

Unexpected stereoselectivity in the Weiss–Cook condensation of dimethyl 1,3-acetonedicarboxylate with pentane-2,3-dione

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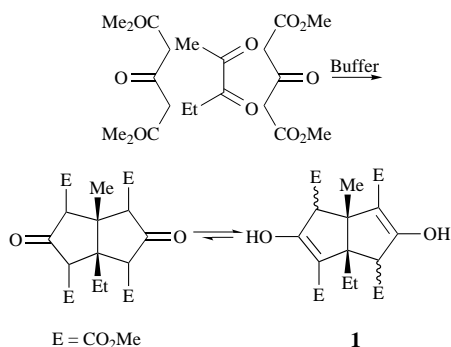
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The Weiss–Cook condensation of dimethyl 1,3-acetonedicarboxylate † with the unsymmetrical pentane-2,3-dione gives only two (1a and 1c) of the four possible epimers of tetramethyl 1-ethyl-3,7-dihydroxy-5-methyl-*cis*-bicyclo[3.3.0]octa-2,6-diene-2,4,6,8-tetracarboxylate in 86% isolated yield. The structures of 1a and 1c have been established by means of single crystal X-ray crystallography.

Introduction

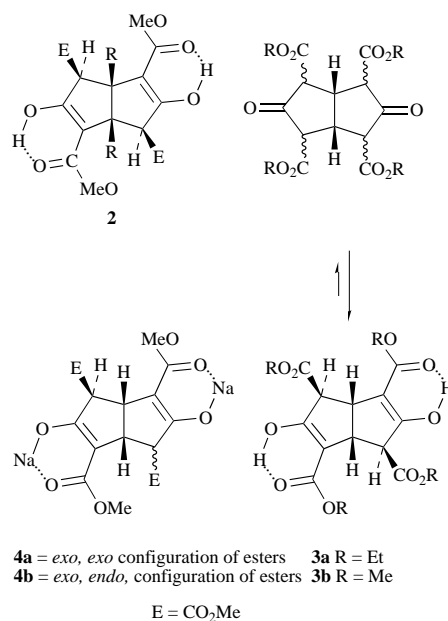
In connection with our interest in the synthesis and study of potentially neutral homoaromatic semibullvalenes,¹ we required the bicyclo[3.3.0]octadiene **1**. The diene **1** had been prepared by the Weiss–Cook condensation of dimethyl 1,3-acetonedicarboxylate † with pentane-2,3-dione (Scheme 1).² The Weiss–Cook condensation is a remarkably versatile reaction which has been employed for the synthesis of a number of polyquinane natural products including modephene, isocomene, pentalenene, quadrone, gymnomitrol and bifurcarenone.³ Moreover, this condensation has been used in the preparation of a number of polyquinanes and polyquinenes of theoretical interest including triquinacenes, fenestranes and semibullvalenes.³



Scheme 1

Results and discussion

To our surprise the coupling of dimethyl 1,3-acetonedicarboxylate with the unsymmetrical pentane-2,3-dione resulted in the isolation of only two epimers of **1** in 86% overall yield and in an approximate ratio of 3:2 (NMR spectroscopy). We were unable to detect any other 2:1 condensation products from this reaction. Tentative assignment of the structure of the major product as epimer **1a** was made by analogy with the well-known 2,6-diene configuration and the *exo,exo* preference (of the ester groups on the tetrahedral centres) of the products isolated in analogous Weiss–Cook condensations,³ such as **2**³ and the bisenols **3a**⁴ and **3b**.⁵ It should be noted that two epimers of the sodium salt of **3b** (**4a** and **4b**) have previously



been isolated and characterized.⁵ Examination of the structures of these tetraesters by ¹H and ¹³C NMR and IR spectroscopy, as well as mass spectrometry supported this assignment. However, the spectroscopic evidence for the structure of **1a** was not conclusive. Similarly, the spectroscopic data for the minor product did not allow unequivocal structure assignment. Consequently, good crystals of both the major and minor products were subjected to single crystal X-ray structure determination.

The X-ray structure of **1a** (Fig. 1) confirmed the predicated *exo,exo* configuration for the major isomer. The unit cell of **1a** consisted of two crystallographically independent molecules. One of these was disordered with almost 50% occupancies of the disordered ethyl group sites. The esters C9–O4–O5–C10 and C13–O8–O9–C14 and C11–O2–O3–C12 and C15–O6–O7–C16 had mean plane least square (MPLA) values of 13.1(1) and 6.0(3)°, respectively, and torsion angles of –18.7(2) (C18–C1–C2–C17), –102.1(2) (C18–C1–C5–C11) and 66.9° (C17–C2–C3–C9) which differ significantly from the corresponding angles in the minor isomer **1c**. The intramolecular hydrogen bonds in the ordered molecule {1.83(3) Å for H1⋯O4 [O1–H1⋯O4 = 148(3)°] and 1.79(3) Å for H10⋯O6 [O10–H10⋯O6 = 147(3)°]} were longer than those found in the disordered molecule {1.88(3) Å for H11⋯O12

† IUPAC name: dimethyl 3-oxopentanedioate.

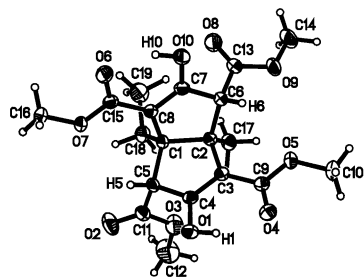


Fig. 1 Stereo ORTEP plot of **1a**

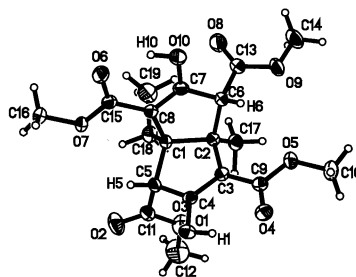
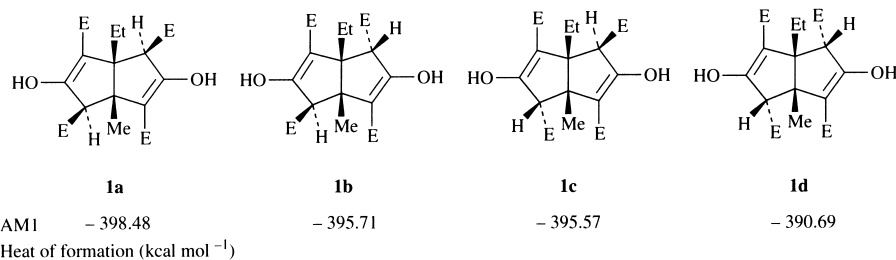


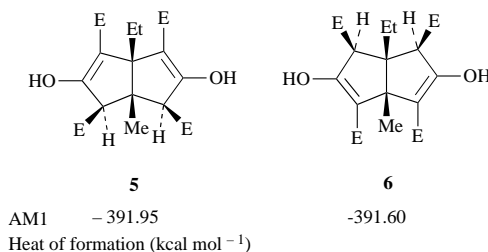
Fig. 2 Stereo ORTEP plot of **1c**



[O11–H11...O12 = 146(3)°] and 1.86(3) Å for H20...O18 [O20–H20...O18 = 143(3)°] as well as for those in **1c**.⁶ The only close range intermolecular interaction [2.55(4) Å] resulted from the ordered molecule H16C...O8^c ($c = -x, 2 - y, 1 - z$) and lay in the *ab* plane.

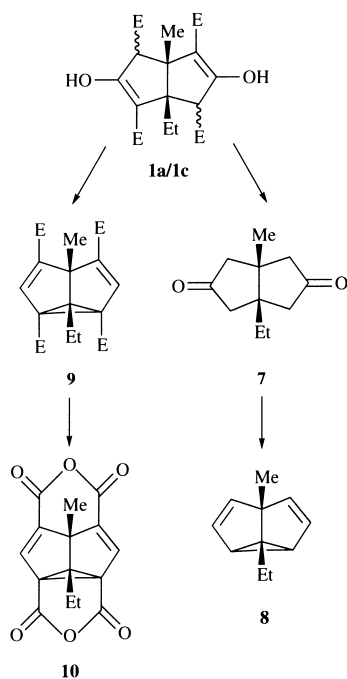
The minor isomer was shown to have the structure **1c** (Fig. 2). In contrast with **1a**, the ester groups C9–O4–O5–C10 and C13–O8–O9–C14 are in an almost eclipsed (parallel) conformation [MPLA = 32.1(1)°] while the remaining esters C11–O2–O3–C12 and C15–O6–O7–C16 lie in the same plane such that the C=O groups are oriented away from each other [MPLA = 9.2(1)°]. The configurations of the alkyl groups are described by the torsion angles C18–C1–C2–C17, C18–C1–C5–C11 and C17–C2–C3–C9 of –22.2(2), 26.4(2) and 58.2°, respectively. The intramolecular hydrogen bonds {1.78(3) and 1.68(3) Å for H1...O4 [O1–H1...O4 = 147(2)°] and H10...O6 [O10–H10...O6 = 146(3)°]} were much shorter than the sum of the van der Waal radii of hydrogen and oxygen.⁶ The crystal packing diagram of **1c** showed a close H6...O1^a ($a = x - 1, y, z$) contact of 2.47(2) Å resulting in the molecular chain-type of stacking along the *c*-axis. Another short range contact H10B...O8^b ($b = x, -1/2 - y, -1/2 - z$) of 2.55(4) Å linked these chains in the *ab* plane perpendicular to the *c*-axis.

Isolation of **1a** as the major product was not unexpected.³ The 2,6- (as in **1**, **2**, **3** and **4**) rather than 2,7- (as in **5** and **6**) arrangement of double bonds was known to be the preferred configuration for the bicyclo[3.3.0]octane ring system,^{3,7} and the *exo,exo* configuration of **1a** was the sterically least encumbered epimer. These conclusions are supported by AM1 calculations⁸ as implemented in the HyperChem⁹ software package (the AM1 energies are shown below).



However, the isolation of **1c**, in which the ester proximate to the bridgehead methyl was *endo*, as the only other product was surprising. Examination of the AM1 energies revealed that **1c** was of very similar energy to **1b** and **1d**, and even to **5** and **6** suggesting that each of these isomers was a feasible product. We postulated that **1c** must be much less soluble than the other isomers and that this solubility difference accounted for its isolation. To test this hypothesis we carried out equilibration studies in aqueous methanolic NaHCO₃ on pure samples of **1a** and **1c**, both in bulk and as NMR experiments. In each case an equilibrium mixture of **1a** and **1c** resulted, but we were never able to detect any other products. Clearly, in solution under the Weiss–Cook condensation conditions only **1a** and **1c** are present in detectable (NMR spectroscopy) concentrations. It is interesting to note that in the variable temperature (265–310 K) 75 MHz ¹³C spectra of **1c** recorded in CDCl₃ there was a small splitting of the methyl signals of the ester groups and a broadening of the carbonyl signals. There was no change in any of the remaining ¹³C signals (except for the expected small variations of chemical shift) with temperature. The splitting and broadening disappeared in the spectra recorded at 320 K in

CDCl₃ and at 297 K in CD₃OD (which presumably disrupts the intramolecular hydrogen bonding between the esters and enols). These observations clearly correspond with restricted rotations of the ester groups, and not the presence of other epimers. If other epimers were present, then additional signals would be expected in the rest of the spectrum (note, the ¹³C spectra of **1a** and **1c** are significantly different, and similar differences would be anticipated between the other epimers). Our AM1 calculations on each epimer of **1** revealed numerous local minima, of very similar energy, for different conformations of the esters.



Although two isomers (**1a** and **1c**) were formed in the condensation of dimethyl 1,3-acetonedicarboxylate with pentane-2,3-dione, hydrolysis and decarboxylation of these tetraesters produced a single diketone **7** which has been elaborated to the unsymmetrically substituted semibullvalene **8**.¹⁰ Similarly, the mixture of **1a** and **1c** was used directly in the synthesis, by a modification of the Grohmann procedure,¹¹ of the semibullvalene **9** which was further elaborated to the bisanhydride **10**.¹ These approaches should be applicable to the preparation of a wide variety of unsymmetrically substituted semibullvalenes.^{1,10}

Experimental

Infrared spectra were recorded on a DigiLab Qualimatic or Model FTS 15180, ¹H and ¹³C NMR spectra on an IBM NR300 and mass spectra on a VG7070 at 70 eV (EI) or using methane chemical ionization (CI). Melting points were determined on a hot stage and are uncorrected. Microanalyses were performed by M-H-W Laboratories. *J* Values are given in Hz.

X-Ray structure determinations

The X-ray diffraction data for **1a** was collected at -100 °C on a Siemens three-circle diffractometer (χ -axis is fixed at 54.74°) equipped with a CCD detector maintained at -54.4(2) °C, using the ω -scan technique.¹² The initial cell constants were determined from reflection data obtained by collecting 60 ten-second frames at the detector resolution of 512 × 512 pixels. However, the final unit-cell values are based on the least square refinement of all the observed reflections. A complete hemisphere of data was scanned on omega (0.3°) with a run time of ten-second frames for a total of 1271 frames collected in three

Table 1 X-Ray crystallographic parameters for **1a** and **1c**

	Compound 1a	Compound 1c
Crystal data		
Empirical formula	C ₁₉ H ₂₄ O ₁₀	C ₁₉ H ₂₄ O ₁₀
Formula weight	412.38	412.38
Colour	Colourless	Colourless
Crystal size (mm)	0.40 × 0.25 × 0.15	0.25 × 0.20 × 0.10
Crystal system	Triclinic	Monoclinic
Space group	<i>P</i> $\bar{1}$	<i>P</i> 2 ₁ / <i>c</i>
Unit cell dimensions: <i>a</i> /Å	10.843(2)	7.788(1)
<i>b</i> /Å	10.984(2)	20.215(2)
<i>c</i> /Å	17.826(4)	13.108(1)
α /°	89.84(3)	
β /°	77.67(3)	102.52
γ /°	74.56(3)	
Volume/Å ³	1995.8(7)	2014.6(4)
<i>Z</i>	4	4
<i>D</i> _c /g cm ⁻³	1.372	1.360
<i>F</i> (000)	872	872
Absorption coefficient/mm ⁻¹	0.112	0.946
Data collection		
Radiation employed, λ /Å	Mo-K α (0.710 73)	Cu-K α (1.541 84)
θ _{max} /°	26.96	54.99
Index ranges	-13 ≤ <i>h</i> ≤ 9 -13 ≤ <i>k</i> ≤ 13 -19 ≤ <i>l</i> ≤ 21	-1 ≤ <i>h</i> ≤ 8 -1 ≤ <i>k</i> ≤ 21 -13 ≤ <i>l</i> ≤ 13
No. of data collected	10 500	3413
No. of unique data	7236 (<i>R</i> _{int} = 0.0222)	2528 (<i>R</i> _{int} = 0.0165)
Data with <i>I</i> > 2σ(<i>I</i>)	6473	2204
<i>T</i> _{max/min}	0.9539/0.9156	0.9969/0.9842
Solution and refinement		
Parameters refined	701	347
<i>R</i> , <i>wR</i> (2σ data)	0.0488 (0.1041)	0.0346 (0.0868)
<i>R</i> , <i>wR</i> (all data)	0.0566 (0.1102)	0.0405 (0.0919)
Goodness-of-fit (GOF)	1.114	1.059
Largest difference peak (e Å ⁻³)	0.360	0.209
Largest difference hole (e Å ⁻¹)	0.227	-0.155
Extinction coefficient	0.0051(6)	0.0036(3)

sets plus a final set of 50 frames using the SMART software.¹³ The crystal decay was monitored from reflection data from 50 frames collected at the beginning and at the end of data collection. The data reduction was accomplished by processing the frames data using SAINT¹⁴ software to give the raw file corrected for Lorentz/polarization (Lp)/decay. Since the raw file contains information about directional cosines, it was used for empirical absorption correction. For **1c**, the diffraction data were collected at 293(2) K on a Siemens R3m/V diffractometer (upgraded to a P4 model) using Cu-K α radiation (λ = 1.541 84 Å). The cell constants were determined from 20 computer centred reflections with 12.4 ≤ 2 θ ≤ 42°. A complete hemisphere of data was collected by ω -scans,¹² with online profile fitting and variable scan speeds using the XSCANS program.¹⁵ Three standard reflections (1 2 -4, 2 1 1 and 3 0 10), monitored every 97 reflections during data collection, showed no crystal decomposition. Data were corrected for Lp effects and for absorption (empirical ψ -scans). The structures were solved by direct methods using SHELXS-90¹⁶ and refined by full-matrix least-squares method using SHELXTL version 5.03.^{17,18} The final data collection and refinement parameters are listed in Table 1. In the case of **1a**, the unit cell contains two crystallographically independent molecules. One of these molecules showed a disorder in the methyl and ethyl groups at the bridgehead carbon atoms C1 and C2. This disorder is modelled by refining the occupancy of the CH₃ component in the ethyl group at 48% (C38) and 52% (C38A). Hydrogen atoms were located from difference Fourier syntheses and refined with

isotropic temperature factors except for those fixed on C29, C38 and C38A (**1a**) and C14 (**1c**) using the Riding model.†

Weiss–Cook condensation of dimethyl 1,3-acetonedicarboxylate with pentane-2,3-dione

Modified from the *Organic Synthesis* general procedure for the Weiss–Cook condensation.² A magnetically stirred mixture of pentane-2,3-dione (20 g, 0.2 mol), dimethyl 1,3-acetonedicarboxylate (70 g, 0.4 mol) and sodium hydrogen carbonate (2.5 g, 0.03 mol) in water (410 cm³)–methanol (150 cm³) was kept at ambient temperature for 24 h. (In later runs the reaction mixture was seeded with a few crystals of the pure epimer **1a** four times during the first hour. This resulted in a more tractable precipitate, but otherwise gave identical results.) The resulting precipitate was filtered off to give an essentially pure mixture of the epimers **1a** and **1c** (70.8 g, 86%) which was used directly in our subsequent reactions.¹ Pure epimers were obtained by fractional crystallization. The above mixture of epimers (25 g) was recrystallized twice from ethyl acetate–hexane, allowing full crystallization (including cooling to 0 °C) before filtration. The resulting solid (6 g) was recrystallized twice from methanol to give pure **1a** (1.8 g).

Tetramethyl 1-ethyl-3,7-dihydroxy-5-methyl-cis-bicyclo[3.3.0]octa-2,6-diene-2,4-exo,6,8-exo-tetracarboxylate 1a. White prisms, mp 118–120 °C; ν_{\max} (KBr)/cm⁻¹ 3500–2800, 3040, 2982, 2956, 1741, 1664, 1630, 1440, 1342, 1233, 1198; δ_{H} (300 MHz; CDCl₃) 10.98 (1 H, s), 10.59 (1 H, s), 4.06 (1 H, s), 3.88 (1 H, s), 3.83 (3 H, s), 3.82 (3 H, s), 3.71 (6 H, s), 1.8 (1 H, dq, *J* 14.3 and 7.6), 1.5 (1 H, dq, *J* 14.3 and 7.0), 1.31 (3 H, s), 0.8 (3 H, observed as t but actually dd, *J* 7.6 and 7.0); δ_{C} (75 MHz; CDCl₃) 171.70, 170.81, 170.65, 170.25, 170.01, 169.35, 110.03, 106.66, 58.58, 58.31, 58.08, 54.91, 52.25, 52.11, 52.08, 51.63, 24.94, 18.04, 10.57; *m/z* (CI) 413 (4.3%), 409 (2.8), 381 (43), 349 (100), 317 (100), 285 (47), 207 (45.4), 175 (19.3); (EI) 380 (13.7%), 348 (14.0), 320 (14.8), 316 (9.7), 287 (15.5), 284 (7.6), 279 (38.9), 257 (20.1), 247 (14.6), 229 (24.3), 219 (32.2), 200 (39.8), 115 (42.5), 91 (75.7), 67 (100) (Found: C, 55.59; H, 5.56. Calc. for C₁₉H₂₄O₁₀: C, 55.34; H, 5.87%).

The mixture of epimers (25 g) was recrystallized twice from ethyl acetate–hexane, only allowing partial crystallization before filtration each time to yield pure **1c** (2 g).

Tetramethyl 1-ethyl-3,7-dihydroxy-5-methyl-cis-bicyclo[3.3.0]octa-2,6-diene-2,4-endo,6,8-exo-tetracarboxylate 1c. White prisms, mp 139–141 °C; ν_{\max} (KBr)/cm⁻¹ 3500–3300, 2983, 2951, 1743, 1666, 1624, 1444, 1350, 1295, 1242, 1209; δ_{H} (300 MHz; CDCl₃) 10.8 (2 H, s), 3.98 (1 H, s), 3.83 (3 H, s), 3.72 (6 H, s), 3.67 (3 H, s), 3.57 (1 H, s), 1.85 (1 H, dq, *J* 14.3 and 7.6), 1.60 (1 H, dq, *J* 14.3 and 7.1), 1.58 (3 H, s), 0.75 (3 H, observed as t but actually dd, *J* 7.6 and 7.1); δ_{C} (75 MHz; CDCl₃ at 320 K) 171.40, 170.46, 170.33, 169.73, 169.44, 169.36, 106.99, 105.39, 60.56,

58.76, 57.18, 57.04, 52.06, 51.78, 51.60, 51.24, 23.53, 21.61, 10.05; *m/z* (CI) 409 (2.9%), 381 (21), 349 (49.7), 317 (100), 285 (25.4), 207 (17.7), 175 (12.9); (EI) 380 (11.8%), 348 (52.6), 320 (100), 316 (26.6), 287 (41.3), 284 (14.8), 279 (92.8), 175 (75.6), 115 (60.5), 91 (65.3), 67 (40.6) (Found: C, 55.26; H, 5.63. Calc. for C₁₉H₂₄O₁₀: C, 55.34; H, 5.87%).

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† Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1997, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/90.

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