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Carbonyl Versus Conjugate Addition of Dipotassiobenzoylacetone with Certain α,β-Unsaturated Ketones

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Received August 1, 1960

Dipotassiobenzoylacetone, prepared with two molecular equivalents of potassium amide in liquid ammonia, condensed with the carbonyl group of chalcone to form the corresponding hydroxy β -diketone. This compound yielded two dehydration products, one of which was the doubly unsaturated β -diketone. The second dehydration product may have the dihydropyrone structure. Dipotassiobenzoylacetone underwent conjugate addition with 2',4',6'-trimethylchalcone.

It has recently been shown³ that the dipotassio or dilithio derivatives of certain β -diketones can be condensed with the carbonyl groups of ketones or aldehydes to form, after acidification, the corresponding hydroxy β -diketones. For example, dipotassiobenzoylacetone, which was prepared with two molecular equivalents of potassium amide in liquid ammonia, was condensed with benzophenone to give hydroxy β -diketone I in 73% yield.

It has now been found that dipotassiobenzoylacetone can be condensed similarly with the carbonyl group of chalcone to produce the unsaturated hydroxy β -diketone II in 66-77% yield (Equation 1).

$$C_{6}H_{3}COCH_{2}COCH_{4} \xrightarrow{2KNH_{4}} K$$

$$C_{6}H_{3}COCHCOCH_{2}K \xrightarrow{1, C_{6}H_{5}CH=CHCOC_{6}H_{5}} C_{6}H_{5}COCHCOCH_{2}K \xrightarrow{1, C_{6}H_{5}CH=CHCOC_{6}H_{5}} C_{6}H_{6}COCH_{2}COCH_{3}CCH=CHC_{6}H_{5} (1)$$

$$OH$$

$$II$$

The properties of II were similar to those observed previously for I.³ Compound II gave a positive enol test, formed a copper chelate, and underwent cyclization with hydrazine to give pyrazole III.



The infrared spectrum of II as well as the spectra of its copper chelate and pyrazole showed bands in the region of 2.8-2.9 μ for the hydroxyl group.⁴

(1) National Science Foundation Predoctoral Fellow, 1958-1960.

(2) National Science Foundation Predoctoral Fellow, 1956-1958.

(3) R. J. Light and C. R. Hauser, J. Org. Chem., in press.

The spectrum of II also gave bands characteristic of the β -diketone structure in the enol-chelate region of 6.1-6.5 μ .⁶ The spectrum of the copper chelate contained a band at 6.58 μ , reported as characteristic of copper chelates of β -diketones not substituted at the methylene group,⁶ as well as the two "perturbed carbonyl" bands⁷ at 6.47 μ and 7.17 μ .

Dehydration of unsaturated hydroxy β -diketone II with methanolic hydrochloric acid produced a 79% yield of the doubly unsaturated β -diketone IV, and the properties of IV were similar to those of V, the corresponding dehydrated product of I.³ Although several geometrical isomers are possible in IV, only one compound was isolated.

$$C_{6}H_{5}$$

$$C_{6}H_{5}COCH_{2}COCH=CH=CHC_{6}H_{5}$$

$$IV$$

$$C_{6}H_{5}COCH_{2}COCH=C(C_{6}H_{5})_{2}$$

$$V$$

The infrared spectrum of IV showed strong bands in the enol-chelate region for the β -diketone structure.⁵ Compound IV gave a positive enol test and formed a copper chelate. The infrared spectrum of the copper chelate contained the characteristic bands^{6,7} at 6.59 μ and 7.08 μ , but the first "perturbed carbonyl" band was absent, as had been the case for the copper chelate of V.⁴

It was possible that dipotassiobenzoylacetone could undergo conjugate addition with chalcone to form triketone VI. The presence of a hydroxy band and the absence of an ordinary carbonyl band in the infrared spectra of II and the copper

(4) See L. J. Bellamy, The Infrared Spectra of Complex Molecules, 2d. ed., Wiley, New York, 1958, pages 95–98.

(5) See Ref. 4, p. 142.

(6) R. P. Dryden and A. Winston reported [J. Phys. Chem., 62, 635 (1958)] that the copper chelates of acetylacetone and similar β -diketones unsubstituted at the methylene group showed infrared bands at 6.10–6.45 μ ("A," attributed to the carbonyl group) and at 6.52– 6.60 μ ("B," attributed to the C=C link). Chelates of their 3-substituted derivatives, however, exhibited only the "A" band in this region.

(7) J. Lecomte, Discussions Faraday Soc., 125 (1950);
L. J. Bellamy and R. F. Branch, J. Chem. Soc., 4491 (1954);
H. F. Holtzclaw, Jr., and J. P. Collman, J. Am. Chem. Soc., 79, 3318 (1957); see also Ref. 4, pp. 145-146.

chelate and pyrazole derivatives of II showed, however, that the addition product did not have the structure VI.

It might be argued that VI could cyclize to form hydroxy β -diketone VII, which could show properties similar to II. The infrared spectrum of the copper chelate of II indicated that it was unsubstituted at the methylene group,⁶ however, which would not be the case for structure VII. Moreover, the expected dehydration product of VII would be VIII, which should not form a copper chelate or give an enol test, whereas IV showed both of these reactions.



The structure of IV, and consequently of II, was supported by two cleavage reactions. A 49% yield of benzoic acid was isolated when IV was hydrolyzed with ethanolic potassium hydroxide. Treatment of IV with sodium hypochlorite produced a low yield (4%) of β -styrylcinnamic acia (IX).

C₆H₅ C₆H₅CH=CHC IX

Acid IX was independently synthesized from ethyl acetate and chalcone (Equation 2), and was shown to be identical with the cleavage product. Hydroxy ester X was made previously,⁸ but was not dehydrated or saponified at that time. Acid IX has previously been made from the Reformatsky reaction of methyl bromoacetate with chalcone.⁹

$$CH_{4}COOC_{2}H_{5} \xrightarrow{1, 2LiNH_{2} (liq. NH_{4})}{2, C_{6}H_{4}CH=CHCOC_{6}H_{5}} \xrightarrow{C_{6}H_{5}}{C_{6}H_{5}} \xrightarrow{C_{6}H_{5}}{OH} \xrightarrow{X} \xrightarrow{1, dehydration}{2, saponification} (2)$$

Also similar to hydroxy β -diketone I, II produced a second dehydration product with cold concen-

(8) W. R. Dunnavant and C. R. Hauser, J. Org. Chem., 25, 503 (1960).

(9) E. P. Kohler, G. L. Heritage, and A. L. Macleod, Am. Chem. J., 46, 223 (1911). trated sulfuric acid. This compound gave no enol test and showed strong infrared absorption bands in the carbonyl region at 5.96 μ and 6.06 μ , the latter band being the more intense. The corresponding product from I had shown a strong band in the infrared at 6.00 μ for a carbonyl group in conjugation with an aliphatic carbon-carbon double bond,^{3,10} and was assigned the dihydropyrone structure XI from its properties and reactions. The second dehydration product of II might have the dihydropyrone structure XII, but evidence for this structure was only slight.

$$C_{6}H_{5} - O = CHC_{6}H_{5}$$

$$C_{6}H_{5} - C_{6}H_{5} - C_{6}H_{5}$$

$$C_{6}H_{5} - C_{6}H_{5}$$

$$C_{6}H_{5} - C_{6}H_{5}$$

In contrast to the reaction with chalcone, dipotassiobenzoylacetone evidently underwent conjugate addition with 2',4',6'-trimethylchalcone to form XIII (Equation 3).



Whereas the infrared spectrum of the product from chalcone showed a hydroxyl band but no ordinary carbonyl band, that of XIII contained a carbonyl band at 5.89 μ^{11} and no band in the hydroxyl region near 2.9 μ . A strong broad band was present in the enol-chelate region for the β -diketone structure.⁵ Triketone XIII was an oil, while II was a crystalline solid. The oil gave a positive enol test and formed a copper chelate. The infrared spectrum of the copper chelate contained the characteristic bands^{6,7} at 6.46 μ , 6.57 μ , and 7.13 μ , and a carbonyl band at 5.89 μ .¹¹

Including the present conjugate addition (Equation 3), examples of the four principal types of carbon-carbon condensations have now been realized at the terminal methyl group of benzoylacetone. The other three types were alkylation,^{12,13} acylation,^{12,14} and carbonyl addition.^{3,12} These reactions all involved the intermediate dipotassiobenzoylacetone, which was formed by treatment

⁽¹⁰⁾ See Ref. 4, p. 136.

⁽¹¹⁾ See Ref. 4, p. 137.

⁽¹²⁾ C. R. Hauser and T. M. Harris, J. Am. Chem. Soc., 80, 6360 (1958).

⁽¹³⁾ R. B. Meyer and C. R. Hauser, J. Org. Chem., 25, 158 (1960).

⁽¹⁴⁾ R. J. Light and C. R. Hauser, J. Org. Chem., 25, 538 (1960).

of the β -diketone with two equivalents of potassium amide.

It is interesting to contrast the ordinary, base catalyzed, Michael reaction between β -diketones and α,β -unsaturated ketones with the reaction between dipotassiobenzoylacetone and chalcone. First, the reaction of β -diketones in the presence of catalytic or equivalent amounts of sodium hydroxide or sodium alkoxide involves ionization of the methylene group and reaction at that site. Dipotassiobenzoylacetone, on the other hand, reacts at the stronger terminal methyl carbanion. Secondly, the stronger carbanion of dipotassiobenzoylacetone reacts preferentially with the carbonyl group of chalcone unless the carbonyl group is sterically hindered (Equations 1 and 3). The weaker monocarbanion of the methylene group, however, reacts preferentially at the conjugated carbon-carbon double bond even when the carbonyl group is not hindered. This reaction has often been complicated by cyclization of the adduct (and sometimes cleavage), but the products isolated showed that conjugate addition had occurred.^{15,16} An example in which the intermediate adduct was isolated is shown in Equation $4.^{16}$

CH2=CHCOCH3

 $+ \xrightarrow{\text{cold}} CH_2CH_2COCH_3 (4)$ $CH_3COCH_2COCH_3 CH_3COCHCOCH_3 (4)$

EXPERIMENTAL¹⁷

Condensation of dipotassiobenzoylacetone with chalcone. Solid benzoylacetone (16.2 g., 0.1 mole) was added through a powder funnel to a stirred solution of 0.21 mole of potassium amide in 300 ml. of commercial, anhydrous liquid ammonia.12 The resulting dark green solution of dipotassiobenzoylacetone was stirred for 30 min., and 20.4 g. (0.1 mole) of solid chalcone was added. A precipitate began to form immediately. After stirring 30 min., excess ammonium chloride was added, and the liquid ammonia was evaporated on the steam bath as an equal volume of ether was added. The ethereal suspension was washed with water and the resulting solution dried over Drierite. The solvent was removed and the residue was recrystallized from ethanol to give 24.5-28.4 g. (66-77%) of 5-hydroxy-1,5,7-triphenyl-6-heptene-1,3-dione (II), m.p. 105-107°. Repeated recrystallization from 95% ethanol raised the melting point to 109.5-110.5°.

Anal. Calcd. for C₂₅H₂₂O₃: C, 81.05; H, 5.99. Found: C, 80.94; H, 6.04.

The infrared spectrum in the carbonyl and enol-chelate region⁵ showed strong bands at 6.24μ and 6.36μ . A medium band was present in the hydroxyl region at 2.80μ . A carbon tetrachloride solution of II also gave a hydroxyl band in the infrared, at 2.84μ . The compound produced a red color with ethanolic ferric nitrate.

Treatment of a 2-g. sample of II dissolved in methanol with aqueous copper acetate and recrystallization of the crude precipitate from dioxane-water produced 1.6 g. (74%)of copper chelate, m.p. 166–167°. An analytical sample had been prepared from the crude precipitate by washing with hot methanol and ether, m.p. 160–162°.

Anal. Calcd. for C₅₀H₄₂O₆Cu: C, 74.84; H, 5.27. Found: C, 75.03; H, 5.40.

The infrared spectrum showed characteristic⁷ strong bands at 6.47 μ , 6.58 μ , and 7.17 μ . A medium band was present in the hydroxyl region at 2.91 μ .

Treatment of II with hydrazine. A 1-g. sample of II was dissolved in 20 ml. of hot 95% ethanol, and an excess (10 drops) of Eastman 95% hydrazine was added. The solution was heated on the steam bath for 1 hr., and then cooled to room temperature. Water was added to precipitate 0.95 g. (96%) of pyrazole III, white solid, m.p. 175–180°. Several recrystallizations from ethanol-water produced an analytical sample, m.p. 178–181°.

Anal. Calcd. for C25H22N2O: C, 81.94; H, 6.05; N, 7.65. Found: C, 82.05; H, 6.26; N, 7.63.

The infrared spectrum showed a band at 2.92 μ for the hydroxyl group and a band at 6.86 μ reported as characteristic of the pyrazole ring.^{3,18}

Dehydration of II with hydrochloric acid. A 1-g. sample of II was dissolved in 25 ml. of methanol containing 3 ml. of concd. hydrochloric acid. The solution was refluxed for 2 hr., cooled, and filtered to produce 0.75 g. (79%) of 1,5,7-triphenyl-4,6-heptadiene-1,3-dione (IV), bright yellow solid, m.p. $157-160^{\circ}$. Recrystallization from ethanol-benzene did not raise the melting point.

Anal. Caled. for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72. Found: C, 85.38; H, 6.04.

The infrared spectrum¹⁹ in the carbonyl and enol-chelate region⁶ showed strong bands at 6.27 μ and 6.34 μ . The compound produced a brown color with ethanolic ferric nitrate.

Treatment of IV with methanolic copper acetate under the usual conditions did not produce the copper chelate, probably because of the low solubility of IV, but it was obtained by the following procedure. To a 1-g. sample of IV dissolved in hot dioxane was added a hot, filtered solution of copper acetate in dioxane. The solution was cooled, and water was added to precipitate 1.1 g. of a yellowish green solid, m.p. 208-212°. Several recrystallizations from benzene-ethanol raised the melting point to 216-218°.

Anal. Caled. for $C_{50}H_{58}O_4Cu$: C, 78.36; H, 5.00; Cu, 8.29. Found: C, 78.36; H, 5.12; Cu, 8.11.

The infrared spectrum¹⁹ of the copper chelate showed characteristic^{6,7} strong bands at 6.59 μ and 7.08 μ .

Cleavage of IV with ethanolic potassium hydroxide. A 3.5-g. (0.01 mole) sample of IV dissolved in 80 ml. of 95% ethanol containing 5.6 g. (0.1 mole) of potassium hydroxide and 20 ml. of water was refluxed on the steam bath for 4 hr. Part of the ethanol was removed under an aspirator, and the solution was diluted with water and extracted with ether. The aqueous alkaline layer was separated and acidified, and the acidified mixture was extracted with ether. The ether solution of the acid materials was then extracted several times with sodium bicarbonate solution. The bicarbonate extracts were combined and acidified, and the precipitate was taken up into ether. This ether layer was washed with saturated sodium chloride solution and dried over sodium sulfate. The solvent was removed leaving 1.0 g. of solid residue, m.p. 100-115°. Recrystallization from water yielded 0.6 g. (49%) of benzoic acid, m.p. 120-121°. There was no depression in the melting point on mixing with an authentic sample of benzoic acid.

⁽¹⁵⁾ M. Scholtz, Arch. Pharm., 254, 547 (1916).

⁽¹⁶⁾ R. N. Lacey, J. Chem. Soc., 1625 (1960).

⁽¹⁷⁾ Melting points were taken on a Fisher-Johns melting point apparatus which had been calibrated with melting point standards. Infrared spectra were determined with a Perkin-Elmer Infracord by the potassium bromide pellet method unless stated otherwise. Elemental analyses were by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

⁽¹⁸⁾ C. S. Rondestvedt and P. K. Chang, J. Am. Chem. Soc., 77, 6532 (1952).

⁽¹⁹⁾ Only a weak band was present in the hydroxyl region near 2.9 μ , which was attributed to moisture in the potassium bromide.

Cleavage of IV with sodium hypochlorite. Sodium hypochlorite was prepared by adding a solution of 5.5 g. (0.05 mole) of sodium carbonate and 2 g. (0.05 mole) of sodium hydroxide in 20 ml. of water to a solution of 10 g. of calcium hypochlorite in 40 ml. of water. The flask was shaken and the contents were filtered. The sodium hypochlorite solution was added to a suspension of 3.5 g. (0.01 mole) of IV in 20 ml. of 10% sodium hydroxide solution, and 25 ml. of dioxane was added. The mixture was heated on the steam bath for 1.5 hr. with occasional swirling and then stirred at room temperature for 5 hr. After filtering, the excess sodium hypochlorite was decomposed by adding 4 g. of sodium bisulfite, and the solution was acidified with 10 ml. of concd. hydrochloric acid. The mixture was diluted with water and extracted with ether. The ether layer was separated, washed with water, shaken with saturated sodium chloride solution, and dried over sodium sulfate. The solvent was removed, leaving 1.8 g. of residue. This solid was taken up in 5 ml. of benzene and placed on a chromatographic column containing 25 g. of alumina. The column was eluted with the following: (1) 100 ml. of petroleum ether (b.p. $30-60^{\circ}$); (2) 100 ml. 1:1 petroleum ether-benzene; (3) 300 ml. benzene; (4) 200 ml. 1:1 benzene-ether; (5) 100 ml. ether. The second part of the benzene-ether eluate contained 0.1 g. (4%) of solid, m.p. 130-142°. Two recrystallizations from hexane-benzene raised the melting point to 140-142°. A mixed melting point with an authentic sample of β -styrylcinnamic acid (IX) described below was 141-143°, and the infrared spectra of the two samples were identical.

Independent synthesis of β -styrylcinnamic acid (IX). A 3-g. sample of ethyl β -hydroxy- β -phenyl- β -styrylpropionate (X)⁸ was dissolved in 20 ml. of 95% ethanol containing 1 ml. of concd. hydrochloric acid, and the solution was heated on the steam bath for 2 hr. It was then diluted with water and extracted with ether. The ether extract was washed with saturated sodium chloride solution and dried over sodium sulfate. The solvent was removed, and the residue was taken up in 20 ml. of ethanol containing 4 g. of potassium hydroxide and 10 ml. of water. The solution was heated on the steam bath for 6 hr., diluted with water, and extracted with ether. The aqueous alkaline layer was removed and acidified. The acidified material was extracted with ether and the ethereal layer was separated and washed with saturated sodium chloride solution. It was dried over sodium sulfate, and the solvent was removed. The residue was recrystallized from methanol-water to give 1.0 g. of a white solid, m.p. 115-135°. Recrystallization of this material from benzene-hexane yielded 0.6 g. (24%) of β -styrylcinnamic acid (IX), m.p. 142-144° (reported⁹ m.p. 145-146°). The infrared spectrum showed a strong carbonyl band at 5.95 μ .

Dehydration of II with sulfuric acid. A 1-g. sample of II was dissolved in 10 ml. of cold concd. sulfuric acid, while cooling in an ice bath, by stirring with a glass rod until solution was complete (about 15 min.). The solution was poured into ice water, and the resulting slurry was extracted twice with ether. The ether extracts were combined, washed with aqueous sodium bicarbonate, shaken with saturated aqueous sodium chloride, and dried over sodium sulfate. The solvent was removed and the residue recrystallized from 95% ethanol to give 0.25 g. (26%, calculated as XII) of light yellow needles, m.p. 177.5-179.5°. Recrystallization did not raise the melting point.

Anal. Calcd. for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72. Found: C, 85.10; H, 5.77.

The infrared spectrum¹⁹ in the carbonyl region¹⁰ showed strong bands at 5.96 μ and 6.06 μ . The compound produced no color with ethanolic ferric nitrate.

Condensation of dipotassiobenzoylacetone with 2',4',6'trimethylchalcone. 2',4',6'-Trimethylchalcone was prepared by the Friedel-Crafts reaction of cinnamoyl chloride with mesitylene in the quantities described by Nesmeyanov and Sazanova.²⁰ A 52% yield of product boiling at 165–170° at 0.5 mm. was obtained which melted at 59–61° after recrystallization from petroleum ether (b.p. 30–60°) (reported²⁰ m.p. 63°, b.p. 196° at 5 mm.).

Solid benzoylacetone (8.1 g., 0.05 mole) was added through a powder funnel to a stirred solution of 0.1 mole of potassium amide in 300 ml. of commercial, anhydrous liquid ammonia, 12 followed by about 30 ml. of anhydrous ether. The resulting dark green solution of dipotassiobenzoylacetone was stirred for 30 min., and a solution of 12.5 g. (0.05 mole) of 2',4',6'trimethylchalcone in 50 ml. of anhydrous ether was added. The solution was stirred for 2 hr. with no apparent change. It was poured into a liquid ammonia solution of 8 g. of ammonium chloride, and the liquid ammonia was replaced with ether. The ethereal suspension was washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, and saturated aqueous sodium chloride. It was dried over sodium sulfate, and the solvent was removed to yield 20.8 g. of an oily residue which would not crystallize. A 10-g. aliquot was dissolved in ether and extracted with 50 ml. of cold 3% sodium hydroxide solution to remove unchanged benzoylacetone. There remained 8.7 g. of oil in the ether layer which still would not crystallize. A 6.7-g. aliquot of this oil dissolved in ether was treated overnight with aqueous copper acetate. The mixture was filtered, and the precipitate was washed with water, ether, and methanol, leaving 6.9 g. (84%) of the crude copper chelate of XIII, m.p. 160-177°. One recrystallization from benzene-ethanol raised the melting point to 169-172°. An analytical sample, m.p. 172-174°, was prepared from another aliquot of oil.

Anal. Calcd. for $C_{56}H_{54}O_6Cu$: C, 75.87; H, 6.14; Cu, 7.16. Found: C, 75.87; H, 6.16; Cu, 7.13.

The 6.9-g. sample of copper chelate was decomposed by shaking with ether and 150 ml. of dilute (1:3) hydrochloric acid. The ether layer was washed with saturated sodium bicarbonate solution, shaken with saturated sodium chloride solution, and dried over sodium sulfate. The solvent was removed leaving 4.9 g. (64% based on starting materials) of an oil, which had an analysis corresponding to 1,5-diphenyl-7-(2',4',6'-trimethylphenyl)heptane-1,3,7-trione (XIII).

Anal. Calcd. for $C_{28}H_{28}O_8$: C, 81.52; H, 6.84. Found: C, 81.43, 81.61; H, 7.06, 7.06.

The infrared spectrum of XIII on sodium chloride plates showed a strong carbonyl band at 5.89 μ^{11} and a strong broad band at 6.20-6.35 μ in the enol-chelate region.⁵ There was no band in the hydroxyl region near 2.9 μ . The oil produced a red color with ethanolic ferric nitrate.

The infrared spectrum¹⁹ of the copper chelate showed characteristic^{6,7} strong bands at 6.46 μ , 6.57 μ , and 7.13 μ , as well as a carbonyl band at 5.89 μ .¹¹

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(20) A. N. Nesmeyanov and V. A. Sazonova, *Izvest. Akad.* Nauk S.S.S.R., Otdel Khim. Nauk, 422-438 (1949); Chem. Abstr., 44, 1403a (1950).