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REACTION OF DIMETHYL β-KETOGLUTARATE WITH 1,2-DICARBONYL COMPOUNDS. IV[1]. FORMATION OF A COMPLEX TETRACYCLIC RING-SYSTEM IN AQUEOUS SOLUTION AT ROOM-TEMPERATURE.

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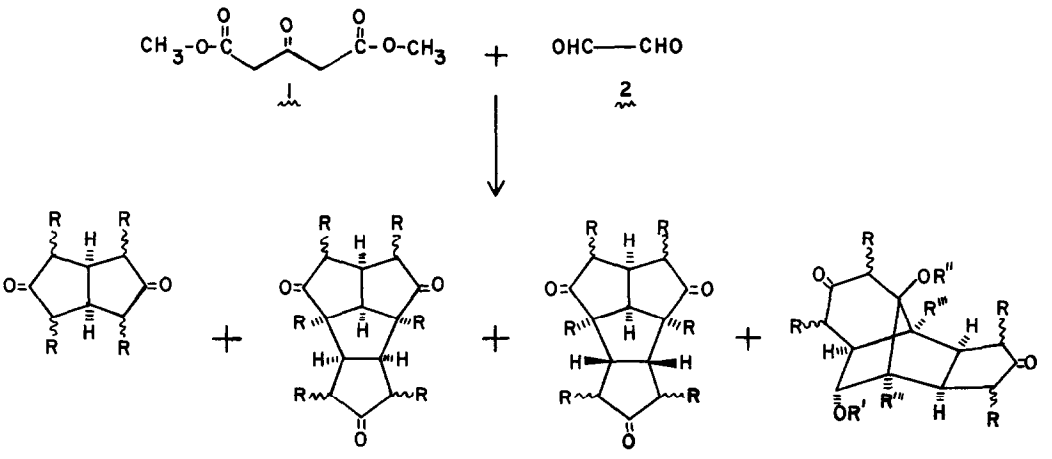
In the preceding communications, we have reported that reaction of dimethyl β-ketoglutarate (1) with glyoxal (2) at room temperature in aqueous solution buffered to pH 3, 4, 5, 6, or 7 gives the cyclic β-keto esters 3[3], 4[4,5], and 5[1,4] which, on acid-catalyzed hydrolysis and decarboxylation, yield the ketones 6[3], 7[3,5], and 8[1]. We now wish to describe the formation and structure of an additional compound 9, which is produced at pH 3-6, and its conversion into 10 by acid. In contrast to the symmetrical overall structures[6] of 3 - 8, compounds 9 and 10 represent a highly complex, non-symmetrical ring-system. The yield of 9 is optimal (~50%) at pH 6.0; only small amounts are obtained at pH 3, or 6.5[7], none at all at pH 7.0[1,7].

Stirring of 1 (281.7g, 1.62 mol) with 2 (117.4g of 40% aqueous solution, 0.81 mol)[8] in buffer of pH 6.0 (140g citric acid·H_2O and 324g anhydrous Na_2HPO_4 in 17.1 ℓ H_2O) for 5 days at room temperature gave a precipitate (107.5g) consisting mainly of 9. Leaching with MeOH removed small amounts of 3, 4, and 5, leaving the remarkably water- and methanol-insoluble 9 (105.3g, 44.5%), which was recrystallized from DMSO/MeOH. $C_{25}H_{28}O_{16}$[9], m.p. 218-20°. IR: 3520, 3450 cm^{-1} (OH); complex carbonyl region. The very complicated NMR spectrum showed signals from six COOMe groups. The formulation of the compound as 9 rests upon that of 10 obtained from it by acid-catalyzed partial hydrolysis[10]; the stereochemistry of the four carbomethoxy groups lost during this reaction remains unknown.

Refluxing 9 (8.08g) with a mixture of sulfuric acid (1.5 ml), water (10 ml) and acetic acid[11] (40 ml) for 3 hrs. gave 10 and its mono-acetate 11 in yields of 43 and 14%, respectively. Treatment of 10 under these conditions gave almost the same equilibrium mixture of 10 and 11. Compound 10,[9] m.p. 179-80° (isopropanol); UV, λ_{max}^{EtOH} 210 nm (ε 242) and 287 nm (ε 90); IR: 3400 cm^{-1} (OH); complex carbonyl region; the NMR spectrum showed 2 OMe singlets (δ 3.88, 3.87) and 2 D_2O-exchange-

able protons (δ 3.13 and 3.47), but was otherwise too complex for interpretation, suggesting a highly non-symmetrical and complicated molecule. The structure and relative stereochemistry of this compound were therefore established by X-ray crystallography[12], which proved it to have the constitution 10. Formation of a ring-system of such complexity in one step under such mild, "physiological" conditions seems unprecedented.



3: R=CO_2CH_3
6: R=H

4: R=CO_2CH_3
7: R=H

5: R=CO_2CH_3
8: R=H

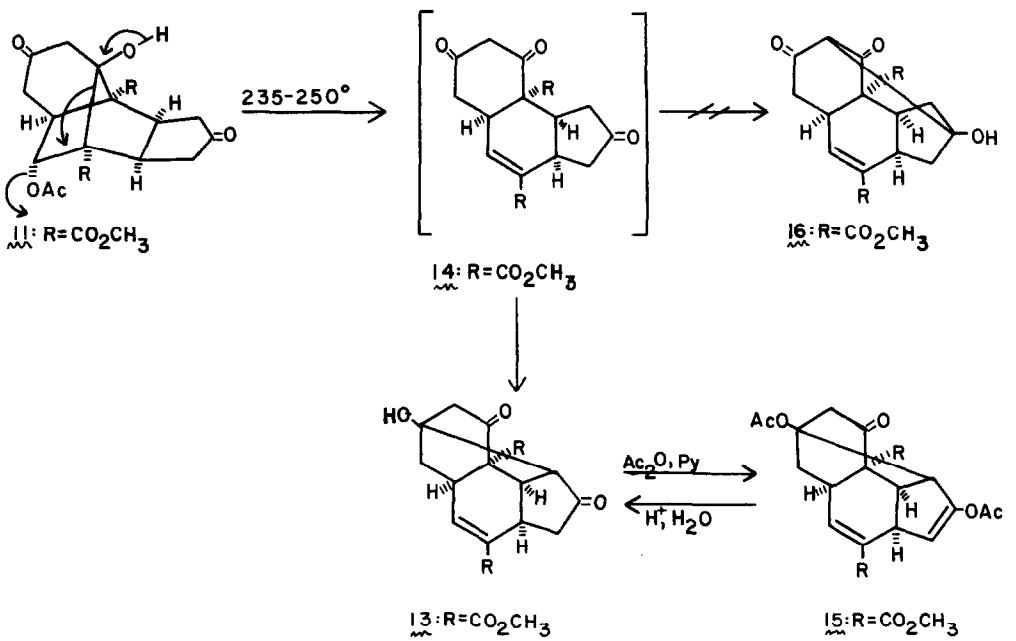
9: R=R‴=CO_2CH_3, R′=R″=H
10: R=R′=R″=H, R‴=CO_2CH_3
11: R=R″=H, R′=Ac, R‴=CO_2CH_3
12: R=H, R′=R″=Ac, R‴=CO_2CH_3

Acetylation of 10 (Ac_2O/py, 25°) gave the mono-acetate 11[9], m.p. 210–12° (isopropanol), together with a small amount of the di-acetate 12[9], m.p. 126–28° (isopropanol). The structure of 11 was proved by X-ray crystallography[12].

In the mass spectrum of 11, the base-peak occurs at m/e = 334 (M^+ – AcOH). This ready loss of AcOH also takes place on pyrolysis (235–250°, 150 mm), which gave a 57% yield of 13, $C_{17}H_{18}O_7$[8], m.p. 222–224° (acetonitrile). UV: λ_{max}^{EtOH} 222 nm (ε 2280); IR: ν 3490 cm^{-1} (OH); 1750, 1730, 1720, 1710 cm^{-1} (C=O); 1650 cm^{-1} (C=C); NMR: s, δ 4.05 (exchanges with D_2O), 7.34 (d, J = 7.8 Hz). Reduction of 13 with $NaBH_4$ gave syrupy material whose IR spectrum showed absorptions at 1710 and 1650 cm^{-1}. These findings strongly suggest the presence of an α,β-unsaturated carbomethoxy group in 13.

It appeared likely that the pyrolysis would proceed as shown below to give structure 14. However, the product obtained did not give the color reaction with $FeCl_3$ typical of 1,3-diketones, and it showed OH absorption in the IR. In addition, acetylation under forcing conditions (excess

Ac_2O, py, 115°) gave a mono-enolic diacetate 15[9], m.p. 181-3°; UV, λ_{max}^{EtOH} 213 nm, (ε = 4450); IR: 1770, 1745, 1720, 1705, and 1650 cm^{-1}; NMR ($CDCl_3$) δ 2.01, 2.13 (2 CH_3CO-); 3.70, 3.76 (2 CH_3O-); 5.88 (s, broad; CH=C(OAc); 7.32 (1 H, d, J = 7.0). On mild treatment with acid, 15 was reconverted to 13. Formation and functionality of 15 show that compound 13 cannot have the expected structure 14, but that it must be derived from this primary product by aldolization, for which ample precedent is available.[13] A priori, aldolization would be expected to involve the strongly activated methylene group between the two carbonyls of the 1,3-cyclohexandione system of 14; this reaction would have produced structure 16, which can be built from Dreiding models with hardly any strain. However, the product still contains a cyclopentanone grouping, as shown by the IR band at 1745 cm^{-1} and the fact that the ^{13}C NMR spectrum exhibits signals from two carbonyl carbons which are almost identical with those present in the spectrum of 11: (11, δ 217.2, 206.5; 13, δ 218.9, 205.3). Consequently, the aldolization must have produced the alternative structure 13, and indeed X-ray crystallographic analysis[12] of the mono-enolic diacetate 15 proved it to be derived from this structure.



Treatment of 13 with excess methanolic NaOMe isomerized it to a new compound of m.p. 210-12°, which was also produced from 11 under the same conditions. Compounds 11 and 13 may be reacting through the same intermediate (14). We hope to report separately on the structure and further transformations of this new compound.

Notes and References

1. K. C. Rice, N. E. Sharpless, U. Weiss, and R. J. Highet, preceding paper.
2. Present address: Faculty of Pharmaceutical Science, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan.
3. U. Weiss and J. M. Edwards, Tetrahedron Letters, 4885 (1968).
4. Compounds 4 and 5 have not yet been completely separated.[1]
5. J. M. Edwards, I. H. Qureshi, U. Weiss, T. Akiyama, and J. V. Silverton, J. Org. Chem. 38, 2919 (1973).
6. X-ray crystallographic analysis has shown[5] that the molecule of 7 in the solid state actually is not quite symmetrical, the terminal cyclopentanone ring being distorted, no doubt to relieve severe crowding. It seems probable that the shape is the same in solution, but no experimental evidence on this point is available.
7. Steven H. Bertz, Harvard University, private communication.
8. This ratio of reactants was found empirically to give the best yields of 9.
9. All new compounds gave satisfactory results on elementary analysis; they had the correct mass-spectrometric molecular weight and the expected spectroscopic characteristics.
10. We assume that no skeletal rearrangement takes place under the influence of the acid. This assumption seems justified, since the structures of both 9 and 10 can be dissected into three units originating from 1 and two units from 2; if 10 were formed from 9 through rearrangement, this feature would hardly survive.
11. Hydrolysis with dilute aqueous HCl[1,5] gave unsatisfactory results, presumably because of the insolubility of 9. The compound is readily decomposed by aqueous alkali with formation of 1.
12. T. Akiyama, T. Lee, and J. V. Silverton, to be published.
13. Cf., inter alia, P. E. Eaton and R. H. Mueller, J. Am. Chem. Soc. 94, 1014 (1972); T. A. Beisler, J. V. Silverton, A. Penttila, D. H. S. Horn, and H. M. Fales, J. Amer. Chem. Soc. 93, 4850 (1971).