Reaction of Dimethyl 3-Ketoglutarate with 1,2-Dicarbonyl Compounds. 8.[1] Selective Base-Catalyzed Decarbomethoxylation of Tetramethyl 3,7-Dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate. Preparation of 2,6-Dicarbomethoxy-*cis*-bicyclo[3.3.0]octane-3,7-dione

Surendra P. Bhatnagar and Ulrich Weiss*

Laboratory of Chemical Physics, National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20014

R. J. Highet

Laboratory of Chemistry, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20014

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Tetramethyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (**1**), very easily available from dimethyl 3-ketoglutarate and glyoxal, readily loses two of its carbomethoxyls on mild warming with 10 mol of NaOMe in Me_2SO/MeOH, giving exclusively the 2,6-diester **3** in >90% yield. The corresponding triester **2**, presumably an intermediate, can be isolated in low yield when a smaller excess of base is taken. Energetic treatment of **3** with NaOMe in Me_2SO/MeOH produces a very small amount of the monoester **4**. Acid-catalyzed hydrolysis and decarboxylation of **3** yield the known *cis*-bicyclo[3.3.0]octane-3,7-dione; the stereochemistry of the parent ring system has thus remained unchanged during the treatment with base. Diazomethane converts **1** and **3** into the enolic dimethyl ethers, **8** and **7**; **8** does not lose carbomethoxyl under the conditions where its parent **1** does so readily.

The removal of carbomethoxy groups from β-keto esters is a reaction which has been given considerable attention in recent years;[2] its utility in synthetic work is obvious. In the papers quoted,[2] this reaction was generally applied to monoesters, yielding the parent ketone. We now wish to describe a reaction where some, but not all, of the carbomethoxy groups were cleaved off specifically from tetramethyl 3,7-dioxo-*cis*-bicyclo[3.3.0]octane-2,4,6,8-tetracarboxylate (**1**). This compound is prepared extremely readily from dimethyl β-ketoglutarate and glyoxal at room temperature in aqueous medium at slightly acidic[3a] or alkaline[3b] reaction.

We have observed that **1**, on being warmed with excess sodium methoxide in Me_2SO containing 10 mol % methanol,[4] can be made to lose one, two, or three of its carbomethoxyls, producing the tri-, di-, and monocarbomethoxy derivatives of *cis*-bicyclo[3.3.0]octane-3,7-dione (compounds **2**, **3**, and **4**, respectively). Of these reactions, the one yielding the dicarbomethoxy compound (shown below to be the 2,6 isomer **3**) is very strongly favored, so that this substance, a potentially useful synthetic intermediate, becomes very readily accessible. In contrast, the tricarbomethoxy derivative **2** was obtained only when a smaller excess of NaOMe was used, and even then the yields were very low; presumably, it is very rapidly converted further into **3**. Finally, the monocarbomethoxy compound **4** can be prepared from **3** by prolonged heating with NaOMe in Me_2SO–MeOH, but even under these drastic conditions only very minute amounts of the compound were produced, most of the **3** surviving unchanged.

Warming the β-keto ester **1**, prepared by the method of ref 3b, with 10 mol of NaOMe at 55 °C in Me_2SO–MeOH for 15 h yielded better than 90% of dimethyl 2,7-dioxobicyclo[3.3.0]-octanedicarboxylate,[5] mp 110 °C (from ethanol), mol wt 254 (mass spectrometry). This ester could have structure **3**, **5**, or **6**. Of these, **5** is eliminated by the fact that the ^{13}C NMR spectrum does not contain any signal from an isolated cyclopentanone carbonyl, and by the very ready formation of the dienol ether **7**,[5] mp 178 °C (from chloroform–petroleum ether), on treatment with diazomethane in ether, i.e., under conditions where the carbonyl of a β-keto ester, but not that of a simple ketone, would be expected to react. Under the same conditions **1**, shown[6] by NMR spectrometry to be present virtually completely as the enol **1a**, readily gave the dimethyl ether **8**, mp 135 °C (from chloroform–petroleum ether).

Of the two remaining structures, **3** was shown to be the correct one by the ^1H and ^{13}C NMR spectra of the compound itself and its ether **7**. In particular, the single-frequency off-resonance decoupled ^{13}C NMR spectrum of **7** showed only *one* doublet for the bridgehead carbons 1 and 5; in the ether derived from **6**, the marked structural differences in the environment of these carbons (one of them being bisallylic) would undoubtedly give rise to very different signals.

Treatment of **1** under otherwise identical conditions with only 3 mol of NaOMe produced small amounts of **3** and of the tricarbomethoxy compound **2**,[5] mp 78 °C (from ethanol). Ester **4**[7] was obtained in minute (1%) yield upon treatment of **3** in the same mixed solvent with 10 mol of NaOMe at 70–80 °C for 36 h, mp 84 °C (from ethanol).

The identification of **2** and **4** rests upon their formation from **1** and **3**, respectively, their mass-spectrometric molecular weights, and their spectroscopic characteristics. Since **1** is known[8] to be derived from *cis*-bicyclo[3.3.0]octane, compounds **2**, **3**, and **4** should likewise belong to the cis series. The inherently improbable possibility of inversion at one of the two backbone carbons during the base-catalyzed decarbomethoxylations was eliminated by acid-catalyzed hydrolysis and decarboxylation[3a] of **3**, which gave *cis*-bicyclo[3.3.0]octane-3,7-dione (**9**) identical with authentic material.

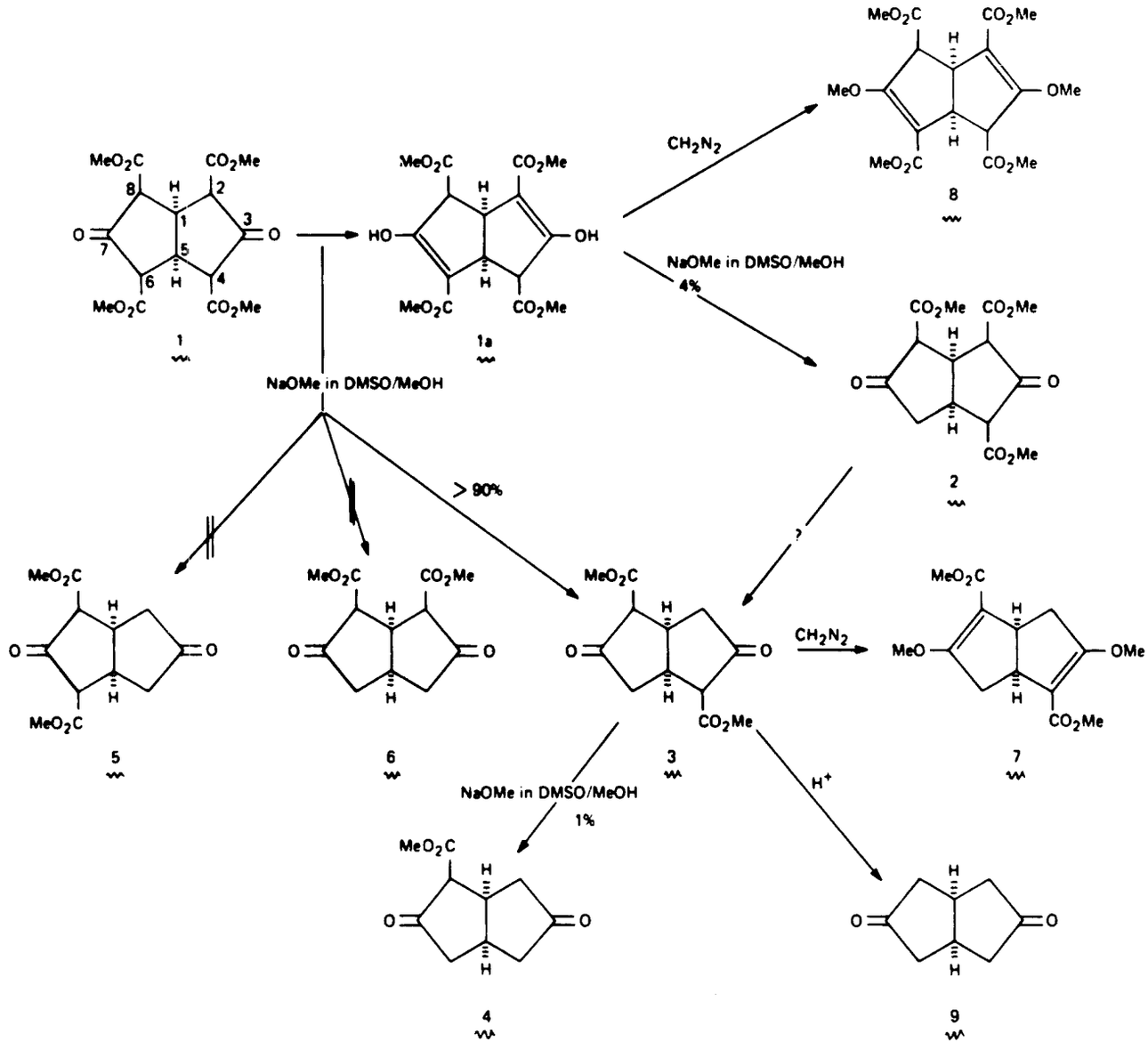
The removal of one, two, or three carbomethoxy groups to give **2**, **3**, and **4** proceeds undoubtedly through loss of dimethyl carbonate in a reversal of the well-known base-catalyzed carbomethoxylation[9] of $-CO-CH_2-$ by this reagent. Cases of reversal of this reaction have been observed.[10] The failure of the enol ether **8** to undergo analogous decarbomethoxylation supports this view.

Evidently, the removal of CO_2Me occurs very readily as long as the number of carbomethoxy groups exceeds that of ketonic carbonyls; as soon as a 1:1 relationship is reached in **3**, further removal becomes much more difficult. These facts, and the formation of **3** to the exclusion of its isomers **5** and **6**, can be explained by the mechanism shown in Scheme II.

Experimental Section

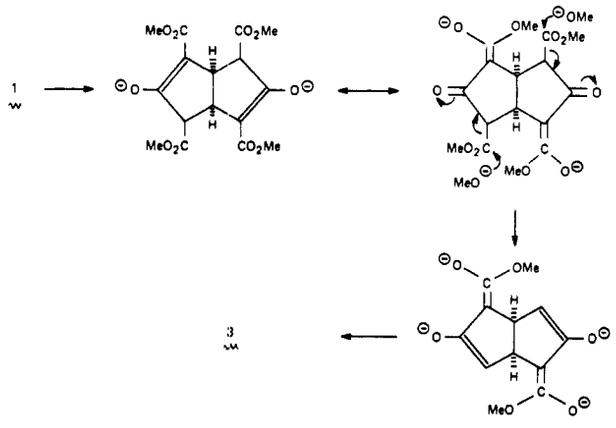
General Methods. Infrared spectra were obtained using a Perkin-Elmer Model 257 grating spectrophotometer. Nuclear magnetic resonance spectra were recorded on either a Varian HR-220 or a Varian A-60 instrument. Mass spectra were obtained on Finnigan

Scheme I



1015D GC/MS or Hitachi Perkin-Elmer RMU-GE mass spectrometers. The ^{13}C NMR spectra were obtained at 15.04 MHz using the JEOL FX-60. Typically, accumulation of 1000 free-induction decays from 300 pulses provided a spectrum from a ~0.3 M solution. Data were accumulated for 1 s with a pulse-repetition rate of 1.2 s; an 8K Fourier transform provided resolution of approximately 1 Hz. Thin-layer chromatography (TLC) was carried out using 250-μm layers of silica gel GF obtained from Analtech, Inc., Newark, Del.; for preparative TLC, 20 × 20 cm glass plates coated with 1000-μm layers of silica gel GF (obtained from Analtech) were used with hexane/acetone (7:3) containing 1% formic acid as solvent system.

Scheme II



Decarbomethoxylation of β-Keto Ester 1. (A) To Dimethyl 3,7-Dioxobicyclo[3.3.0]octane 2,6-dicarboxylate of mixture A (**3**). β-keto ester 1[3b] (3.7 g, 10 mmol) and sodium methoxide (5.4 g, 100 mmol) in 150 mL of Me_2SO containing 10 mol % methanol was stirred at 55 °C in an oil bath for 15 h. The ether extract of the acidified (10% aqueous HCl) reaction mixture was washed with brine solution, dried over anhydrous sodium sulfate, and evaporated in vacuo. The residue (2.45 g), which was mainly ester **3** by TLC, was recrystallized from ethanol: fine needles; mp 110 °C; yield 2.3 g (90%); ν ($CHCl_3$) 1755, 1730, 1660, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.90 (6 H), 3.50 (2 H), 2.5–2.9 (4 H), 10.5 (2 H); ^{13}C NMR ($CDCl_3$) 38.5 (C-4, 8), 38.9 (C-1, 5), 51.2 (CO_2CH_3), 103.0 (C-2, 6), 165.6, 169.7 (C-3, 7 and CO_2CH_3); M^+ *m/e* 254. Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.41; H, 5.50.

(B) To Trimethyl 3,7-Dioxobicyclo[3.3.0]octane-2,4,6-tricarboxylate **2**. A mixture of β-keto ester **1** (1.5 g, 4.05 mmol) and sodium methoxide (0.656 g, 12.15 mmol) in 60 mL of Me_2SO containing 10 mol % of methanol was stirred at 55 °C for 15 h. The reaction mixture was worked up as in expt A. The residue showed three spots on TLC (r_f 0.181, 0.280, 0.360). The three compounds were separated by preparative TLC. The major component was identified as unreacted starting material, the other two were characterized as ester **3** and **2**. Ester **2** was crystallized from ethanol: yield ~4% (0.05 g); mp 78 °C; ν ($CHCl_3$) 1755, 1670, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.81 (9 H), 3.6–3.7 (3 H), 2.5–2.9 (2 H), 10.4 (2 H); M^+ *m/e* 312. Anal. Calcd for $C_{14}H_{16}O_8$: C, 53.84; H, 5.16; Found: C, 53.57, H, 5.11.

Enol Ether 7 of 3. Ester **3** (0.5 g, 1.96 mmol) was added to an ice-

cold ethereal solution containing diazomethane (0.250 g, 5.9 mmol), and was left overnight in the refrigerator. On evaporation of solvent the enol ether **7** was obtained in almost quantitative yield: mp 178 °C (from chloroform/petroleum ether); ν ($CHCl_3$) 1675, 1640, 1275–1200, 1075–1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.84 (s, 6 H), 3.75 (s, 6 H), 3.5 (2 H), 2.6–2.9 (4 H); ^{13}C NMR ($CDCl_3$) 37.9 (t, single-frequency off-resonance decoupling, C-4, 8), 39.8 (d, C-1, 5), 50.8 (q, CO_2CH_3), 57.7 (q, CH_3O-C-3.7), 106.1 (s, C-2, 6), 165.6 (s), 169.7 (s), (C-3, 7 and CO_2CH_3).

Partial Decarbomethoxylation of β-Keto Ester 3 to the Monoester 4. A mixture of β-keto ester **3** (1 g, 3.9 mmol) and sodium methoxide (2.12 g, 39 mmol) in 60 mL of Me_2SO containing 10 mol % methanol was stirred at 70–80 °C for 36 h. The reaction mixture was worked up as before; the residue showed two spots on TLC; both components were isolated by preparative TLC. The major compound was found to be unreacted starting material. The other component, isolated in about 1% yield (0.007 g), mp 84 °C (from ethanol), was identified as ester **4**: ν ($CHCl_3$) 1755, 1730, 1660, 1630 cm^{-1}; ^1H NMR ($CDCl_4$) δ 3.8 (3 H), 3.5 (2 H), 2.09–3.01 (6 H); M^+ *m/e* 196.

Decarbomethoxylation of Ester 3 to the Diketone 9. The ester **3** (0.5 g, 1.96 mmol) was refluxed with 6 N HCl (10 mL) for 3.5 h. The reaction mixture was cooled, and ice-cold water was added. Extraction with methylene chloride, washing with brine solution, drying (Na_2SO_4), and evaporation gave a residue which was crystallized from methanol, mp 84–85 °C. The compound was found identical with the authentic sample of **9** by mixture melting point, co-TLC, superimposable infrared, NMR, and mass spectra.

Enol Ether 8 of β-Keto Ester 1. Ester **1** (0.5 g, 1.35 mmol) was added to an ice-cold ethereal solution containing diazomethane (0.250 g, 5.9 mmol); the solution was left overnight in the refrigerator. On usual workup the enol ether **8** was obtained; it was crystallized from chloroform/petroleum ether in 90% yield (0.48 g): mp 135 °C; ν ($CHCl_3$) 1740, 1685, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (6 H), 3.57 (6 H), 3.50 (6 H), 3.90 (2 H), 3.60 (2 H); ^{13}C NMR 49.0 (d, C-1, 5), 51.4 (q, C-2, 6 CO_2CH_3), 52.8 (q, C-4, 8, CO_2CH_3), 58.9 (d, C-4, 8), 59.0 (q, C-3, 7 OCH_3), 108.5 (s, C-2, 6), 164.5, 165.5 (s, C-3, 7/C-2, 6 CO_2CH_3), 171.9 (s, C-4, 8 CO_2CH_3); M^+ *m/e* 398. Anal. Calcd for $C_{18}H_{22}O_{10}$: C, 54.27; H, 5.57. Found: C, 54.46; H, 5.53.

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Registry No.—**1**, 58648-36-5; **2**, 62708-46-7; **3**, 62708-47-8; **4**, 62708-48-9; **7**, 62708-49-0; **8**, 62708-50-3; **9**, 51716-63-3; dimethyl β-ketoglutarate, 1830-54-2; glyoxal, 107-22-2.

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Pentacyclic Steroids. Synthesis of 4,6β-Ethanoestradiol, 4,6β-Ethanoestrone, and 17α-Ethynyl-4,6β-ethanoestradiol

Anil C. Ghosh* and Braja G. Hazra

SISA Incorporated and Sheehan Institute for Research, Inc., Cambridge, Massachusetts 02138

William L. Duax

Medical Foundation of Buffalo, Buffalo, New York 14203

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Synthesis of a new series of pentacyclic steroids, 4,6β-ethanoestradiol (**1**), 4,6β-ethanoestrone (**2**), and 17α-ethynyl-4,6β-ethanoestradiol (**3**), is described. Estrone is converted into the key intermediate 17β-acetoxy-3-methoxy-1,3,5(10)-estratriene-6β-acetic acid (**13**) in 11 steps. Friedel–Crafts cyclization of the acid chloride of **13** with aluminum chloride provides compounds **14** and **15**. Further structural modifications lead to **1**, **2**, and **3**. The absolute configuration of the *p*-bromobenzoate derivative of **1** has been confirmed by x-ray crystallography. Fusion of the ethano bridge at positions C-4 and C-6 from the β face leads to a unique class of steroids in which the B ring assumes a highly distorted conformation.

Substitution of the steroidal skeleton at C-6 has led to a number of important oral contraceptives.[1,2] Examples include dimethisterone, Provera (17α-acetoxy-6α-methylpregn-4-ene-3,20-dione), and megesterol acetate. Activity of such compounds has been explained on the assumption that the presence of alkyl substitution at C-6 prevents metabolic hydroxylation at this position. The syntheses of steroidal compounds with an ethano bridge across C-4 and C-6 are of special interest, since significant changes in the stereochemistry of steroidal skeleton can be effected with such substitutions. Studies with Dreiding models show that fusion of an ethano bridge at positions C-4 and C-6, from the β face, in the estrone molecule leads to a unique class of steroids in which the B ring assumes a highly distorted conformation. Little is known in the literature[3] about the formation and biological activities of steroids containing such a distorted B ring. We report here the synthesis of three such compounds, 4,6β-ethanoestradiol (**1**), 4,6β-ethanoestrone (**2**), and 17α-ethynyl-4,6β-ethanoestradiol (**3**). Further modifications could lead to a new class of steroids, whose biological profile remains to be examined.

The starting material was estrone (**4**), which was converted into **5** in three steps (Scheme I).[4] Hydrolysis, methylation, and acetylation[5] led to compound **6**. Reformatsky reaction upon **6** provided **7**, which on dehydration with formic acid gave a mixture of the esters **8** and **10**. Hydrolysis of this product with potassium hydroxide led to the unsaturated acids **9** and **11**. NMR spectra of the esters **8** and **10** (δ 5.98, endo olefinic H,