

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA]

The Monoethylene Ketal of 1,3-Cyclohexanedione

BY MARSHALL W. CRONYN AND JUDSON E. GOODRICH

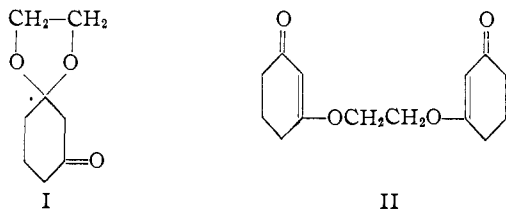
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The monoethylene ketal of 1,3-cyclohexanedione has been prepared and some of its reactions have been studied. The ketone has been subjected to the Reformatsky reaction, cyanohydrin formation and catalytic reduction. The sensitivity of the ketal toward basic reagents limits its usefulness as a protective group in this particular system.

In order to investigate the usefulness of monoethylene ketals as protective agents in 1,3-dicarbonyl systems, and as part of a search for intermediates in the synthesis of substituted 2-azabicyclo[3.3.1]nonanes, the preparation and properties of the monoethylene ketal of 1,3-cyclohexanedione (I) were studied.

Cyclic ketals have had extensive use in carbohydrate chemistry¹; but they had seldom been used as protective groups for carbonyls until Salmi² introduced a general method for their preparation. Recently there have been several applications of cyclic ketals as blocking agents for carbonyls³ and Schinz⁴ and co-workers have studied the ketals of keto-esters rather extensively. Several preparations of cyclic monoketals of dicarbonyl systems have been reported^{3c,5} but the only reaction of a monoketal of a 1,3-dicarbonyl system which has been described is the reduction of the α -carbonyl of the γ -ethylene ketal of ethyl acetoneoxalate.^{3c}

The application of Salmi's procedure to the reaction of 1,3-cyclohexanedione and ethylene glycol gave a mixture of unreacted 1,3-cyclohexanedione, the monoketal (I) (35%), the diketal, and the di-(3-keto- Δ^1 -cyclohexenyl) ether of ethylene glycol (II). These products were obtained after a three-hour reaction time; at which point 55% of the theoretical amount of water had been removed. If the reaction time was increased, the yield of monoketal increased only slightly; the total amount of starting material which could be recovered decreased.

(1) E. Fischer, *Ber.*, **23**, 1167 (1895).

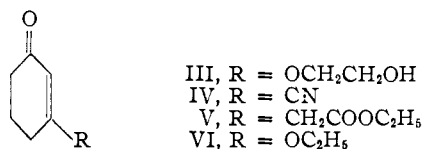
(2) E. J. Salmi, *ibid.*, **71B**, 1803 (1938); E. J. Salmi and V. Rannikko, *ibid.*, **72B**, 600 (1939); E. J. Salmi and I. J. Jansson, *Suomen Kemistilehti*, **12B**, 28 (1939) [*C. A.*, **34**, 423 (1940)]; E. J. Salmi and K. Kyrki, *ibid.*, **19B**, 97 (1946) [*C. A.*, **41**, 5480 (1947)]; E. J. Salmi and U. Tamminen and P. Louhenkuru, *ibid.*, **20B**, 1 (1947) [*C. A.*, **42**, 537 (1948)].

(3) (a) M. Kühn, *J. prakt. Chem.*, **156**, 103 (1940); (b) A. Hinz, G. Meyer and G. Schucking, *Ber.*, **76B**, 676 (1943); (c) A. Rossi and A. Lauchenauser, *Helv. Chim. Acta*, **30**, 1501 (1947); (d) M. Stoll, J. Hulstkamp and A. Rouve, *ibid.*, **31**, 543 (1948).

(4) H. Schinz and G. Schappi, *ibid.*, **30**, 1483 (1947); L. Willmann and H. Schinz, *ibid.*, **32**, 2151 (1949); E. Vogel and H. Schinz, *ibid.*, **33**, 116 (1950); P. Seifert, E. Vogel, A. Rossi and H. Schinz, *ibid.*, **33**, 725 (1950).

(5) J. Boëseken and F. Tellegen, *Rec. trav. chim.*, **57**, 133 (1938); A. C. Neish and F. J. McDonald, *Can. J. Research*, **25B**, 70 (1947); A. L. Wilds, J. W. Ralls, W. C. Wildman and K. E. McCaleb, *This Journal*, **72**, 5794 (1950).

The monoketal (I) was sensitive to mild basic reagents. When it was allowed to reflux for an hour in 0.1 *N* sodium bicarbonate solution, the ketal ring opened to give the enol ether (III). The enol ether could be rapidly distilled, but the continued heating necessary for fractionation converted the open enol to the cyclic ketal (I) again. The sensitivity of the ketal to base parallels the facile β -elimination of other 3-substituted cyclohexanones.



The ultraviolet absorption spectra of the monoketal (I), the glycol enol ether (II), and the β -hydroxyethyl enol ether (III) are given in Fig. 1. It can be seen that the monoketal (I) contains some of the open enol (III) but in an amount less

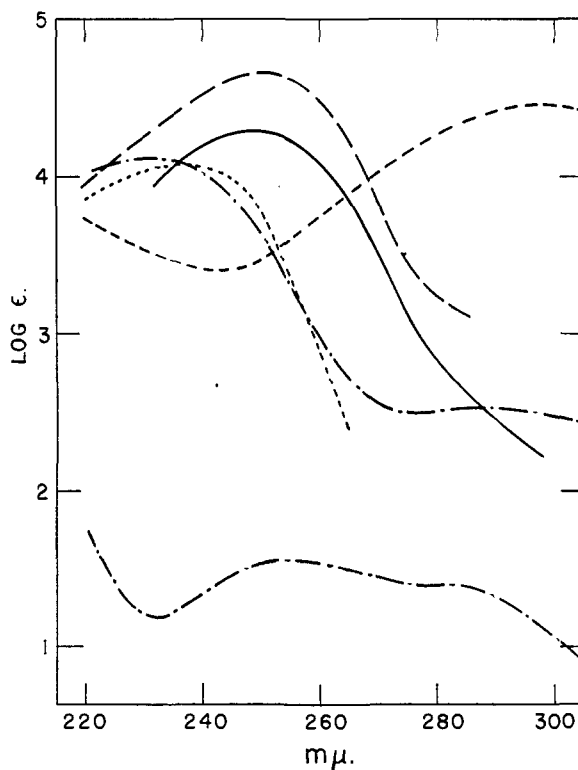


Fig. 1.—Ultraviolet absorption spectra for the monoethylene ketal of 1,3-cyclohexanedione (I), — — —; di-(3-keto- Δ^1 -cyclohexenyl) ether of ethylene glycol (II), — — —; 3-(β -hydroxyethoxy)- Δ^2 -cyclohexenone (III), - · - ·; 3-cyano- Δ^2 -cyclohexenone (IV), — · — ·; ethyl Δ^2 -cyclohexanone-3-acetate (V), · · · ·; diethyl 3-carboxymethylene- Δ^2 -cyclohexenyl acetate (VIII), - - - -.

than 1%. The ratio of the intensities of II and III is slightly over the expected two to one; however, considering the method used in the isolation of the enol (III), it would undoubtedly contain a little of the monoketal (I).

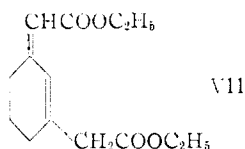
By heating in dilute sodium hydroxide solution the monoketal (I) was hydrolyzed to give 1,3-cyclohexanedione; thus the alkaline hydrolysis of the enol ether (III), which is a vinylogous ester, also proceeds readily in this system.

Since the monoketal I is sensitive to either acidic or basic reagents the number of reactions which can be applied to the free carbonyl group are limited. A cyanohydrin could not be obtained in liquid hydrogen cyanide with potassium cyanide as a catalyst, but the bisulfite of the ketone gave the cyanohydrin with sodium cyanide. The ketal cyanohydrin was not isolated but was hydrolyzed and dehydrated in dilute acid to give 54% of 3-cyano- Δ^2 -cyclohexenone (IV).

The monoketal (I) was much less reactive toward the Reformatsky reagent from ethyl bromoacetate than cyclohexanone; however, by using forcing conditions a 36% yield of ethyl Δ^2 -cyclohexenone- β -acetate (V) was obtained after hydrolysis of the Reformatsky reaction product.

Hydrogenation of the monoketal over Raney nickel gave the hydroxy ketal which was hydrolyzed and dehydrated in dilute acid to give an over-all yield of 67% of Δ^2 -cyclohexenone.

Since Woods and Tucker⁶ were able to obtain β -substituted cyclohexenones by reaction of the enol ether (VI) with Grignard reagents, it was expected that perhaps the enol ether might react with the Reformatsky reagent to give the ester V; however, when the enol ether was allowed to react with the Reformatsky reagent using the same conditions that were employed for the ketal the disubstituted product (VII) was obtained. When an equivalent amount of ethyl bromoacetate was used, a mixture of mono- and disubstituted products was obtained.



Experimental⁷

Monoethylene Ketal of 1,3-Cyclohexanedione (I). A mixture of 56 g. (0.5 mole) of 1,3-cyclohexanedione⁸ and 33 g. (0.53 mole) of ethylene glycol was heated in 500 ml. of benzene with a few crystals of *p*-toluenesulfonic acid. In three hours 10 ml. of water was removed from the refluxing mixture with a modified Dean-Stark⁹ trap. The cooled solution was washed with 150 ml. of 8% sodium bicarbonate solution. The bicarbonate solution was washed several

(6) G. F. Woods and I. W. Tucker, *THIS JOURNAL*, **70**, 2174 (1948).

(7) Analyses by the Microanalytical Laboratory of the Department of Chemistry, University of California. The absorption spectra were taken in 95% ethanol using a Beckman model DU spectrophotometer.

(8) R. B. Thompson, *Org. Syntheses*, **27**, 21 (1947). Commercially prepared Raney nickel catalyst (Raney Catalyst Co., Chattanooga, Tenn.) was used and the hydrogenation was allowed to proceed 18 hours at room temperature. The product was stable for several months when stored in ordinary containers.

(9) Dean and Stark, *Ind. Eng. Chem.*, **12**, 486 (1920). A second condenser was introduced to cool the condensate before separating the water and returning it to the still.

times with benzene and the combined benzene solutions were dried, the benzene was removed and the residue was distilled from a Claisen flask to give 38 g. of distillate; b.p. 95–115° at 2 mm., and 18 g. of residue.

The distillate was fractionated¹⁰ to give 27 g. (35%) of the monoketal (I); b.p. 84–85° (1 mm.); n_D^{25} 1.4738; λ_{max} , 256 m μ (log ϵ 1.54), plateau 280 m μ (log ϵ 1.36).

Anal. Calcd. for C₈H₁₂O₃: C, 61.52; H, 7.75. Found: C, 61.43; H, 7.82.

On addition of the monoketal to a 0.005 *N* solution of 2,4-dinitrophenylhydrazine in 1.5 *N* hydrochloric acid¹¹ a precipitate was formed which could be filtered after about 20 minutes. The derivative hydrolyzed and completely redissolved if allowed to stand overnight in the acid solution. After recrystallization from ethanol the derivative had a m.p. of 177–178°.

Anal. Calcd. for C₁₄H₁₆N₄O₆: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.02; H, 4.93; N, 16.50.

The benzene-insoluble material from the Claisen distillation was combined with the residue from the fractionation to give about 19 g. of crude diketal; m.p. 50–55°. After three recrystallizations from ligroin the m.p. was 65–66°; b.p. 100° (1.0 mm.).

Anal. Calcd. for C₁₀H₁₆O₄: C, 59.98; H, 8.06. Found: C, 59.95; H, 8.19.

The addition of ether to the benzene solution, from which the diketal had been removed, brought about the separation of the di-(3-keto- Δ^2 -cyclohexenyl) ether of ethylene glycol (II). After crystallization from water 6 g. was obtained with a m.p. of 130–132°. Recrystallization from benzene-petroleum ether gave a product with a m.p. of 135–136°; λ_{max} , 250 m μ (log ϵ 4.65).

Anal. Calcd. for C₁₄H₁₈O₄: C, 67.18; H, 7.25. Found: C, 67.35; H, 7.15.

Both the pure diketal and the enol ether (II) were hydrolyzed to 1,3-cyclohexanedione in 80–90% yield by refluxing with 0.1 *N* hydrochloric acid.

About 18 g. of impure 1,3-cyclohexanedione was recovered by acidification and extraction of the bicarbonate extract of the original reaction mixture.

3-(β -Hydroxyethoxy)- Δ^2 -Cyclohexenone (III).—The monoketal (II) (2.4 g.) was allowed to reflux for one hour with 10 ml. of 0.1 *N* sodium bicarbonate. The solution was saturated with sodium chloride and extracted with three 10-ml. portions of chloroform. The extract was dried, the solvent was removed and the residue was evaporatively distilled at 0.5 mm. to give 1.4 g. of oil; n_D^{25} 1.5210; λ_{max} 249 (log ϵ 4.29). When an attempt was made to fractionate a larger sample of the same reaction product the distillate was entirely the monoketal (I) as indicated by refractive index and ultraviolet absorption.

Ethylene Ketal of 3-Hydroxycyclohexanone.—The monoketal (I) (9.6 g.) reacted with the theoretical amount of hydrogen in six hours over 2.4 g. of Raney nickel¹² in 30 ml. of absolute alcohol at 25 pounds hydrogen pressure. Fractionation of the product gave 6.6 g. (68%) of the ethylene ketal of 3-hydroxycyclohexanone; b.p. 89° (1.0 mm.); n_D^{20} 1.4828.

Anal. Calcd. for C₈H₁₄O₃: C, 60.74; H, 8.92. Found: C, 60.80; H, 8.93.

Δ^2 -Cyclohexenone.—The monoketal (12.0 g.) was hydrogenated as above and the crude product was allowed to stand 24 hours at room temperature with 25 ml. of 3 *N* hydrochloric acid. The solution was saturated with ammonium sulfate and extracted with six 15-ml. portions of ether. After the solvent had been dried and removed, the residue was fractionated to give 5.1 g. (69%) of Δ^2 -cyclohexenone; b.p. 65° (16 mm.); n_D^{20} 1.4860.

Both the 3-hydroxy ketal and Δ^2 -cyclohexenone gave the same 2,4-dinitrophenylhydrazone, m.p. 162.8–163.2° or 163.8–164.6° starting with a bath at 160°; lit. 163°,¹³ 116–

(10) All fractionations were carried out in a 60 × 0.6 cm. column packed with wire gauze according to J. R. Bowers and L. M. Cook, *Anal. Chem.*, **15**, 290 (1943).

(11) O. H. Brady and G. V. Bismie, *Analyst*, **51**, 77 (1926).

(12) The catalyst used was the commercially prepared material obtained from the Raney Catalyst Co., Chattanooga, Tenn.

(13) P. D. Bartlett and G. F. Woods, *THIS JOURNAL*, **62**, 2933 (1940).

117°,¹⁴ 170–170.5°,¹⁹ 167.5–169°,¹⁵ 163°,¹⁶ 164–165°,¹⁷ sinter 163°, m.p. 171.5°.¹⁸

Anal. Calcd. for C₁₂H₁₂N₄O₄: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.92; H, 4.35; N, 20.47.

Ethyl Δ²-Cyclohexenone-3-acetate (V).—A mixture of 11.7 g. (0.075 mole) of the monoketal (I), 13.4 g. (0.08 mole) of ethyl bromoacetate, 2 g. of cleaned granulated zinc, and a crystal of iodine was refluxed and stirred for 5.5 hours in 100 ml. of benzene. During this time fresh portions of zinc and iodine were added at half-hour intervals and after two hours another 13.4-g. portion of bromoester was added. Acidification of the reaction product with cold 10% sulfuric acid and extraction of the benzene solution with bicarbonate gave 2 g. of 1,3-cyclohexanedione. Fractionation of the neutral residue after removal of the benzene gave 5.0 g. (36%) of V; b.p. 108° (1 mm.); *n*²⁰_D 1.4879; λ_{max} 233 mμ (log ε 4.14).

Anal. Calcd. for C₁₀H₁₄O₃: C, 65.91; H, 7.74. Found: C, 65.70; H, 7.55.

The dinitrophenylhydrazone melts at 107–108° after crystallization from alcohol.

Anal. Calcd. for C₁₆H₁₃O₆N₄: C, 53.03; H, 5.01; N, 15.46. Found: C, 53.04; H, 4.94; N, 15.83.

3-Cyano-Δ²-cyclohexenone (IV).—A solution of 24.7 g. (0.13 mole) of sodium metabisulfite in 40 ml. of water was added dropwise with stirring and cooling to 40 g. (0.256 mole) of the monoketal (I). To the resulting homogeneous solution was added 12.7 g. (0.26 mole) of sodium cyanide in 25 ml. of water. The mixture was stirred at room temperature for 20 hours; it was then filtered, and the filtrate was extracted with ether. The ether was removed and to the residue was added 40 ml. of 3 N hydrochloric acid; the homogeneous solution was allowed to stand 24 hours during which time the product separated from solution. The aqueous solution was saturated with ammonium sulfate, extracted with ether, the ether was removed, and the residue

was fractionated to give 16.8 g. (54%) of the cyanoketone (IV); b.p. 105° (3.8 mm.); *n*²¹_D 1.5104; λ_{max} 236 mμ (log ε 4.08).

Anal. Calcd. for C₇H₇NO: C, 69.40; H, 5.82; N, 11.57. Found: C, 69.11; H, 5.94; N, 11.97.

Both the crude cyanohydrin and the unsaturated cyanoketone gave the same dinitrophenylhydrazone; m.p. 204–204.5° after recrystallization from ethanol.

Anal. Calcd. for C₁₃H₁₁N₅O₄: C, 51.83; H, 3.68; N, 23.25. Found: C, 51.68; H, 3.89; N, 22.88.

The cyanoketone readily formed an ethylene ketal; b.p. 96° (1 mm.); *n*¹⁹_D 1.4968.

Anal. Calcd. for C₉H₁₁O₂N: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.03; H, 6.92; N, 8.14.

3-Ethoxy-Δ²-cyclohexenone (VI).—A mixture of 1,3-cyclohexanedione (28 g., 0.25 mole), 50 ml. of absolute ethanol and a few crystals of *p*-toluenesulfonic acid in 500 ml. of benzene was allowed to reflux under a modified Dean-Stark trap for 16 hours. Removal of the solvent and fractionation of the residue gave 24.8 g. (71%) of the enol ether (VI)²⁰; b.p. 76° (1.0 mm.); *n*²⁰_D 1.5030. The enol ether gave no derivative with the D.N.P. solution.

Diethyl 3-Carboxymethylene-Δ²-cyclohexenylacetate (VII).—Application of the Reformatsky reaction to 10 g. of the enol ether, using the same conditions as for the monoketal, gave 6.8 g. (37%) of a product, b.p. 110° (1 mm.), *n*¹⁷_D 1.5311, λ_{max} 298 mμ (log ε 4.44).

Anal. Calcd. for C₁₄H₂₀O₄: C, 66.64; H, 7.99. Found: C, 66.56; H, 8.16.

When the reaction was carried out with less bromoester a mixture of mono- and disubstituted products was obtained. From 9.5 g. of enol ether (VI) and 15 g. of ethyl bromoacetate there was obtained 6.8 g. of a product with a b.p. of 108–109° (1.0 mm.); *n*²⁴_D 1.5178; λ_{max} 233 mμ (log ε 3.86) and 298 mμ (log ε 4.32).

(20) Woods and Tucker⁵ prepared the enol ether by the action of ethyl iodide on the silver salt of 1,3-cyclohexanedione. The azeotropic method with *p*-toluenesulfonic acid as a catalyst has been used recently on substituted 1,3-cyclohexanediones by R. L. Frank and H. K. Hall, *ibid.*, **72**, 1645 (1950).

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(14) F. C. Whitmore and G. W. Pedlow, *ibid.*, **63**, 758 (1941).

(15) K. Dimroth and K. Resin, *Ber.*, **75B**, 322 (1942).

(16) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

(17) A. J. Birch, *ibid.*, 1270 (1947).

(18) M. Orchin, *THIS JOURNAL*, **66**, 535 (1944).

(19) H. Adkins and G. Rossow, *ibid.*, **71**, 3836 (1949).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

Mechanisms of Elimination Reactions. VI. The Kinetics of Dehydrochlorination of Various 2,2-Diarylchloroethanes^{1,2}

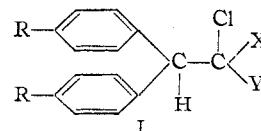
BY STANLEY J. CRISTOL, NORMAN L. HAUSE, ALFRED J. QUANT, HAROLD W. MILLER, KENDRICK R. EILAR AND JOHN S. MEEK

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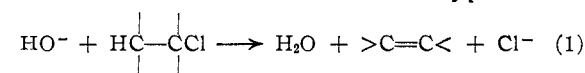
A study of the kinetics of dehydrochlorination of fourteen para substituted 2,2-diaryl-monochloro-, -dichloro- and -trichloroethanes with ethanolic sodium hydroxide at various temperatures has been conducted, and the energies and entropies of activation have been calculated. A discussion of the effects of increasing alpha chlorine substitution upon dehydrochlorination reactivities and upon the energies of activation is included.

No systematic study of the effects of adding halogen atoms to the α-carbon atom of alkyl halides in their second-order elimination of the elements of hydrogen halide with alkali seems to have been made. In the course of our work on elimination reactions, it seemed worthwhile to initiate such a study.

The compounds studied were of the type



where X and Y may be hydrogen or chlorine atoms, and the reactions studied were of the type



Some of the data desired have already been published,³ but this paper completes the work on these

(3) S. J. Cristol, *ibid.*, **67**, 1494 (1945).

(1) This work was supported by the Office of Naval Research and was presented in part before the Division of Organic Chemistry at the San Francisco Meeting of the American Chemical Society, March, 1949.

(2) Previous paper in series: S. J. Cristol and N. L. Hause, *THIS JOURNAL*, **74**, 2193 (1952).