[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF UTAH]

Seven-membered Ring Compounds. IV.[1] Benzosuberoneglyoxylates

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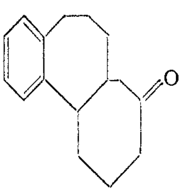
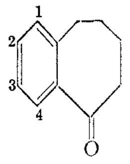
In the glyoxylation of benzosuberone, the enol lactone, IV, was unexpectedly obtained. Similarly, 8-methyl- and 2,3-dimethoxybenzosuberones gave lactones whereas 2,3,4-trimethoxybenzosuberone gave the expected product. IV was found to be readily opened by alcohols or amines. A mechanism for its formation is proposed which includes the fact that an adjacent methoxy group inhibits lactone formation. The reduction of IV and the pyrolysis of III support the proposed structures. The unexpected formation of the lactone is ascribed to the resonance stabilization due to the planarity possible in such seven-membered ring compounds.

In the course of work designed to obtain I starting with benzosuberone (II) we proposed as the initial step the preparation of the glyoxylate, III, using the conventional procedure.


I



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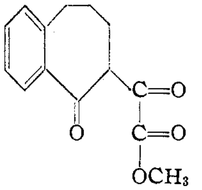
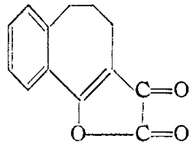


III



IV

The unusual behavior of benzosuberone with methyl oxalate, which is in sharp contrast to ring systems such as α-tetralone with methyl oxalate, is the subject of this report.

When benzosuberone and methyl oxalate were condensed according to the published procedure,[3] a clear colored benzene solution was obtained and the orange enol lactone, IV, of the glyoxylic acid was the isolated product.[4] Recrystallization of IV from methanol produced the yellow ester, III, originally expected as the direct product of glyoxylation. Initially we therefore missed the production of IV as the intermediate since methanol is a common solvent in glyoxylate recrystallization. Still further information on the course of this condensation was available after crystals of the glyoxylic acid became available. Acidification of the aqueous alkaline extract of the reaction mixture and cooling gave at once the crystalline glyoxylic acid.

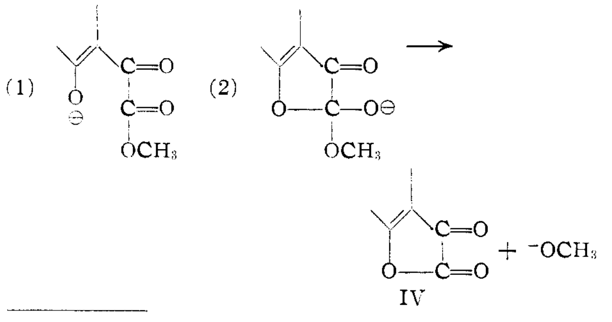
On thermal decarbonylation of the ester, III, poor yields of the β-keto ester expected were obtained until it was observed that the change, III to IV, takes place in the open air and is accelerated by heating *in vacuo*. It was then demonstrated that pure IV began to decompose at bath temperatures above 140° with gas evolution and tar formation. Therefore, decarbonylation of III was carried out by heating rapidly to 185° and the lactone, IV, formed was converted back to III by the addition of methanol. The pyrolysis was then resumed. This treatment, repeated four times in a single run gave an 80% yield of the β-keto ester.

The formulas, III and IV, were supported by the behavior with ferric chloride. The lactone, IV, in alcoholic ferric chloride, slowly developed a rusty-red color, the rate being determined by the rate of ethanolysis. The ester, III, gave the identical color instantly.

If, as is proposed, IV was produced directly in the oxalic ester–benzosuberone condensation, obviously any ester of oxalic acid might be used. This was confirmed using ethyl or butyl oxalate.

The reported glyoxylation of 2,3,4-trimethoxybenzosuberone[5] using ethyl oxalate encountered no enol lactone. We have confirmed this using methyl oxalate and have found that on pyrolysis the methyl glyoxylate was converted in high yield to the expected β-keto ester. We have found also that 2,3-dimethoxybenzosuberone, related but lacking a methoxyl group in position 4, formed an enol lactone analogous to benzosuberone. 8-Methylbenzosuberone similarly formed an enol lactone.

In order to account for the formation of IV in the glyoxylation of benzosuberone as contrasted to the usual product when 2,3,4-trimethoxy-II is used, the mechanism proposed[6] for acetoacetic ester condensations was extended. We propose that the resonance hybrid, 1, from III, reacts to form 2, similar to the addition of a carbanion to an ester.[6]



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[1] Paper III, THIS JOURNAL, **74**, 758 (1952).

[2] Atomic Energy Commission Pre-doctoral Fellow in the Physical Sciences, 1950–1952. A part of the doctoral research of H. W. Johnson.

[3] W. E. Bachmann, W. Cole and A. L. Wilds, THIS JOURNAL, **62**, 824 (1940).

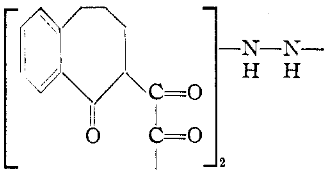
[4] The glyoxylate lactones that we have found reported all have strong enolic properties. The formula proposed, IV, does not permit enolization. *Cf.* ref. 7 and A. Kötz, K. Blendermann and J. Mayer, *Ber.*, **45**, 3702 (1912); A. Kötz and J. Meyer, *J. prakt. Chem.*, **88**, 261 (1913); A. E. Bradfield, E. R. Jones and J. L. Simonsen, *J. Chem. Soc.*, 315 (1935); L. Ruzicka and P. L. Plattner, *Helv. Chim. Acta*, **21**, 1717 (1938). Phenolic or naphtholic glyoxylic lactones are an exception. *Cf.* A. B. Neill and E. D. Amstutz, THIS JOURNAL, **73**, 3687 (1951).

[5] D. Caunt, W. D. Crow, R. D. Haworth and C. A. Vodoz, *J. Chem. Soc.*, 1631 (1950).

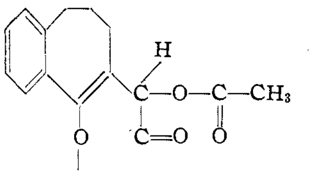
[6] C. R. Hauser and B. E. Hudson, Jr., "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 266.

The methoxyl anion then splits off and the analogous final step cannot take place since no enolizable proton is available. The non-ionic product, IV, is then found in solution in benzene, in contrast to the sodio compounds which usually separate. To account for the different behavior in the case of 2,3,4-trimethoxy-II, we propose that the proximity of the electrons of the methoxy group at position 4 on the benzenoid ring, inhibits the formation of the resonance hybrid 1, thus preventing the change, 1 to 2.

The lactone, IV, was easily opened[7] by aniline and by aqueous dimethylamine to give the anilide and the dimethylamide, respectively. Reaction with hydrazine gave V. Aqueous sodium bicarbonate on IV gave, on acidification, the glyoxylic acid which reverted to IV on gentle heating.



V



VI

Catalytic reduction of IV proceeded with ease and one mole of hydrogen was consumed. In the isolation of the product, air oxidation gave only IV. Reduction in acetic anhydride gave stable material, VI.

Atomic models of IV and the (unknown) enol lactone of 1-keto-1,2,3,4-tetrahydro-2-naphthylglyoxylic acid presented difficulties in closure of the lactone ring in both cases. The additional methylene group in the seven-membered ring decreased the difficulty in closure and permitted coplanarity of the benzenoid ring, the ethylenic bond and the lactone ring. This increase in resonance stability due to planarity might account for the fact that the six-membered ring lactone has not been found. Models suggest also that an eight-membered ring analog of IV is an intermediate case whereas coplanarity is not possible in a nine-membered ring analog of IV.

Assistance in the form of a Frederick Gardner Cottrell grant is gratefully acknowledged.

Experimental[8]

Enol Lactone of Benzosuberone-6-glyoxylic Acid (IV).—The published method[3] for the condensation of methyl oxalate and a cyclic ketone was used except that a nitrogen atmosphere was not required. If the benzene, methyl oxalate and sodium methylate was refluxed,[3] very poor yields were obtained. When the components were shaken until the solids dissolved, a light orange solution was obtained free of precipitate after standing overnight. It was poured into ice-water, the benzene layer was washed with cold 2% sodium hydroxide and the alkaline solution was acidified with hydrochloric acid. A light yellow oil separated and solidified when cooled at −20°. The yellow crystals became orange at *ca.* 105°, melted at 157–158° and a mixture with benzosuberone-6-glyoxylic acid gave the same melting point behavior.

In most runs, the oil which separated on acidification was dissolved in benzene and the benzene was distilled *in vacuo* from a water-bath. Long orange needles formed in the residue. The heating was continued for 1 hour and the wet crystals were filtered from oil. From 25 g. of benzosuberone, 26 g. (78%) of IV was obtained. Recrystallization from ethyl acetate gave brilliant orange prisms, m.p. 156.9–157.2°. These gave no immediate response with alcoholic ferric chloride but gradually gave a rusty-red color. They dissolved only very slowly in sodium carbonate solution.

Anal. Calcd. for $C_{13}H_{10}O_3$: C, 72.87; H, 4.71; mol. wt., 214. Found: C, 72.86; H, 4.71; mol. wt. (cryoscopic, benzil), 213.

Using ethyl oxalate and sodium ethylate instead of the methyl compounds and the identical procedure, IV was obtained in 39% yield. Butyl oxalate and sodium butylate gave IV in 38% yield.

The lactone, IV, 0.750 g., in dry reagent benzene changed from orange to yellow at once when 0.36 cc. of aniline was added forming the **anilide**. After the mixture had been shaken for 15 minutes and heated at 50° for 30 minutes, the solvent was removed leaving 0.420 g. of yellow crystals, m.p. 117–120°. A sample for analysis crystallized from benzene–petroleum ether (60–70°) in bundles of long thin prisms, m.p. 117–118°.

Anal. Calcd. for $C_{19}H_{17}O_3N$: C, 74.25; H, 5.59. Found: C, 74.58; H, 5.60.

When 0.500 g. of IV was dissolved in 3 cc. of 25% aqueous dimethylamine without cooling and allowed to stand for 1 hour, the yellow crystalline **dimethylamide** was obtained on acidification. The compound crystallized from benzene–petroleum ether (60–70°) in bright yellow rectangular prisms (0.460 g.), m.p. 130–140°. Further recrystallization from benzene–petroleum ether gave material, m.p. 139–140° (dec.).

Anal. Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61. Found: C, 69.56; H, 6.69.

The product, when ammonia was used, turned red on acidification and melted, after crystallization from cyclohexane and a small amount of benzene, at 148–153.5° (dec.) but could not be obtained analytically pure.

The bis-glyoxylhydrazide, V, was obtained from 1.0 g. of IV and 0.21 cc. of 95% hydrazine in benzene. Recrystallization from acetic acid gave colorless flat prisms, m.p. 283.5–287°, which produced a dark red color in alcoholic ferric chloride.

Anal. Calcd. for $C_{26}H_{24}O_6N_2$: C, 67.81; H, 5.25. Found: C, 67.72; H, 5.41.

Methyl Benzosuberone-6-glyoxylate (III).—When the above lactone (10 g.) was heated with 10 cc. of methanol to the boiling point on the steam-bath, the crystals dissolved after 10 minutes with a pronounced fading of the color. When cooled to −10° and scratched, 10.8 g. (93%) of light yellow crystals (III) was obtained. These melted after several crystallizations from methanol at 52.0–52.7° and gave immediately with alcoholic ferric chloride the identical shade obtained previously with IV.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.11; H, 5.69.

The ester was stable when stored in a closed container. Exposure to the air or drying in a vacuum gradually increased the color of the crystals suggesting formation of the lactone. Sublimation of III at 100° and 2 mm. gave orange crystals, m.p. 155–157°, not depressed by mixing with IV.

Ethyl benzosuberone-6-glyoxylate was obtained from IV (0.500 g.) by the method used for the methyl ester. The yellow oil, which gave an immediate wine-red ferric chloride test, could not be crystallized. It was dissolved in 3 cc. of anhydrous pyridine and 0.7 cc. of benzoyl chloride was added. Addition of aqueous sodium bicarbonate and extraction with ether gave the **benzoate derivative** as long needles which melted after recrystallization from ethanol at 84.5–85°.

Anal. Calcd. for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.21; H, 5.51.

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[7] In contrast to the glyoxylate lactones of W. E. Bachmann, G. I. Fujimoto and L. B. Wick, THIS JOURNAL, **72**, 1995 (1950).

[8] Melting points are uncorrected.

Benzosuberone-6-glyoxylic Acid.—The lactone, IV (0.500 g.), dissolved when warmed with 5% aqueous sodium bicarbonate for 1 hour. The filtered solution was extracted three times with 10-cc. portions of benzene and acidified with hydrochloric acid. The yellow crystals which were obtained were repeatedly dissolved in 5% sodium bicarbonate and carefully reprecipitated by hydrochloric acid to obtain an analytical sample. The product softened and became orange at 107° and melted at 157.5–158°.

Anal. Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.99; H, 5.47.

Warming the free acid with benzene on the water-bath sufficed to convert it to IV.

Reduction of IV with Hydrogen.—One-half gram of IV in 40 cc. of acetic anhydride with 50 mg. of platinum oxide was shaken under hydrogen at a pressure slightly above atmospheric. In 7 minutes, 71 cc. of hydrogen (theor., 68 cc.) was consumed and the solution was colorless. The solution, after standing under hydrogen for several days, was filtered and poured into 800 cc. of water, cooled by the addition of pieces of ice. After the addition of benzene, mixing and standing for 3 hours, the benzene layer was washed repeatedly with aqueous sodium bicarbonate and finally with water. Distillation of the benzene and addition of methanol to the residue gave 0.250 g. of slightly sticky crystals, VI, softening at 146°, m.p. 163–166° (dec.). A second crop (0.350 g.), purified by solution in benzene, concentration and addition of methanol, gave colorless groups of tiny crystals, m.p. (in at 135°) 168.5–170.5°. The ferric chloride test was negative.

Anal. Calcd. for $C_{15}H_{14}O_4$: C, 69.75; H, 5.46. Found: C, 69.90; H, 5.08.

With ethyl acetate as solvent, the above reduction gave a colorless solution which slowly became orange during the isolation. Only IV could be obtained.

Methyl Benzosuberone-6-carboxylate.—The pyrolysis of III with powdered glass[3] or with glass and powdered iron[9] was unsatisfactory. A claisen distilling flask containing 80 g. of III and 50 mg. of powdered boric acid[10] was placed in an oil-bath preheated to 185°. After 3 minutes, gas evolution subsided and the flask was removed and allowed to cool briefly. About 10 cc. of methanol was cautiously added and heating at 185° was resumed for 2 minutes. In this manner, four additions of methanol were made. The pressure in the cooled flask was lowered to 20 mm. to remove methanol and the product was distilled at 118° (0.55 mm.). A redistillation at 0.55 mm. gave 57.0 g. (80.5%) of oil which crystallized when moistened with 5 cc. of methanol. Further purification from methanol gave colorless crystals, m.p. 47.6–48°.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.25; H, 6.52.

The product gave a deep blue color with alcoholic ferric chloride.

Enol Lactone of 2,3-Dimethoxybenzosuberone-6-glyoxylic Acid.—2,3-Dimethoxybenzosuberone[11] (1.87 g.) gave a clear orange solution when condensed with methyl oxalate as described for benzosuberone. The lactone (1.6 g., 69%) melted after crystallization from ethyl acetate at 191.5–192.3°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.68; H, 5.15. Found: C, 65.53; H, 5.24.

Methyl 2,3-Dimethoxybenzosuberone-6-glyoxylate.—One gram of the above lactone dissolved in 20 cc. of warm methanol after 10 minutes. On cooling, 0.95 g. (83%) of light yellow needles separated. These slowly changed to the lactone on heating as shown by the m.p. 121.7–192°. An analytically pure sample from methanol gave the same melting point.

Anal. Calcd. for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.66; H, 5.81.

Methyl 2,3,4-Trimethoxybenzosuberone-6-glyoxylate.[12]—Trimethoxybenzosuberone[11] (13.08 g.), following the published directions[3] including refluxing of the methyl oxalate, benzene and sodium methylate, gave a cloudy yellow mixture. After 5 hours at room temperature, the flask contained the precipitated sodium salt of the product. The light yellow solid obtained from the aqueous alkaline solution on acidification weighed 16.91 g., m.p. 106–109°. Recrystallization from methanol gave 16.43 g. (93%) of the same compound, m.p. 106–109°, and repeated recrystallization from methanol brought the melting point to 105–107°. The pale yellow plates gave an instantaneous red-brown color with ferric chloride and a yellow solution in aqueous sodium hydroxide.

Anal. Calcd. for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99. Found: C, 60.99; H, 6.01.

Methyl 2,3,4-Trimethoxybenzosuberone-6-carboxylate.—The above glyoxylate (21.0 g.) produced carbon monoxide slowly over a 40-minute period at a bath temperature of 185–190°. The dark brown product crystallized from methanol at −5° when seeded. A second crystallization from methanol at −5° gave 17.3 g. (90%) of faintly tan solid, m.p. 89–91°. To remove unreacted material, a solution in benzene was passed through acid-washed alumina and the first colorless fractions from the column, after repeated crystallization from methanol melted at 94.2–96.5°.

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.32; H, 6.34.

With chromatographically purified material, alcoholic ferric chloride gave a black color. A bright red solution was obtained when aqueous sodium hydroxide was added to the compound in alcohol.

8-Methylbenzosuberone.—Benzaldehyde (0.025 mole), ethyl propylidenemalonate[13] (0.1 mole) and methanolic benzyltrimethylammonium hydroxide, following the method previously used,[11] gave 4.6 g. (79%) of **β-methylcinnamylidenemalonic acid**; yellow crystals, m.p. 112–114° (dec.). Repeated recrystallization by warming with benzene and a small amount of methanol followed by evaporation of the methanol gave the pale yellow monomethyl ester, m.p. 136.5–137.5° (dec.).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73. Found: C, 68.31; H, 5.68.

Purification using other solvents was not successful due to decomposition.

Catalytic hydrogenation[11] gave **γ-phenylisobutylmalonic acid** (54%) when crystallized from petroleum ether (60–90°). Repeated crystallization from the same solvent and finally from benzene–cyclohexane gave colorless crystals melting at 112.5–113.5°.

Anal. Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.33; H, 6.95.

Pyrolysis[11] of the malonic acid gave **γ-methyl-δ-phenylvaleric acid**, b.p. 176–181° (15 mm.), 129–135° (0.25–0.52 mm.); m.p. 36–45° (64%). The crystals, from petroleum ether (30–60°), melted at 44–45.5°.

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.04; H, 8.13.

Cyclization in polyphosphoric acid[11] gave **8-methylbenzosuberone**, b.p. 153–155° (14 mm.) (80%), as a colorless oil.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.21; H, 8.22.

The oxime crystallized from cyclohexane and sublimed easily at 75° and 0.1 mm. to give fine elongated prisms, m.p. 120–121.5°.

Anal. Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99. Found: C, 76.31; H, 7.92.

Enol Lactone of 8-Methylbenzosuberone-6-glyoxylic Acid.—The condensation conditions used on benzosuberone gave a clear red solution with the 8-methyl homolog. The product on recrystallization from ethyl acetate formed orange crystals (75%), m.p. 135.4–136.1°.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.58; H, 5.30.

On warming with methanol, the solution became yellow but no crystalline product could be isolated. The yellow oil gave a solid sublimate at room temperature and 0.12 mm. which was the lactone.

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[9] A. H. Blatt, Ed., "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.

[10] V. Prelog and W. Hinden, *Helv. Chim. Acta*, **27**, 1854 (1944).

[11] P. D. Gardner, W. J. Horton, G. Thompson and R. R. Twelves, THIS JOURNAL, **74**, 5527 (1952).

[12] Work of P. D. Gardner.

[13] A. C. Cope, C. M. Hofmann, C. Wyckoff and E. Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).