2** were "cleaner", showing fewer side products to be present. This was especially important when equimolar amounts of **1** and **2** were mixed. Starting with sodio-**2**, only **3** and **5** were present at pH 8, allowing their combined mass to be measured, and the amounts of both were large enough

(1) Presented in part at the Third IUPAC Symposium on Organic Synthesis, Madison, WI, June 16, 1980. Part 7 in a series of Chemistry Under Physiological Conditions. Part 6, ref 27; 5, ref 7; 4, ref 11; 3, Bertz, S. H. *J. Org. Chem.* **1981**, *46*, 4088–90; 2, ref 37a; 1, ref 2.

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(3) Weiss, U.; Edwards, J. M. *Tetrahedron Lett.* **1968**, 4885–7.

(4) Wedemeyer, K.-F. "Methoden der Organischen Chemie"; Müller, E. Ed.; Georg Thieme: Stuttgart, 1976; Vol. VI/1c, 891–9.

(5) Jackman, D. E., personal communication.

(6) Sands, R. D. *J. Org. Chem.* **1983**, *48*, 3362–3.

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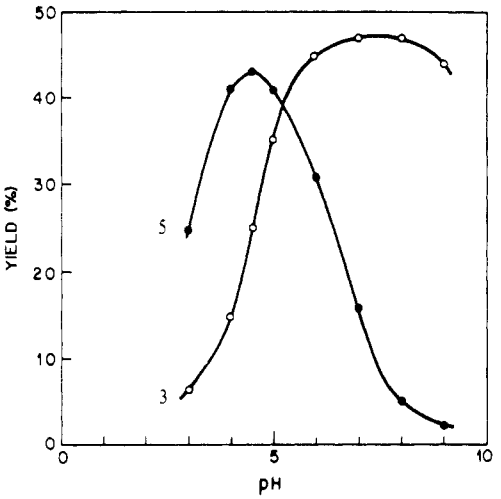


Figure 1. The pH dependencies of the yields of 3 and 5.

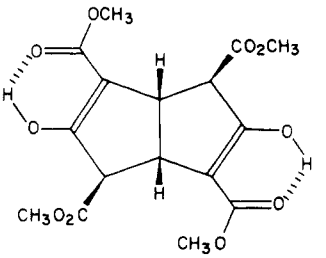
to be measured accurately by ^{1}H NMR. Thus by running reactions at various pH values and measuring the ^{1}H NMR spectra of the crude products using identical instrumental parameters, one can obtain the amounts of **3** and **5** in all of them by integration of peaks known to be due to one or the other of them. Both products were isolated in pure form from larger scale reaction mixtures.

The results of this pH study are plotted in Figure 1, which shows that **3** and **5** have remarkably different pH dependencies. Whereas the yield of **5** is maximal (43%) at pH 4.5, that of **3** reaches a much broader maximum at pH 7.5 where it is 47%, calculated from the amount of sodio-**2** (91% based upon **1** as the limiting reagent). The yield of **3** calculated from the amount of **2** was higher if more **1** was used (see next paragraph); the 1:1 reactant ratio was chosen for the pH study to ensure that measurable amounts of **3** and **5** were produced over the entire pH range studied. Preparative scale reactions for product **3** were carried out with a 2:1 reactant ratio at pH 8, since this was the pH at which the reaction mixtures set up at pH 7–8 tended to buffer themselves. The conditions employed by Sands[6] involve much less base than used here and result in a mixture of **3** and **5**. Furthermore, his reaction mixture starts out warm, which is also deleterious. External heating of the buffered reaction mixtures lowers the yield and the quality of the product. Initial cooling does not appear to affect the yield as long as the reaction mixtures are allowed to warm to room temperature.

With a 2:1 ratio of **1** to **6** (i.e., a 2.67:1 ratio of **1** to **2**), the yields starting with 0.01, 0.05, and 0.1 mol of **6** (hydrolyzed to **2** before admixture with **1**, of course) were 60, 64, and 67%, respectively, based on the amount of **1** used. (The corresponding yields are 80–90% based on **2**, considering the fact that the yield of **2** from **6** is ~75%.) The yield of isolable material dropped to 48–50% when the scale was increased to 0.4 mol of **1** and the **2** from 0.2 mol of **6**. The decline did not involve the heat generated by the reaction mixture, which became warm to the touch, as the provision of external cooling (an ice-water bath) had no effect on the yield.

The yield of **3** decreased slowly as the ratio of **1** to **2** was decreased. Using 0.2 mol of **1**, it went from 67% with 0.075 mol of **2** (from 0.1 mol of **6**) to 66% with 0.1 mol of **2** (from 0.15 mol of **6**) and finally 58% with 0.15 mol **2** (from 0.2 mol of **6**). Moreover, the quality of the product deteriorated as more **2** was used, degenerating from a white crystalline solid to a tacky orange gum. Therefore, for preparative scale reactions, we used the 2.67:1 ratio of **1** to **2** (2:1 ratio of **1** to **6**).

Addition of a neutral aqueous solution of **2** to a refluxing methanolic solution of sodio-**1**[11] (2 equiv) gave a 35% yield of **3**. The analogous reaction of glyoxal gives, upon acidification, a 75% yield of tetramethyl 3,7-dioxobicyclo-[3.3.0]octane-2,4,6,8-tetracarboxylate (**7**).[11] The yield of



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3 from a similar experiment run at room temperature was 38%; thus, strongly basic conditions are deleterious. In a related experiment performed by D. E. Jackman,[5] a mixture of 2 equiv of diethyl 3-oxoglutarate and 1 equiv of sodio-**2** was refluxed in ethanol to give, after acidification, a 42% yield of the tetraethyl analogue of **3**.

In addition to the four main variables, certain other details also had important consequences. If, instead of adding **1** to a basic solution of **2**, it was added to the initial, acidic hydrolysis solution and the pH was then adjusted to 8, the yield of **3** was lowered from 67% to 55% (using 0.2 mol of **1** and 0.1 mol of **6**). It did not matter whether the methanol cosolvent was added before or after the **1**; however, it was again necessary to make the solution of **2** alkaline first, or some reacetalization of **2** occurred. The acidification of the reaction mixture at the end of an experiment required some care. If the pH was lowered to 3–5, a crystalline white solid was isolated; however, if too much acid was added (pH 1–2), a sticky solid resulted.

Compound **3** is extraordinarily impervious to aqueous acid. After 3 h of vigorous reflux in 20% HCl, 97% of it was recovered unchanged simply by filtering the reaction mixture. The addition of acetic acid as cosolvent enabled the conversion of **3** to **4** in 83% yield, but only after 6 h of strong boiling. In contrast to these results, **7** is completely hydrolyzed and decarboxylated after 0.5 h in refluxing 20% HCl.[12]

Discussion

Our initial surprise upon isolating **3** was due to the fact that a number of 2-substituted malondialdehyde derivatives (nitro, phenyl, benzoyl, ethoxycarbonyl) react with **1** to give good yields of phenols under alkaline conditions.[4] In spite of the familiar "driving force" provided by aromatization, the reaction of the parent compound takes a different course, forming **3** in direct analogy to the Weiss reaction of **1** with glyoxal to form **7**.[3,11] The fact that the best yields of **3** are obtained under "physiological conditions" (aqueous solution, pH ~7.5, ambient temperature) is reminiscent of the formation of tropinone from succindialdehyde, methylamine, and 3-ketoglutaric acid.[13] It has been said[14] that "reactions which occur spontaneously and smoothly in aqueous media at ordinary tem-

(11) Bertz, S. H.; Rihs, G.; Woodward, R. B. *Tetrahedron* **1982**, *38*, 63–70.
(12) (a) Vossen, G. Dissertation, Bonn, 1910. (b) Yates, P.; Hand, E. S.; French, G. B. *J. Am. Chem. Soc.* **1960**, *82*, 6347–53.
(13) Schöpf, C.; Lehmann, G. *Justus Liebigs Ann. Chem.* **1935**, *518*, 1–37.
(14) Woodward, R. B., "Perspectives in Organic Chemistry"; Todd, A., Ed.; Interscience: New York, 1956; p 168.

peratures command the special admiration of many chemists".

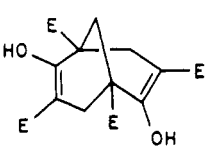
Product **3** also bears an interesting resemblance to "Meerwein's ester" (**8**), which has been one of the most valuable entries to the bicyclo[3.3.1]nonane system to date.[15] Like **3**, **8** is prepared in one step (56% from dimethyl malonate and formaldehyde).[15a] Mislow and coworkers have recently shown that **8** is completely enolized,[15b] as is the case for **3** (vide infra).

Mechanistic Considerations. Another case in which the yield of a phenol was better at pH 5 than at pH 8 was due to the decomposition of one of the reactants at the higher pH.[16] In our case the inverse pH dependence must be explained by a fundamental bifurcation in the mechanism of the reaction, since two products are formed, each of which incorporates both starting materials.

The first step is perforce an aldol reaction. The partition of the resulting 1:1 adduct (**9**) between cyclization to diol **10** (which leads to **5** via **11** and **12**) and elimination to enone **13** (which leads to **3** via **14**, **15**, and **16**) provides the most plausible explanation for the experimental results, based upon precedents in the literature. Aldols similar to **9** have been prepared in 50–75% yields from substituted glyoxals and β-keto acids.[17] The further reaction of **9** with **1** to give **17** is unlikely, since an intramolecular aldol reaction affording a six-membered ring (i.e. **10**) is favored over the corresponding intermolecular one.[18] Also, if the intermolecular aldol reaction were to be faster than the intramolecular one in the case of two symmetrical, bifunctional reactants such as **1** and **2**, the product would be a polymer.[19] In fact, as the reactant ratio approaches 1:1, the white crystalline **3** is replaced by a tacky gum (cf. Results), indicating that some polymerization may indeed be intervening. The extent of polymerization is not large, since hydrolysis–decarboxylation of the gum gives nearly the same yield as the solid.

As the pH is increased from 4 to 9, however, E1cb elimination[20] is expected to compete with cyclization, growing until at pH >8 it is virtually uncontested. The fact that the *E*-isomer of the olefin (**13**) is favored[21] prevents subsequent cyclization, because such eliminations are usually irreversible.[22] The further reaction of **13** with **1** is undoubtedly facile (vide infra), which also tends to prevent back-reaction to **9**. Although *Z*-olefin **18** cannot be ruled out as a potential precursor of **5**, it is not likely that a significant amount of **3** arises by the further reaction of **18** with **1**. As favorable as such a Michael reaction might be, the aldol reaction **18** → **11** is not only intramolecular, it is favorably constrained as well.

An abundance of precedents[23] for the reactions of diethyl 3-oxoglutarate (the ethyl ester analogue of **1**) with aldehydes points to **14** (from **13** and **1**) as the intermediate from which **3** is ultimately derived. The products, which have general structure **20** (E = CO_2Et; R = H, Me, *i*Pr, Ph),



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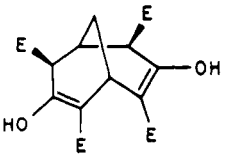

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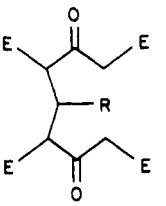

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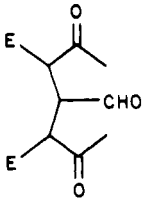

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are the result of an aldol reaction followed by elimination of water and then the Michael addition of a second equivalent of diethyl 3-oxoglutarate to the unsaturated intermediate, as we purpose for the formation of **14**. This sequence, aldolization–elimination–addition, has been established in the formation of **8** from dimethyl malonate and formaldehyde.[15c,24] It also explains the formation of **21** from glyoxal and ethyl acetoacetate in 20% yield under conditions similar to ours.[25a] In contrast, under optimal conditions glyoxal and acetoacetic acid only yield 4% of 3,5-octadiene-2,7-dione,[25b] which is formed by two aldol–elimination sequences, one at each aldehyde group, as is the case for **19**. Furthermore the conditions employed were significantly different from ours; the authors report that deviation from them (e.g., in the direction of ours) resulted in "complete failure" ["völligen Misserfolg"].[25b] Taken together these results suggest that **14** rather than **19** is the principal progenitor of **3**.

Like **9**, **16** is an obligatory intermediate given the principle of microscopic reversibility. Just as there is only one reasonable bond to form first in going from **1** and **2** to **3**, there is only one reasonable bond to break first in the retrosynthesis from **3** back to **1** and **2**. This strategic bond[26] is the one formed last in the synthetic direction (**16** → **3**). We have shown that such Michael reactions are involved in the Weiss reaction between **1** and glyoxal in buffered solutions and that the corresponding retro-Michael reactions are important when the products are strained.[27] The strain in the bicyclo[3.3.1] ring system[28] is much less than that in the intermediates we studied.[27]

Thus we propose that the last three steps of the overall sequence (i.e., **14** → **15** → **16** → **3** as in Scheme I) are basically the same as the first three steps (i.e., **1** + **2** → **9** → **13** → **14**), viz. aldolization, elimination of water, and Michael addition. The last three steps are undoubtedly faster than the first three, as they are all unimolecular, whereas two of the first three are bimolecular. It is unlikely that significant **15** is due to the interception of **11** by **1**.

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(17) Schechter, M. S.; Green, N.; LaForge, F. B. *J. Am. Chem. Soc.* **1949**, *71*, 3165–73.

(18) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102.

(19) Bowden, M. J. "Macromolecules, An Introduction to Polymer Science"; Bovey, F. A., Winslow, F. H., Eds.; Academic Press: New York, 1979; p 195–201.

(20) Saunders, W. H.; Cockerill, A. F. "Mechanisms of Elimination Reactions"; Wiley: New York, 1973; p 8–23.

(21) Nielsen, A. T.; Houlihan, W. J. "Organic Reactions"; Cope, A. C., Ed.; Wiley: New York, 1968; Vol 16, p 12.

(22) Ref 21, p 7,10.

(23) Knoevenagel, E. *Justus Liebigs Ann. Chem.* **1895**, *288*, 321–60. See also Rabe, P.; Elze, F. *Justus Liebigs Ann. Chem.* **1902**, *323*, 83–112.

(24) For a complete scheme, see ref 48, p 322.

(25) (a) West, E. S. *J. Am. Chem. Soc.* **1925**, *47*, 2780–9. (b) Karrer, P.; Eugster, C. H. *Helv. Chim. Acta* **1949**, *32*, 1934–5.

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(27) Bertz, S. H.; Kouba, J.; Sharpless, N. E. *J. Am. Chem. Soc.* **1983**, *105*, 4116–7.

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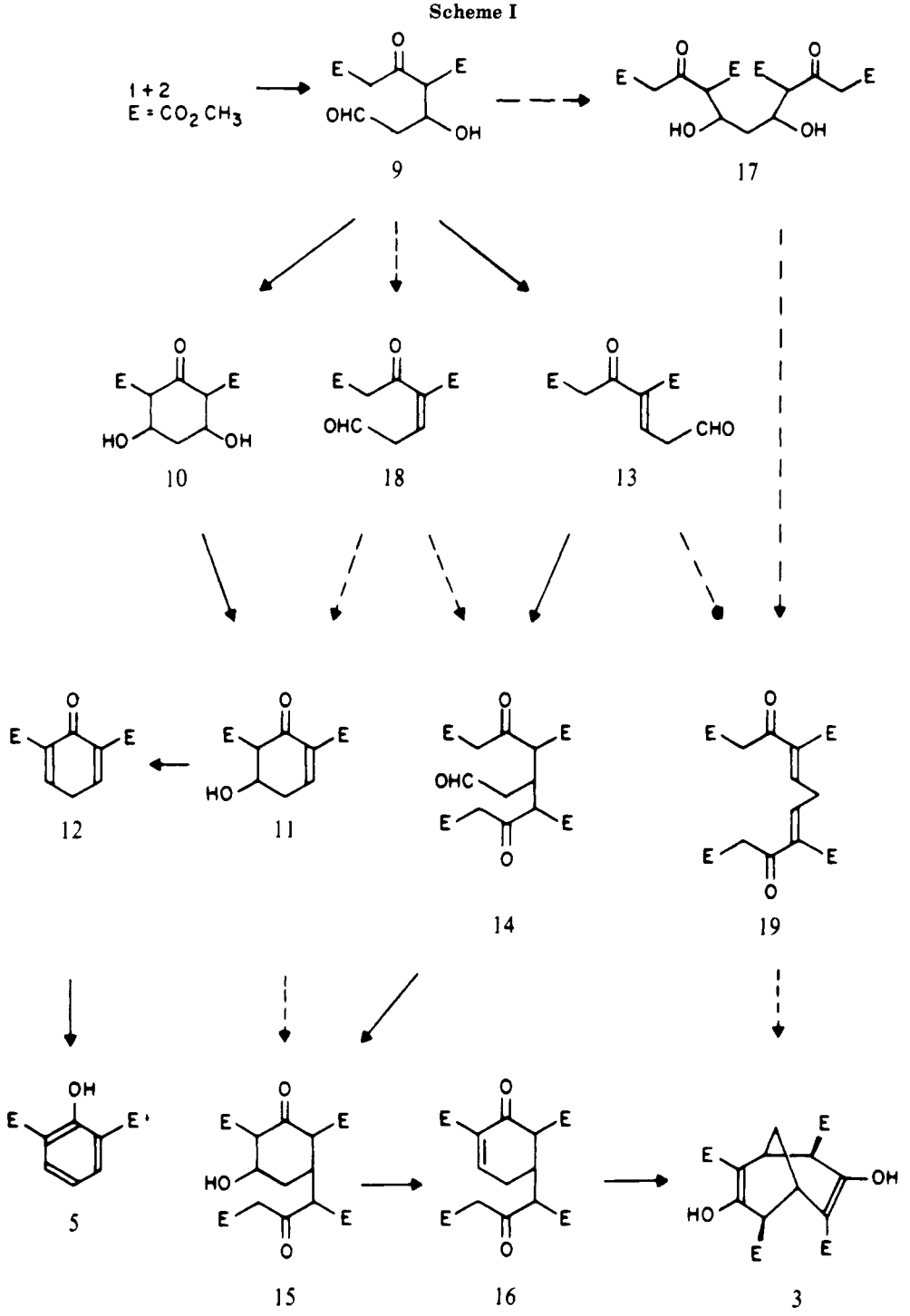
Scheme I



Since the introduction of a double bond α to a keto group increases the acidity of the α' as well as the γ-protons,[29] the elimination of the second molecule of water (**11** → **12**) is expected to be faster than the first (**10** → **11**), making the steady-state concentration of **11** small. A number of cyclohexenones bearing leaving groups have been reported to aromatize easily under acidic or basic conditions at room temperature.[30]

The dienone **12** is an unstable phenol tautomer which has yet to be observed.[31] Nonetheless, the possibility that a small fraction of **3** comes via **12** must be admitted, for bicyclo[3.3.1]nonane derivatives have been prepared from **1** and quinone monoacetals[32] or 6,6-dialkyl-3-oxocyclohexa-1,4-dienes.[33] (Note that there are two identical Michael acceptors per molecule of **12**, which accelerates its bimolecular addition relative to that of **11**, **13**, or **18**.) When a mixture of **1** and **5** is subjected to the reaction conditions, no **3** is observed. There are many examples of reactions in which **1** reacts with 2 equiv of an aldehyde to yield a tetrahydro-γ-pyrone[34] or, if an amine is present, a γ-piperidone.[35] These products are stable heterocyclic

(29) Caine, D. "Carbon-Carbon Bond Formation"; Augustine, R. L. Ed.; Marcel Dekker: New York, 1979; Vol 1, p 284.
(30) Ref 4, p. 689–96.
(31) March, J. "Advanced Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1977, p 73 and references therein. See also Zaidi, J. H.; Waring, A. J. *J. Chem. Soc., Chem. Commun.* **1980**, 618–9.
(32) McDonald, I. A.; Dreiding, A. S. *Helv. Chim. Acta.* **1973**, *56*, 2523–34.
(33) Stetter, H.; Mayer, J. *Chem. Ber.* **1959**, *92*, 2664–6.
(34) Petrenko-Kritschenko, P.; Stanischewsky, S. *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 994–6.

analogues of 12 and provide support for the formation of 5 via 10, 11, and 12, since in 2 the two aldehyde groups are simply connected by a one-carbon bridge.

It is not surprising that the ratio of 3:5 varies with pH, as all the reactions contributing to the overall mechanism discussed above are pH-dependent. The yields of both 3 and 5 fall off at pH <4.5 because the initial formation of 9 from 1 and 2 is slow there (mostly starting material 1 is recovered) and at pH >8.5 because both 1 and 2 are converted to their Na enolates, which are not expected to react with each other at an appreciable rate. (Examples are known in which multienolates react with a β-keto ester enolate.[36]) It is the range pH 4.5–8 which is most interesting, and it is here that the yield of 5 decreases monotonically while that of 3 increases. The reason for the inverse pH dependence of phenol formation appears to be a change in the mechanism from cyclization to elimination in an initial 1:1 intermediate, as discussed above. This elimination shunts the starting materials to product 3, short-circuiting the driving force of aromatization. The idea that an intermediate is partitioned between two paths that lead to either 3 or 5 is a robust one. For example, if 12 were to have a significant lifetime, the partition could be between aromatization and Michael addition of 1. Or, if elimination of water from 9 is much faster than the second aldol reaction that gives rise to 10, the partition would be between 13 and 18.

Comparing the reaction between 1 and 2 with the analogous reaction between 1 and glyoxal[3,11,27,37] helps to illuminate both of them. In the glyoxal reaction, the intermediate analogous to 11 is 2,5-bis(methoxycarbonyl)-4-hydroxycyclopentenone,[37] which does not eliminate a second molecule of water because the product, a cyclopentadienone, would be antiaromatic. For the reaction of 1 with glyoxal, then, the path analogous to 11 → 15 → 16 → 3 is reasonable, whereas with 2 it is not (vide supra). A dimerization product of the 4-hydroxycyclopentenone was isolated and, like 5, its formation had an inverse pH dependence. The explanation we advanced[37] was the partition of an aldol (cf. 9) between cyclization (cf. 10) and elimination (cf. 13), although here too an alternative possibility is partition of the aldol between *Z*- and *E*-olefins.

Bicyclo[3.3.1]nonane-3,7-dione. The conversion of 3 to 4, a known compound, confirms the presence of the bicyclo[3.3.1]nonane skeleton. It also provides an alternative to a recently published "convenient synthesis" of 4.[38] Our preparation gives 4 in 56% yield after two steps on a 100-mmol scale; that of Gilbert et al. proceeds in 71% yield after three steps from 2-adamantanone on a 66-mmol scale. Our procedure appears quite competitive, especially in view of the significantly lower cost of the starting materials and the fact that no highly reactive reagents (e.g., $LiAlH_4$) are involved. Our new procedure is certainly the one to use if 3 is desired, since it is the only one extant for this new substance. The contrast in the conditions required to hydrolyze and decarboxylate 3 compared to 7[12] cannot be due to solubility differences alone, as with acetic acid cosolvent the reaction mixture containing 3 becomes homogeneous within 1 h but requires 6 h for complete decarboxylation. Structural factors must account for the extraordinary difference in reactivity. It is reasonable to expect that if the nonhydrogen-bonded esters of 3 were exo oriented, as they are in 7,[11] they would be shielded from hydrolysis by the methano bridge. On the other hand, if they were endo disposed, 3 would still be expected to hydrolyze more slowly than 7.

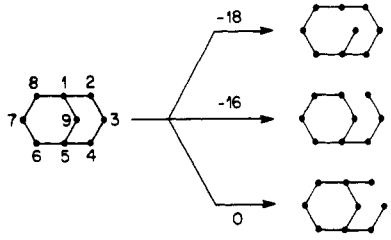


Figure 2. One-bond disconnections of the bicyclo[3.3.1]nonane skeleton. The numbers over the arrows are values of $\Delta C(\eta)$.

Spectral Data. The ^1H NMR spectrum of 3 in chloroform-*d* consists of a 2 H triplet at δ 1.95 (J = 3.3 Hz), another 2 H triplet at δ 3.24 (J = 3.3 Hz), and singlets at δ 3.30 (2 H), 3.77 (6 H), 3.84 (6 H), and 12.33 (2 H). The δ 3.30 resonance from hydrogens at C(4)/C(8) is a broadened singlet at field strengths of 60, 90, and 220 MHz; therefore, the dihedral angle between these protons and those at C(1)/C(5) must be close to 90°.[39] This is only possible if the ester groups at C(4) and C(8) have the exo configuration, and the conformations of the two six-membered rings are close to the half-chair.[40] The half-chair is expected for a cyclohexene derivative, and the far-downfield resonance at δ 12.33 is consistent with complete enolization, as found by Mislow for Meerwein's ester,[15b] and by several groups for 7[11,12] and its ethyl ester analogue.[41] The fact that the hydrogens at C(1)/C(5) and those at C(9) give rise to triplets proves that the bridgehead hydrogens are equivalent and establishes the C_2 symmetry of the molecule rather than the alternative C_s symmetry of the other possible bis(enol), 22. The fact that the peaks at δ 1.95 and 3.30 are both broadened at all field strengths suggests a weak coupling between the protons at C(4) and C(8) and those at C(9) which are connected by W paths.[42]

The ^{13}C NMR spectrum of 3 (see Experimental Section) supports the conclusions that the structure is a bis(enol) and that the bridgeheads are equivalent. The ^{13}C NMR spectrum of 4 is in good agreement with the previously reported one.[43]

The IR spectrum also supports the bis(enol) structure with intramolecular H-bonding via conjugate chelation, as has been discussed for 7[11,12] and 8.[15b]

Mislow and co-workers proposed that the bis(enol) form of Meerwein's ester 8 is stabilized by the conjugate chelation involving intramolecular hydrogen bonding abetted by relief of steric strain though the removal of the endo hydrogens on C(3) and C(7) in the preferred twin-chair conformation of the hypothetical bis(keto) tautomer. In the hypothetical bis(keto) tautomer of 3, there are no endo hydrogens at C(3) and C(7); therefore, the intramolecular H-bonding alone is sufficient to stabilize the bis(enol).

Topological Analysis of Bicyclo[3.3.1]nonane Synthesis. It has been shown that the increase in molecular

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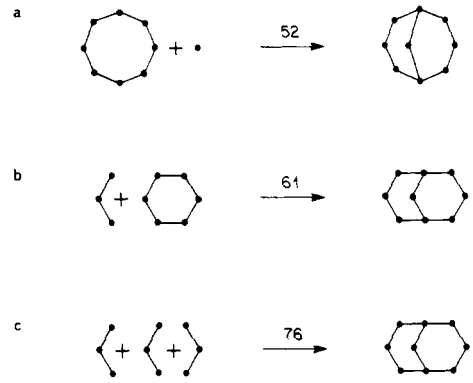

Figure 3. Degrees of convergence in the construction of the bicyclo[3.3.1]nonane skeleton. The numbers over the arrows are values of $\Delta C(\eta)$.

complexity generated by the Weiss reaction of **1** and glyoxal is comparable to that of the Diels–Alder reaction between the same number of components of about the same size.[44a] This conclusion also holds true for the present reaction of **1** and **2**. Figure 2 shows the abstracted graphs[45] for **3** and possible precursors generated by one-bond disconnections and also lists the corresponding values of $\Delta C(\eta)$.[44a] Negative numbers indicate simplification in the retrosynthetic direction (increased complexity in the synthesis direction). The C(1)–C(9) and C(5)–C(9) bonds are topologically the most strategic ones, followed closely by the equivalent C(1)–C(2), C(4)–C(5), C(5)–C(6), and C(1)–C(8) bonds. The equivalent C(2)–C(3), C(3)–C(4), C(6)–C(7), and C(7)–C(8) bonds are topologically the least strategic ones. While the use of this disconnection may not increase or decrease the molecular complexity,[44a] its use may increase the excess complexity of the route (i.e., the sum of the complexities of the intermediates en route from the starting materials to the target).[44b]

The C(1)–C(2) and symmetry-related bonds are the ones identified as strategic bonds by LHASA;[26] the C(1)–C(9) and C(5)–C(9) bonds are ruled out by the heuristic that rings larger than seven-membered ones are difficult to make. In fact, eight-membered rings are readily made by transition metal catalyzed reactions (e.g., cyclooctatetraene and cyclooctadiene by Ni-catalyzed reactions[46]), and the reaction of 1,5-cyclooctadiene with nickel tetracarbonyl yields bicyclo[3.3.1]nonan-9-one (60%) in a single step.[47] A number of other examples of bicyclo[3.3.1]nonane syntheses from cyclooctane derivatives are available.[48] There are a few examples of the formation of the C(2)–C(3) bond in the key step;[48] these generally proceed in low to moderate yields (23–63%). There is no doubt that this is the least effective general approach, in agreement with our calculations. Due to their ubiquity, cyclohexane derivatives have been the most widely used precursors to bicyclo[3.3.1]nonanes, and most of the annulations have been of the C(1)–C(2) type,[48] in harmony with Corey's heuristics.[26] Nevertheless, our calculations indicate that approaches based on eight-membered rings deserve more investigation.

The reaction of 1,5-cyclooctadiene with nickel tetracarbonyl is abstracted in Figure 3a along with the annulation of cyclohexyl derivatives (Figure 3b) and the reaction of **1** and **2** (Figure 3c). The increase in complexity is greater for our approach because it is convergent. As a result of its functional form,[49a] $C(\eta)$ is a good mathematical model for convergence.[49b] Not only does it confirm that division of a molecule into equal halves at each retrosynthetic stage is more efficient than non-equal halves (cf. linear synthesis),[50] it predicts that dissection into n pieces is most efficient when all n are of equal complexity, and n is as large as possible. There are not many organic reactions that join more than two molecules together. The reaction of **1** and **2** joins three molecules with the creation of four C–C bonds, which is reflected in its dramatic increase in complexity. Note that in the genesis of **8**,[15c,24] seven molecules are joined with the creation of eight C–C bonds (and the destruction of two others). Interestingly, the last step corresponds to the least-favorable one-bond disconnection of Figure 2. Just as there are exceptions to guidelines based upon logic and heuristics, there are exceptions to topologically derived guidelines. As mentioned in the previous paragraph, the C(2)–C(3) disconnection generally appears to be the least useful, based on a survey of the bicyclo[3.3.1]nonane literature.[48]

The syntheses of **3** and **8** are both reflexive,[51] which also contributes to their efficiency. It is the symmetry present in **3** (actually, in the bis(keto) tautomer of **3**) that makes it possible to prepare it in one step from symmetrical starting molecules, two of which are the same, so that problems associated with selectivity are obviated.[51] This symmetry is a two-edged sword, however, as monofunctionalizing **4** will be complicated by the same selectivity problems that make the analogous bicyclo[3.3.0]octane-3,7-dione so difficult to monofunctionalize.[52] These problems are due to the fact that an effective control strategy[51] remains to be developed.

Conclusion

Because it is the first detailed pH study, this work represents a significant increase in knowledge about the interactions of dimethyl 3-oxoglutarate (**1**) with 1,3-dicarbonyl compounds. In addition it helps illuminate the corresponding reaction of **1** with 1,2-dicarbonyl compounds, especially glyoxal. It may be hoped that our discovery extending Weiss' bicyclo[3.3.0]octane synthesis to the bicyclo[3.3.1]nonane series will inspire its generalization to further bicyclo[3.3.n] systems.[53] In any case, **3** is likely to become a valuable starting material for many bicyclo[3.3.1]nonane derivatives. Our synthesis of **3** is based upon a reflexive plan which makes efficient use of symmetry. We use the heuristically determined strategic bond, which we calculate to be close to the topological strategic bond in (retrosynthetic) simplifying power.

Experimental Section

General Information. Melting points were determined with a Mettler FP-5 or a Meltemp apparatus and are uncorrected. Evaporation under reduced pressure was done on a Büchi rotary evaporator. Solvents and chemicals were reagent grade, used

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Table I

pH[a]	extract, g	2I (δ 3.95)[b]	2I (δ 3.84)[b]	mol % 5[c]	I (δ 3.95)/ I (pH 8)	I (δ 3.84)/ I (pH 8)	yields % 5[d]	yields % 3[d]
3.0	1.9	40	10	80	4.9	0.14	25	6.6
4.0	2.1	58	20	74	7.1	0.28	41	15
4.5	2.4	54	30	64	6.6	0.42	43	25
5.0	2.2	56	46	55	6.8	0.65	41	35
6.0	2.1	44	62	41	5.4	0.87	31	45
7.0	2.1	23	64	26	2.8	0.90	16	47
8.0	1.9	8.2	71[e]	10[f]	1.0	1.0	5.2[g]	47[g]
9.0	1.6	4.4	77[e]	5.4	0.54	1.1	2.4	44

[a] Average uncertainty ±0.2 unit due to imperfect buffering. [b] Integrals measured using identical instrumental parameters, δ 3.95 is the ester peak of **5**, δ 3.84 and 3.77 are due to the esters of **3**. [c] $100 \times 2I$ (δ 3.95)/[$2I$ (δ 3.95) + $2I$ (δ 3.84)]. [d] % X = [g of X/g of X (pH 8)] × [I/I (pH 8)] × [% X (pH 8)]; see also *g*. [e] I (δ 3.84) + I (δ 3.77). In the other mixtures the δ 3.77 peak was not completely resolved, see also *b*. [f] This corresponds to 5.7% by weight of **5**, 94.3% **3**. [g] % X (pH 8) = 1.9 (wt % X) ÷ (mol wt of X) ÷ (0.010 mol); see also *f*.

without further purification. NMR spectra were obtained on Varian T-60 or HR-220 or Bruker WH-90 instruments; IR spectra were measured with a Perkin-Elmer 597 spectrophotometer. **CAUTION**: Malondialdehyde reacts with amino acids[54a] and nucleic acids,[54b] and has been reported to be carcinogenic[54c] and mutagenic.[54d]

Tetramethyl 3,7-Dihydroxybicyclo[3.3.1]nona-2,6-diene-2,4,6,8-tetracarboxylate (3). A mixture of 16.4 g (0.10 mol) of 1,1,3,3-tetramethoxypropane (**6**, Aldrich) and 50 mL of 2.0 M HCl was stirred in a 250-mL round-bottom flask covered with a rubber septum at 25 °C for 2 h, resulting in a yellow solution. The ^{1}H NMR spectrum of a sample extracted into $CDCl_3$ had ceased to change by this time: ^{1}H NMR ($CDCl_3$) δ 5.65 (dd, J = 8, 13 Hz, 1 H), 7.43 (d, J = 13 Hz, 1 H), 9.45 (d, J = 8 Hz, 1 H). Ca. 20% of another isomer was also present, the ^{1}H NMR spectrum of which matched that of **2** from sodio-2 (see below). The pH was adjusted to 8 with 35 mL of 5.0 M NaOH, and 35.0 g (0.20 mol) of dimethyl 3-oxoglutarate (**1**, Aldrich, 97%) was added, followed by 50 mL of methanol and 5 mL of 5 M NaOH to give a homogeneous red solution with pH 8. Solid began to separate within 0.5 h. After stirring at 25 °C for 3 days, the reaction mixture was acidified to pH 2 by adding 9 mL of 10 M HCl with rapid stirring. The sticky tan solid that precipitated was collected by suction filtration, washed with 10 mL of water, and dried under vacuum over phosphorus pentoxide to constant weight: 25.6 g (67%).

When this procedure was repeated with only one change, viz. the amount of **6** was increased to 24.0 g (0.15 mol), the yield was 25.4 g (66%). Repeating it with 38.2 g (0.20 mol) of **6** gave 22.4 g (58%).

Heating 16.4 g (0.10 mol) of **6**, 10 mL of 1.0 M HCl, and 15 mL distilled water at 50 °C for 15 min resulted in an orange solution. The pH was adjusted to 8 with 13 mL of 5 M NaOH, and the rest of the experiment was conducted as above to give 25.5 g (66%).

1,1,3,3-Tetramethoxypropane (8.2 g, 0.05 mol) was stirred with 25 mL of 2.0 M HCl for 2 h. Titration to pH 10 with 17.5 mL of 5.00 M NaOH (75% yield of **2**) was done slowly, especially toward the end. Methanol (25 mL) was added, followed by **1** (17.4 g, 0.10 mol) to give a red solution, pH 7.3. After stirring for 3 days at ~25 °C, the pH was reduced from 8 to 3 with 3 mL of 10 M HCl. Filtration gave 12.3 g (64%) of white solid dried to constant weight.

Recrystallization of crude **3** from methanol gave white crystals, mp 175–176 °C. Anal. Found: C, 53.19; H, 5.54. Calcd for $C_{17}H_{20}O_{10}$: C, 53.13; H, 5.24. ^{1}H NMR ($CDCl_3$) δ 1.95 (t, J = 3.3 Hz, 2 H), 3.24 (t, J = 3.3 Hz, 2 H), 3.30 (s, 2 H), 3.77 (s, 6 H), 3.84 (s, 6 H), 12.33 (s, 2 H). ^{13}C NMR ($CDCl_3$) δ 22.5, 30.1, 50.3, 52.2, 52.7, 102.0, 168.1, 170.8, 171.8. IR ($CHCl_3$) 3700–2300, 1730, 1660, 1620, 1350, 1300-1150, 1100, 995 cm^{-1}. MS (130 °C, 70 eV), m/e (%) 384 (7), 352 (29), 321 (22), 320 (100), 293 (11), 288 (17), 261 (17), 260 (12), 179 (36), 147 (15), 69 (12), 59 (17), 15 (16).

2 from Sodio-2. A 0.1-g portion of sodiomalondialdehyde[8] was shaken briefly with 0.5 mL of 1 M HCl. Extraction with 0.5 mL of $CDCl_3$, which was dried by passing it through a column of Na_2SO_4, gave the sample for study. ^{1}H NMR ($CDCl_3$) δ 5.67 (t, J = 4 Hz, 1 H), 8.40 (d, J = 4 Hz, 2 H), 13.8 (broad s, 1 H).

3 from Sodio-2. To a solution of 5.6 g (0.05 mol) of sodiomalondialdehyde[8] and 0.69 g of $NaH_2PO_4 \cdot H_2O$ in 25 mL of distilled water was added 25 mL of methanol, 17.4 g (0.10 mol) of dimethyl 3-oxoglutarate and 8 mL of 5 M NaOH to give an orange solution (pH 8). Acidification and filtration after 3 days produced 12.9 g (67%).

Larger Scale Preparation of 3. A mixture of 32.8 g (0.20 mol) of **6** and 100 mL of 2.0 M HCl was stirred for 1 h at 25 °C. Titration of the resulting solution to pH 10 required 176 mL of 2.00 M NaOH (76% **2**). Addition of 69.8 g (0.40 mol) of dimethyl 3-oxoglutarate (**1**) and 100 mL of methanol gave a red solution (pH 7.7). Acidification with 10 mL of 10 M HCl after 3 days at 25 °C yielded 37.6 g (49%). Repeating this procedure with three changes, viz. the hydrolysis of the **6** was allowed to run for 3 h, 34 mL of 10 M NaOH was used to titrate it to pH 10 (70% **2**), and the methanol was added before the **1**, gave 36.5 g (48%).

A mixture of 32.8 g (0.20 mol) of **6** and 100 mL of 2.0 M HCl was stirred for 1.5 h at 25 °C. It was then cooled to 0 °C and titrated to pH 10 with 71 mL of 5.00 M NaOH (78% yield of **2**), added dropwise during 30 min from an addition funnel. After 100 mL of methanol was added and allowed to cool, 69.6 g (0.40 mol) of **1** was added, followed by 70 mL more of methanol to achieve homogeneity. The cooling bath was allowed to melt and warm to 25 °C (5 h). After 3 days, the reaction mixture, which was considerably less colored than previous ones, was acidified to pH 3 with 10 mL of 10 M HCl. Filtering, washing with 10 mL of water, and drying under vacuum over phosphorus pentoxide afforded 36.6 g (48%).

Bicyclo[3.3.1]nonane-3,7-dione (4). A 500-mL round-bottom flask fitted with a reflux condenser (attached to a bubbler) and containing 19.2 g (50 mmol) of **3** suspended in 100 mL of acetic acid, 50 mL of 10 M HCl, and 50 mL of water was placed in a 130 °C oil bath. The solid that foamed up into the condenser was washed down with acetone (~10 mL), which suppressed further foaming. ^{1}H NMR spectra of samples withdrawn after 3 h and 5 h indicated incomplete decarboxylation. After 6 h at 120–130 °C, the reaction mixture was poured onto 200 cm^3 of crushed ice and extracted with four 200-mL portions of dichloromethane, which were combined and counter-extracted with two 100-mL portions of saturated bicarbonate. Drying over Na_2SO_4 and evaporation gave 7.7 g of off-white solid, which was sublimed at 120 °C/(0.05 torr) to give 6.3 g (83%), mp 200 °C (sealed capillary). A further 0.10 g (1%) was obtained by silica gel chromatography of the sublimation residue.

Repeating the procedure on a 58 g scale gave a 72% yield[55] after crystallization from benzene, mp 250–5 °C (lit.[38] ~250 °C).

Anal. (sublimed material). Found: C, 69.86; H, 8.11. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. ^{1}H NMR ($CDCl_3$) δ 2.2 (m), 2.5

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(55) The yield was lower on the larger scale because of difficulties encountered in neutralizing the large amount of acetic acid. Large amounts of sodium carbonate were required, and local excesses of alkali dimerize such ketones. A better workup has been found to be extraction of the reaction mixture with dichloromethane and evaporation of the solvent under reduced pressure until most of the acetic acid is gone. The residue is taken up in fresh dichloromethane, neutralized with sodium bicarbonate solution, dried over sodium sulfate, and evaporated. See also: Bertz, S. H.; Cook, J. M.; Gawish, A.; Weiss, U. *Org. Synth.*, in press.

(m), 2.8 (m). ^{13}C NMR ($CDCl_3$) δ 31.5, 32.8, 47.9, 208.7. IR ($CHCl_3$) 2920, 1723, 1716, 1330, 1100 cm^{-1}.

2,6-Bis(methoxycarbonyl)phenol (5). 1,1,3,3-Tetramethoxypropane (16.4 g, 0.10 mol) was stirred with 100 mL of 1.0 M HCl for 2 h, 2.76 g (0.02 mol) of $NaH_2PO_4 \cdot H_2O$ was added, and the solution was titrated to pH 3 with 12 mL of 10 M NaOH. Dimethyl 3-oxoglutarate (17.4 g, 0.10 mol) was added, followed by 100 mL of methanol, and the pH was adjusted to 5.0 with 2 M NaOH (~8 mL). After an hour, the pH was readjusted to 5.0 with 2 M HCl, which was repeated after the mixture had stirred overnight. After 3 days it was acidified to pH 3 with 2 mL of 10 M HCl. Filtration gave 7.4 g (19%) of a sticky solid that was proved to be mainly **3** by ^1H NMR. The filtrate was extracted with three 75-mL portions of dichloromethane, dried over sodium sulfate, and evaporated to 14 g of brown oil. This material was treated with 50 mL of 2 M NaOH, and the precipitate was filtered to give 3.17 g of tan solid. An additional 0.15 g of this solid was obtained by acidifying the filtrate, extracting it with dichloromethane, counter-extracting the dichloromethane with saturated bicarbonate, evaporating the organic layer, and treating the residual oil with 10 mL of 2 M NaOH. The combined sodium salts were acidified by stirring with 10 mL of 2 M HCl; the solid present after 30 min was filtered off and dried under vacuum to give 2.88 g (14%) of **5**, mp 64–67 °C. Anal. Found: C, 59.96; H, 4.93. Calcd for $C_{10}H_{10}C_5$: C, 57.14; H, 4.80. Recrystallization from 10 mL of hot methanol gave 2.10 g (10%), mp 68–70 °C (lit.[56] 71 °C). ^1H NMR ($CDCl_3$) δ 3.97 (s, 6 H), 6.95 (t, J = 8 Hz, 1 H), 8.08 (d, J = 8 Hz, 2 H), 11.8 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 52.5, 116.6, 118.5, 136.3, 161.6, 168.1. IR ($CHCl_3$) 3600–2700, 2940, 1720, 1700, 1680, 1610, 1465, 1325, 1300, 1145, 995 cm^{-1}.

Study of the pH Dependence of the Formation of 3 and 5. Sodiomalondialdehyde[8] (1.12 g, 10.0 mmol) and $NaH_2PO_4 \cdot H_2O$ (0.69 g, 5.0 mmol) were added to each to eight 50-mL round-bottom flasks, followed by 5 mL of water and 5 mL of methanol. The pH was adjusted to the value in Table I with either 2 M HCl or 2 M NaOH. Dimethyl 3-oxoglutarate (1.50 mL, 1.80 g, 10.3 mmol) was added, followed by another 5 mL of methanol. The pH was readjusted to the desired value with acid or base as necessary, and finally the total amount of water added was brought to 10 mL. The septum-capped flasks were stirred at 25 °C for 7 days, during which time the pH was periodically readjusted to its nominal value (initially every hour, later once a day). The reaction mixtures were then acidified to pH 3 and immediately extracted with two 30-mL portions of dichloromethane. Drying over sodium sulfate and evaporation under reduced pressure followed by removal of the last traces of solvent in vacuum gave the amounts of crude products listed in Table I. The 0.10-g quantity of insoluble material present in the pH 9 reaction mixture was removed by filtration. The products were transferred with $CDCl_3$ (1% Me_4Si) to 5-mL volumetric flasks, which were brought to volume and inverted several times to homogenize the contents. The ^1H NMR spectrum of each solution was measured and integrated under identical conditions. Since one of the reaction mixtures (pH 8) contained only **3** and **5**, it was possible to calculate the yield of each. The yields of these two products in the other reaction mixtures were then determined by using the ratios of their integrals to those of the pH 8 mixture and the ratio of the weights of the crude extracts to the pH 8 weight. Allowing the $CDCl_3$ solution from the pH 9 reaction mixture to evaporate gave 1.3 g of **3** (33% based on sodio-**2**, 63% based on **1**).

Other Small Scale Reactions. 1,1,3,3-Tetramethoxypropane (2.2 g, 13 mmol) was stirred with 5.0 mL of 2.0 M HCl for 1.5 h, 0.69 g (5.0 mmol) of $NaH_2PO_4 \cdot H_2O$ was added, and the pH was adjusted to 6.5 with 3.5 mL of 5.0 M NaOH. Dimethyl 3-oxoglutarate (1.5 mL, 1.8 g, 10.3 mmol) was added followed immediately by 10 mL of methanol and 1.5 mL of water. The pH was held at 7.0 ± 0.1 by adding a few drops of 2 M HCl or 2 M NaOH as necessary. After stirring at room temperature (~25 °C) for a week, the workup was the same as for the reaction mixtures in the pH study, except that it was not acidified. The ^1H NMR spectrum of the crude product showed significantly more peaks other than those due to **3** and **5**. Trituration with methanol and filtration gave 0.46 g (12%) of **3**.

A mixture of 1.64 g (10 mmol) of **6** and 5.0 mL of 2.0 M HCl was stirred for 1.5 h, and 9.0 mL of 2.0 M NaOH was added, followed by 3.5 g (20 mmol) of dimethyl 3-oxoglutarate and then 10 mL of methanol (pH 7.0). After 3 days at 25 °C, the reaction mixture was acidified from pH 8 to pH 4, and the white solid was collected. The weight of vacuum-dried product was 2.29 g (60%).

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Thiopyranothiopyran Chemistry. 5. Synthesis of Dibenzo[*b*,*g*]thiopyrano[3,2-*b*]thiopyran-6,12-dione (Thioepindolidione)

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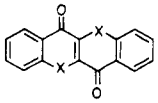
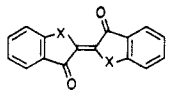
The novel thioepindolidione, a derivative of a thiopyrano[3,2-*b*]thiopyran, was synthesized from thiochroman-4-one. The absorption and fluorescence characteristics of thioepindolidione are compared with those of thioindigo and epindolidione.

Epindolidione (**1**) is a well-known yellow electrophoretic pigment.[1] The hitherto unknown thio analogue dibenzo[*b*,*g*]thiopyrano[3,2-*b*]thiopyran-6,12-dione (thioepindolidione, **2**) can be regarded as a derivative of the novel class of thiopyrano[3,2-*b*]thiopyrans (**3**),[2] of which few examples are known.[3] Furthermore, although thioepindolidione (**2**) is isomeric to thioindigo (**5**),[4] the differences in absorption characteristics and pigment properties between epindolidione (**1**)[5] and indigo (**4**)[6] are quite dra-



1, X = NH
2, X = S

3



4, X = NH
5, X = S

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