Tetrahedron Letters No. 44, pp 3763 - 3766, 1975. Pergamon Press. Printed in Great Britain.

THE REACTION OF DIMETHYL β-KETOGLUTARATE WITH 1,2-DICARBONYL COMPOUNDS. III[1]. *EXO*-TETRACYCLO[5.5.1.$0^{2,6}$.$0^{10,13}$]TRIDECANE-4,8,12-TRIONE

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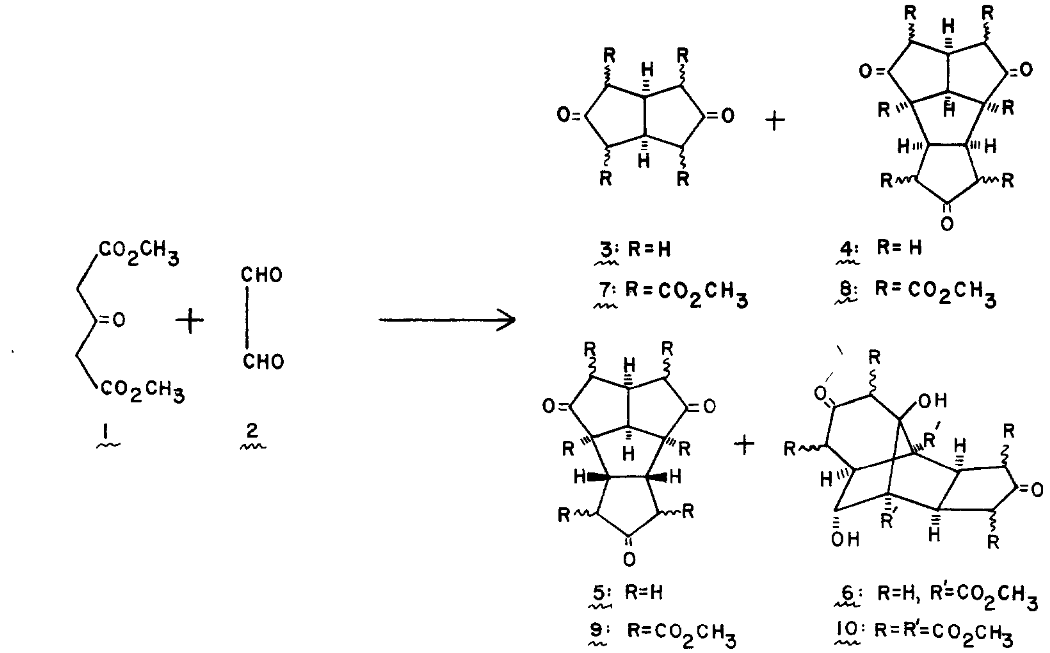
(Received in USA 24 April 1975; received in UK for publication 23 September 1975)

We have reported earlier[2,3] that reaction of dimethyl β-ketoglutarate (**1**) with glyoxal (**2**) in slightly acidic aqueous solution at room-temperature yields a precipitate of cyclic β-keto esters. Acid-catalyzed hydrolysis and decarboxylation of these intermediates gave bicyclo-[3.3.0]octane-3,7-dione (**3**)[2] and *endo*-tetracyclo[5.5.1.$0^{2,6}$.$0^{10,13}$]tridecane-4,8,12-trione (**4**)[3].

Further study has now shown that more clear-cut results are obtained if the pH is kept constant throughout the reaction of **1** and **2** by working in citrate-phosphate buffers of pH 3-7. Through this modification, we have found two new products of this reaction: the *exo*-stereoisomer **5** of **4**, which is the subject of this communication, and another compound **6** described in Paper IV of this series[4,5].

On reaction of **1** and **2** at pH 3,4,5, or 6, a precipitate appeared after a few days which consisted of the esters **7**[2], **8**, **9**, and **10**[4], the precursors of **3**,**4**,**5**, and **6**, respectively. Of these, **7**[2] and **10**[4] have been obtained pure. Compounds **8** and **9** proved to have very similar solubilities and Rf values. They have not yet been separated completely; the product, m.p. 173-6°, described earlier[3] as **8** presumably contained both this compound and some of its then unsuspected stereoisomer **9**. The precipitate formed at pH 6.0 consisted largely of **10**[4]; **7**,**8**, and **9** can be obtained by acidification of the filtrate to pH 2. In contrast, no solid appeared at pH 7.0 during one week. However, acidification (HCl) to pH 2 yielded a copious precipitate consisting of **7**,**8**, and **9** and probably some additional minor constituents; none of the remarkably water-insoluble **10** was present. The total recovery of material, while still low, was much higher than that obtained at pH 3,4, or 5: 30 g of the ester mixture from 52 g (0.3 mole) of **1** and 29 g of a 40% aqueous solution of **2** (0.2 mole).

The crude β-keto esters (30 g) were refluxed with 6N HCl (100 ml) for 3.5 hours. Extraction with $CHCl_3$, washing of the organic layer with 10% aqueous K_2CO_3[6] and water, and evaporation, gave a mixture of ketones, from which the volatile **3** (3.5 g) was removed by distillation at 115-120°/0.2 mm, and **4** by crystallization from a small volume of ethanol; evaporation of the filtrate, addition of ethyl acetate, and seeding produced a second crop of **4** (combined yield, 0.7 g). Concentration of the mother-liquors, column chromatography (silica gel 80-325 mesh; 20% hexane in ethyl acetate), and crystallization from methanol yielded 355 mg pure **5**,$C_{13}H_{14}O_3$[7], m.p. 133-5°.



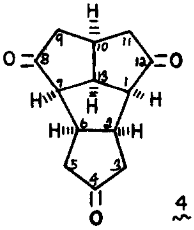
The IR spectrum of **5** was almost identical with that of **4**; all carbonyl groups present are thus contained in five-membered rings. This fact, and the great resemblance of the complex nmr spectra of the two compounds, strongly suggested that **5** might be the exo-stereoisomer of **4**. Correctness of this interpretation was established by comparison of the dipole moments and [^{13}C] nmr spectra.

Calculation of the theoretical dipole moments by CNDO/2 molecular orbital techniques[8,9] gave 5.85 D for **4** and 3.57 D for **5**. The experimental values were 6.80 and 4.39 D, respectively (determined in anhydrous dioxane at room temperature with a Sargent Model V Oscillometer). Agreement between these values is satisfactory within the limits of accuracy of calculation and measurement. In particular, the differences, $\delta(4-5)_{\text{calc'd}}$, 2.28 D, and $\delta(4-5)_{\text{observed}}$, 2.41 D, are very similar. The larger deviations of the observed absolute values from the calculated ones may be due to some systematic deviation in assigning atomic coordinates from Dreiding models.

Striking support for the proposed structure **5** was obtained from the ^{13}C nmr spectra of **4** and **5** (Table I). The spectra of both compounds show three peaks of one-carbon intensity (one carbonyl and two methine carbons) caused by atoms lying in the plane of symmetry of the molecule; both spectra also show five peaks of two-carbon intensity, corresponding to atoms rendered equivalent by the plane of symmetry: one carbonyl, two methylene carbons, and two methine carbons. The differences in the chemical shifts of corresponding atoms in **4** and **5** are trivial, except for those of carbons 3 + 5 and 1 + 7, where unexplained downfield shifts occur on going from **5** to the more crowded endo-isomer **4**.

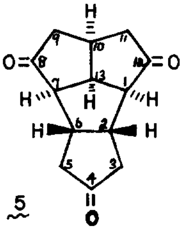
Table I

^{13}C nmr Spectral Data of 4 and 5



4

5



Types of Carbon Atom	Chemical Shift, δ 4	5	δ4 - δ5
A) Three carbonyls			
8 + 12	219.6	218.6	+ 1.0
4	216.4	216.5	- 0.1
B) Two pairs of -CH$_2$- next to carbonyl			
9 + 11	47.5	46.1	+ 1.4
3 + 5	39.4	43.3	- 3.9
C) Six →CH			
2 + 6	46.1	46.5	- 0.4
1 + 7	54.7	58.3	- 3.6
10	30.9	31.5	- 0.6
13	50.8	48.0	+ 2.8

The close agreement of the spectra of 4 and 5 shows beyond doubt that both compounds have the same overall structure.

It is noteworthy that the isolated yield of 5 obtained by us or other workers[5] is ~1/2 of that of 4. This is surprising, since 5 should be free of steric crowding, while X-ray crystallography has shown[3] significant distortion of the cyclopentanone ring of 4 (at least in the solid state), undoubtedly in order to avoid serious mutual crowding between the carbonyl oxygens at C-8 and C-12 and the protons at C-3 and C-5. This preference for the isomer which would appear sterically much less favorable is surprising and not readily explained.

Notes and References

1. We wish to consider our two earlier Communications[2,3] as parts I and II of this series.
2. U. Weiss and J. M. Edwards, *Tetrahedron Letters*, 4885 (1968).
3. J. M. Edwards, I. H. Qureshi, U. Weiss, T. Akiyama and J. V. Silverton, *J. Org. Chem.* *38*, 2919 (1973).
4. K. C. Rice, U. Weiss, R. J. Highet, T. Lee and J. V. Silverton, accompanying paper.
5. The reaction of **1** and **2** in buffers of pH 2.0 to 7.0 has been studied independently by S. H. Bertz in Prof. R. B. Woodward's laboratory (Harvard University), and by Dr. J. M. Cook at the University of Wisconsin, Milwaukee; their findings agree with ours in every significant aspect.
6. This extract contains a sizeable amount of an acidic fraction, which we have not investigated any further.
7. Satisfactory analytical and mass-spectrometric data were obtained for **5**.
8. J. A. Pople and M. Gordon, *J. Amer. Chem. Soc.* *89*, 4253 (1967).
9. J. A. Pople and G. A. Segal, *J. Chem. Phys.* *44*, 3289 (1966).