[CONTRIBUTION NO. 2318 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Small-ring Compounds. XXI. 3-Methylenecyclobutanone and Related Compounds[1]

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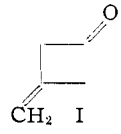
Experiments leading to the preparation of 3-methylenecyclobutanone are described. The desired substance was obtained only admixed with 3-methylcyclobutenone and this fact prevented evaluation of possible cross-ring π-type electronic interaction between the double bond and the carbonyl group.

Introduction

No definite evidence for cross-ring π-type electron interaction was found in a study of 1,3-dimethylenecyclobutane[2] although LCAO calculations suggest that such interaction might lead to a small but significant delocalization energy. Substitution of a more electronegative group isoelectronic with the methylene group for one of the methylene groups of 1,3-dimethylenecyclobutane would be expected to lead to a larger, and possibly more easily observable, cross-ring π-type interaction. To test this possibility, an attempt was made to synthesize 3-methylenecyclobutanone (I) since it would possess the desired structural features and appeared to be obtainable from intermediates already available.[2]



I

Synthesis of 3-Methylenecyclobutanone.—The synthesis of I started from 3-methylenecyclobutanecarboxylic acid[2,3] (II) and is outlined in Fig. 1. The dimethylamide III was prepared as described previously[2] and was converted to V in 70% yield by oxidation with sodium metaperiodate and a catalytic amount of osmic acid in a modification of the procedure of Johnson and Lemieux[4] for the oxidation of simple olefins. The keto-acid IV was also prepared by periodate oxidation in 70% yield and was converted into V in 22% yield by the action of thionyl chloride and dimethylamine. The ketals VI and VII were prepared in 69 and 98% yields, respectively, from III and the corresponding hydroxyl compounds in the presence of acidic catalysts. Reduction of the ketals to the amino compounds VIII and IX with lithium aluminum hydride proceeded smoothly in yields of 95 and 92%, respectively. The N-oxides X and XI were prepared by treatment of the corresponding amines with 10% hydrogen peroxide solution. Both N-oxides usually were obtained as sirups and on pyrolysis afforded the methylene ketals XII and XIII in 61 and 72% yields (based on VII and IX as starting materials), respectively.

It might appear that oxidation of the methylene group of any of several of the intermediates used in the preparation of 1,3-dimethylenecyclobutane[2] by reagents such as potassium permanganate, chromic acid and ozone would lead more directly to the desired product. Unfortunately, the three reagents named invariably led only to uncharacterizable products in poor yield.

Conversion of the ketals XII and XIII to I by acidic hydrolysis was fraught with difficulties. Several combinations of solvents and acid catalysts were used. Solvent mixtures with water-miscible organic components led to separation problems which were made more difficult in the case of XIII because of the production of ethanol as one of the products. Ketal exchange with acetone, which has been very successful for the liberation of steroidal ketones from their ketals,[5,6] gave unidentified condensation products. That compound I was indeed produced by acid hydrolysis of XIII was easily seen by following the course of the reaction with the aid of n.m.r. spectra. Figure 2 shows the changes with time of the n.m.r. spectrum of the organic phase of a heterogeneous, perchloric acid-catalyzed hydrolysis of XIII. The n.m.r. spectrum of pure XIII shows the same type of spin–spin splitting between the ring and vinyl hydrogens as observed with 1,3-dimethylenecyclobutane.[2] That this splitting was observed throughout the hydrolysis indicates that the exocyclic double bond did not rearrange into the ring to any great extent under these conditions. In preparative experiments, hydrolyses of XII and XIII were carried out as just described and were generally followed by the n.m.r. or infrared spectrum of the organic phase. When starting with XIII, separation of the ketonic products from water and ethanol proved troublesome and, although the ketonic products from XII were not contaminated with ethylene glycol, they did contain some water.

On the basis of the n.m.r. and infrared spectra (Figs. 2 and 3), the product was a mixture of ketones I and XIV along with a small amount of a hydroxylic compound in ratios which varied from preparation to preparation. Separation of the two ketones could not be effected and matters were not made easier by the fact that compound I rearranged quite rapidly to XIV at slightly above room temperature. The rearrangement could be followed by both infrared and ultraviolet spectroscopy. Because of the ease of rearrangement of I, distillations were carried out at reduced pressure below room temperature. The ultraviolet spectra of I and XIV are not reported in detail because of the uncertainty in the purity and composition

(1) Supported in part by the Petroleum Research Fund of the American Chemical Society. Grateful acknowledgment is hereby made to the Donors of this Fund.

(2) F. F. Caserio, Jr., S. H. Parker, R. Piccolini and J. D. Roberts, THIS JOURNAL, **80**, 5507 (1958).

(3) D. E. Applequist and J. D. Roberts, *ibid.*, **78**, 4012 (1956).

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(5) L. H. Sarett, *et al.*, THIS JOURNAL, **75**, 429 (1953).

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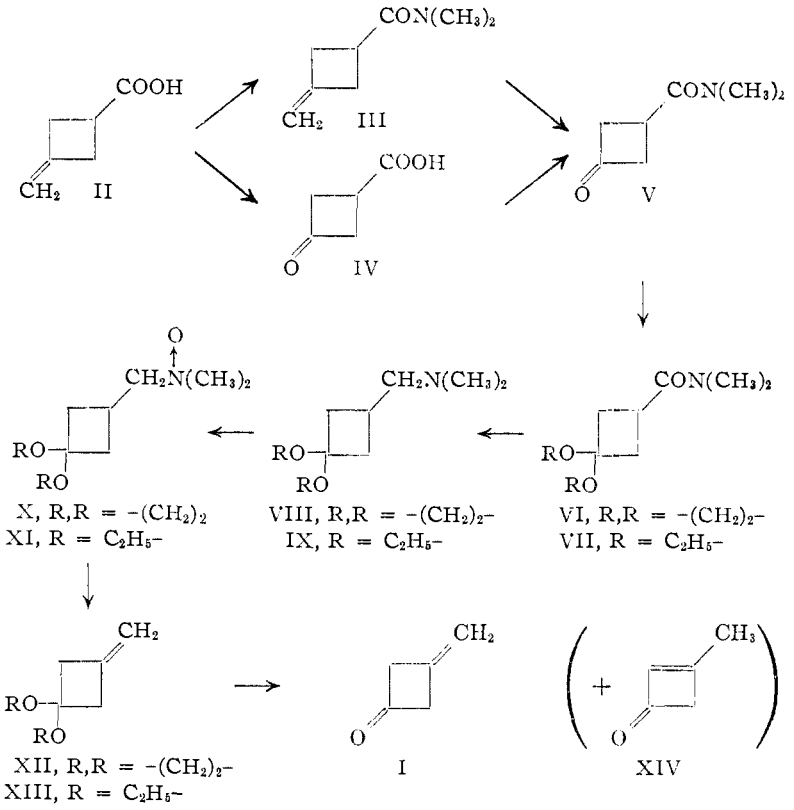

Fig. 1.—Synthesis of 1-methylenecyclobutanone.

of the material obtained. In ethanol, I appears to have a maximum at 214 mμ (ε *ca.* 1100–2000) and a very broad band at 285 ± 30 mμ (ε *ca.* 24) while XIV has a maximum at 225 mμ (ε *ca.* 7000–9000). One ketone mixture gave an impure, yellow 2,4-dinitrophenylhydrazone which had an ultraviolet spectrum similar to dinitrophenylhydrazones of known unconjugated derivatives.[7]

Hydrogenation of the mixture of I and XIV gave a single ketone XVI whose dinitrophenylhydrazone was identical with that obtained from 3-methylcyclobutanone prepared by hydrolysis of the ketal XV from catalytic hydrogenation of XIII.

The difficulty experienced in attempts to separate the ketones I and XIV from the ethanol in the hydrolysis of XIII suggested use of the cyclic ketal XII in place of XIII. This substitution actually introduced a more serious difficulty because XII hydrolyzed exceedingly slowly and the resulting I largely rearranged to XIV before even 25% of the cyclic ketal had hydrolyzed. The extent of rearrangement for the heterogeneous hydrolysis mixtures was determined with the aid of n.m.r. and infrared spectra taken on aliquots of the organic phase at various times. Qualitatively, the rates of hydrolysis for the ketals increased in the order XII < XIII < XV, 13 hours being required for about 36% hydrolysis of XII, about 10 hours for 50% hydrolysis of XIII and about 2 hours for complete hydrolysis of XV. The differences in the strain energies of the starting ketal and ketonic products might account for the observed rate sequence. It seems significant that the double bond of XIII provides no apparent driving force to enhance the hydrolysis of XIII.

(7) J. D. Roberts and C. Green, THIS JOURNAL, **68**, 214 (1946).

Experimental

3-Ketocyclobutanecarboxylic Acid (IV).—To a stirred, ice-cooled mixture of 300 ml. of ether, 300 ml. of water, 15 g. (0.134 mole) of II and 0.14 g. of osmic acid was added 60.5 g. (0.283 mole) of powdered sodium metaperiodate in small portions over 0.5 hr. The mixture became colorless after 5 hr. of stirring at room temperature and the solid phase increased considerably. The mixture was allowed to stir overnight and the ether layer was separated. The aqueous layer was filtered using suction and the filtrate was continuously extracted with ether for 18 hr. The filter cake was triturated with six 50-ml. portions of chloroform. The combined organic extracts were dried over a mixture of anhydrous magnesium sulfate and carbon black, filtered and concentrated using a 30-cm. Vigreux column. The concentrate was almost black and was treated with decolorizing carbon, filtered and the product allowed to crystallize. After two crystallizations from benzene–*n*-hexane there was obtained 10.7 g. (70%) of slightly yellow needles, m.p. 68–69°. Five recrystallizations from benzene–*n*-hexane gave colorless needles, m.p. 69–70°.

Anal. Calcd. for $C_5H_6O_3$: C, 52.64; H, 5.31. Found: C, 52.74; H, 5.17.

N,N-Dimethyl-3-ketocyclobutanecarboxamide (V). A. From N,N-Dimethyl-3-methylenecyclobutanecarboxamide (III).—Starting with 200 ml. of ether, 200 ml. of water, 31.3 g. (0.224 mole) of III, 142 mg. of osmic acid and 109 g. (0.508 mole) of sodium metaperiodate, the procedure for preparation of IV was followed except that the continuous ether extraction required about 3 days. In a subsequent preparation, chloroform proved to be a more efficient extraction solvent. The black concentrate was distilled at reduced pressure through a short Vigreux column and gave 21.9 g. (69%) of yellow product, b.p. 108–111° (1 mm.), $n^{25}D$ 1.4850. Repeated distillations at 1 mm. pressure resulted in a colorless product.

Anal. Calcd. for $C_7H_{11}O_2N$: C, 59.55; H, 7.86; N, 9.78. Found: C, 59.20; H, 7.79; N, 9.82.

B. From 3-Ketocyclobutanecarboxylic Acid (II).—A solution of 1.8 g. (0.016 mole) of II and 4 g. (0.033 mole) of thionyl chloride in 10 ml. of benzene was refluxed 0.5 hr. on a steam-bath and then evaporated to about 5 ml. To the ice-cooled solution was added slowly 4 g. (0.09 mole) of dimethylamine dissolved in 10 ml. of benzene. After the addition was completed, 100 ml. of ether was added and the precipitate of dimethylamine hydrochloride removed by filtration. The ether solution was concentrated using a 30-cm. Vigreux column and the dark-red residue was distilled three times through a micro apparatus giving 0.5 g. (23%) of product, b.p. 112–120° (1–2 mm.), $n^{22.2}D$ 1.4860. The infrared spectrum of this product was superimposable on that of the product by method A above.

N,N-Dimethyl-3-ketocyclobutanecarboxamide Ethylene Ketal (VI).—A solution of 20 g. (0.3 mole) of dry ethylene glycol, 4.0 g. (0.028 mole) of V, 4.2 g. (0.028 mole) of ethyl orthoformate and 0.1 g. of *p*-toluenesulfonic acid (monohydrate) was allowed to stand overnight at room temperature. The acid catalyst was neutralized by the addition of several small pellets of potassium hydroxide and the solution was diluted with 50 ml. of water. The aqueous solution was extracted with five 15-ml. portions of chloroform. The extracts were combined, dried momentarily over anhydrous magnesium sulfate, filtered and the solvent distilled from a steam-bath through a 30-cm. Vigreux column. The residue was distilled and gave 3.0 g. (61%) of product, b.p.

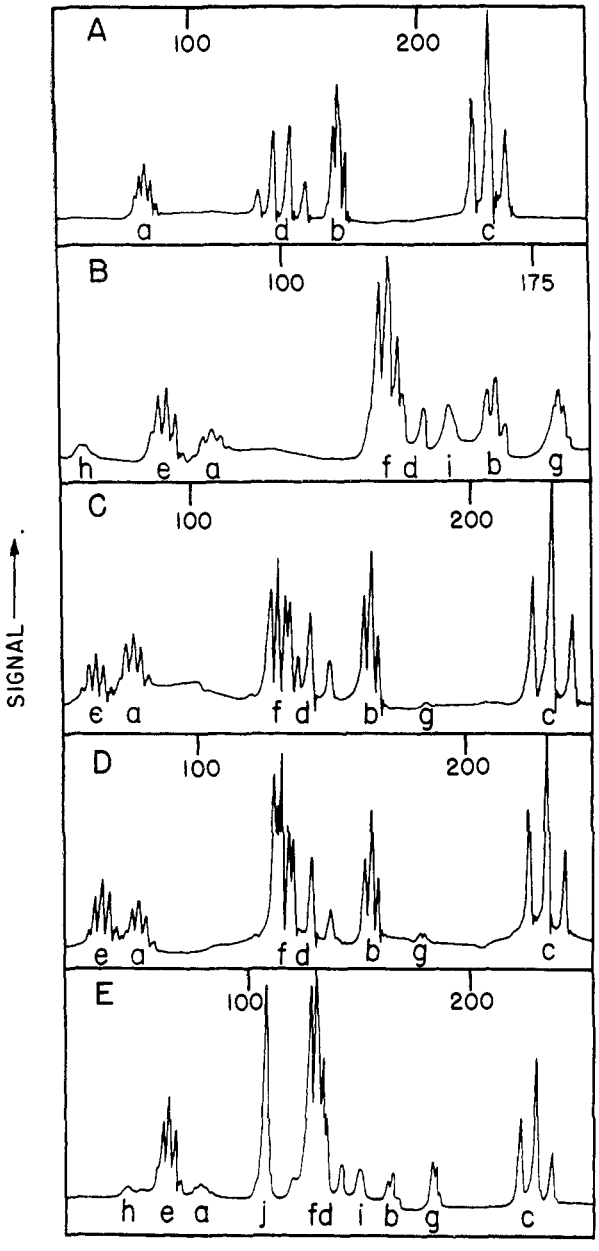

Fig. 2.—Proton nuclear magnetic resonance spectra at 40 mc. with tentative resonance assignments: A, 3-methylene-1,1-diethoxycyclobutane (III), pure liquid (a, vinyl protons; b, ring protons; c, β-C_2H_5 protons; d, α-C_2H_5 protons); B, mixture of XII with 3-methylenecyclobutanone (I) (e, vinyl protons; f, ring protons) and 3-methylcyclobutenone XIV (g, methyl protons; h, vinyl proton; i, ring methylene protons); note that the β-CH_2CH_3 protons of XIII are off scale to the right; C, non-aqueous layer from acidic hydrolysis of XIII, after 0.5 hr.; D, after 4 hr. (note appearance of some XIV); E, after 12 hr. (j, OH of water and/or C_2H_5OH).

114° (1 mm.). Subsequent preparations afforded yields of 64 and 69%. The analytical sample, $n^{25}D$ 1.4855, was purified by repeated simple distillation at 1 mm. pressure.

Anal. Calcd. for $C_9H_{15}O_3N$: C, 58.36; H, 8.16. Found: C, 58.42; H, 8.22.

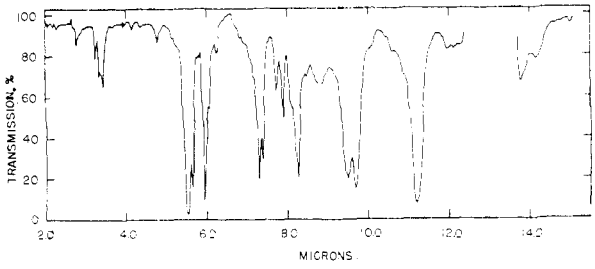

Fig. 3.—Infrared spectra of a mixture of I and XIV, carbon tetrachloride solution.

N,N-Dimethyl-3,3-diethoxycyclobutanecarboxamide (VII) was prepared from V in absolute ethanol by a manner similar to that for VI except that dry hydrogen chloride was used as catalyst and an excess of ethyl orthoformate was present. From 19.3 g. (0.137 mole) of V, 60 g. (0.41 mole) of ethyl orthoformate and 100 ml. of absolute ethanol there was obtained 27.2 g. (98%) of VII with b.p. 110° (1 mm.), $n^{25}D$ 1.4607.

Anal. Calcd. for $C_{11}H_{21}O_3N$: C, 61.36; H, 9.83; N, 6.50. Found: C, 61.10; H, 9.74; N, 6.55.

3-Ketocyclobutylcarbinyldimethylamine Ethylene Ketal (VIII).—To an ice-cooled, stirred solution of 5.4 g. (0.14 mole) of lithium aluminum hydride in 500 ml. of dry ether was added dropwise 12.0 g. (0.065 mole) of VI over about 0.5 hr. The mixture was stirred at room temperature for about 1 hr. and then was refluxed for 2 hr. The mixture was cooled in ice and the ethereal layer was removed. The residual solid was washed several times with ether. The combined ether solutions were partially evaporated on a steam-bath through a 30-cm. Vigreux column. The concentrate was centrifuged free of some suspended matter, further reduced in volume on a steam-bath and distilled under reduced pressure. The yield of VIII was 10.9 g. (98%), b.p. 90–92° (9 mm.), $n^{25}D$ 1.4555. Two other preparations gave yields of 92 and 95%. The analytical sample was purified by repeated vacuum distillation and had b.p. 91° (10 mm.), $n^{25}D$ 1.4550.

Anal. Calcd. for $C_9H_{17}O_2N$: C, 63.13; H, 10.01. Found: C, 63.08; H, 10.05.

3,3-Diethoxycyclobutylcarbinyldimethylamine (IX) was prepared by reduction of VI with lithium aluminum hydride in the same manner as described for VIII. The yields of IX were 86.5 and 92% in two preparations. The product had b.p. 51–54° (1 mm.) and $n^{25}D$ 1.4329.

Anal. Calcd. for $C_{11}H_{23}O_2N$: C, 65.60; H, 11.51. Found: C, 65.84; H, 11.56.

3-Ketocyclobutylcarbinyldimethylamine oxide ethylene ketal (X) was prepared from VIII and 10% hydrogen peroxide using a procedure described previously.[2] The N-oxide melted below 100° and generally was obtained as a viscous sirup.

The picrate was prepared in benzene and recrystallized from benzene–chloroform, m.p. 143.2–144 (uncor.).

Anal. Calcd. for $C_{15}H_{20}O_{10}N_4$: C, 43.27; H, 4.84. Found: C, 43.43; H, 4.84.

3,3-Diethoxycyclobutylcarbinyldimethylamine oxide (XI) was prepared as described for X. A crystalline picrate could not be formed nor was XI obtained in solid form. The sirup was decomposed without purification as described below.

3-Methylenecyclobutanone Ethylene Ketal (XII).—Decomposition of X was carried out by the procedure described previously[2] at a bath temperature of 225 ± 15°. The crude product was washed three times with 5-ml. portions of 1 *N* hydrochloric acid, twice with 5-ml. portions of 5% sodium carbonate solution and once with 5 ml. of saturated sodium chloride solution. Distillation gave 10.0 g. (61%) of XII, b.p. 91–92.5° (100 mm.). The analytical sample was purified by repeated vacuum distillation and had $n^{25}D$ 1.4597.

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.59; H, 7.95.

3-Methylene-1,1-diethoxycyclobutane (XIII).—The procedure described for the preparation of XII was followed with

XI and resulted in a 72% yield of XIII, b.p. 84–85° (50 mm.), $n^{25}D$ 1.4310.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 69.24; H, 10.30.

Acid Hydrolysis of 3-Methylenecyclobutanone Ethylene Ketal.—A heterogeneous mixture of 3.6 g. (0.018 mole) of XII and 5 ml. of 0.24 *M* perchloric acid solution was shaken mechanically for 13 hours at room temperature. The hydrolysis was followed by infrared spectroscopy using small aliquots of the organic phase and, after 13 hours, the line at 1770 cm.$^{-1}$ assigned to the conjugated ketone XIV was found to be increasing in intensity faster than the line at 1807 cm.$^{-1}$ assigned to I. The spectra indicated that the hydrolysis was far from complete. The purple organic layer was separated. The aqueous phase was saturated with sodium chloride and extracted with three 15-ml. portions of methylene chloride. The organic phases were combined and dried over anhydrous magnesium sulfate overnight in a refrigerator. The drying agent was removed by filtration and the now orange solution was fractionated under reduced pressure using an efficient concentric-tube column to remove the solvent, b.p. −3° (100 mm.). The residue was transferred to a micro concentric-tube column and was fractionated at reduced pressure. Two fractions were obtained of about 0.1 ml. each, b.p. 20° (10 mm.), both of which were mixtures of I, XIV and a hydroxylic component (presumably water) with I predominating as shown by the infrared spectra. A total of 2.3 g. (64%) of starting material was recovered by short-path reduced-pressure distillation.

In another experiment with 0.1 g. of XII and 1 ml. of acid solution, the mixture gave a 2,4-dinitrophenylhydrazone derivative which was very difficult to recrystallize, but after three recrystallizations from a benzene–hexane mixture was yellow and had m.p. 138–140°.

Anal. Calcd. for $C_{11}H_{10}O_4N_4$: C, 50.38; H, 3.84. Found: C, 51.41; H, 4.02.

Attempts to repeat this preparation were unsuccessful.

Acid Hydrolysis of 3-Methylene-1,1-diethoxycyclobutane (XIII).—A mixture of 1.0 g. (0.0064 mole) of XIII and 1.5 g. (0.064 mole of water) of 0.11 *M* perchloric acid was shaken mechanically for about 12 hr. at which time the n.m.r. spectrum of the organic phase indicated that about 50% of the starting material had hydrolyzed. The mixture was saturated with sodium chloride and the top yellow layer was removed and fractionated at 10 mm. using a semi-micro concentric-tube column. About 0.4 ml. of distillate was obtained which from its infrared, ultraviolet and n.m.r. spectra appeared to contain about 50% ethanol. The product gave a **2,4-dinitrophenylhydrazone**, m.p. 82–85°, which consisted of red and orange particles. Five recrystallizations from *n*-hexane yielded about 9 mg. of yellow needles, m.p. 116.4–116.8°.

Anal. Calcd. for $C_{11}H_{10}O_4N_4$: C, 50.38; H, 3.84. Found: C, 50.03; H, 4.47.

3-Methylcyclobutanone (XVI). A. From 1-Methylene-3,3-diethoxycyclobutane (XIII).—A solution of 2.5 g. of XIII in 20 ml. of absolute ethanol was hydrogenated over 0.1 g. of platinum dioxide in a low-pressure apparatus. The catalyst was centrifuged and the ethanol was mostly distilled at atmospheric pressure through a 30-cm. spiral-wire packed column. The concentrated residue containing XV was shaken mechanically with 4 ml. of 0.15 *M* perchloric acid. Hydrolysis was complete in 2 hr. and the resulting homogeneous solution was saturated with sodium chloride and extracted with three 5-ml. portions of ether. The combined extracts were dried over anhydrous magnesium sulfate and the ether removed by fractionational distillation through a 30-cm. spiral-wire packed column. The residue was distilled at atmospheric pressure through a micro distillation apparatus and yielded four fractions of which only the last two, about 0.2 g., b.p. *ca.* 110°, were free from ether although still apparently contaminated with ethanol and water. The crude product gave a **2,4-dinitrophenylhydrazone** which was recrystallized five times from *n*-hexane and gave orange needles of m.p. 108.5–109.5° (uncor.).

Anal. Calcd. for $C_{11}H_{12}O_4N_4$: C, 50.00; H, 4.58. Found: C, 50.06; H, 4.68.

In a second preparation from XIII, the hydrogenation was performed in the absence of solvent. The small amount of ethanol encountered as a by-product was removed by fractionation through a micro concentric-tube column. About a 50% yield of XVI was obtained; b.p. 112–113° (atm.), 71.5–72° (200 mm.) and $n^{25}D$ 1.4140. The ultraviolet spectrum had λ_{max} 280.5 mμ (ε 15.2 in 95% ethanol).

Anal. Calcd. for C_5H_8O: C, 71.39; H, 9.58. Found: C, 71.19; H, 9.72.

B. From the 3-Methylenecyclobutanone (I)–3-Methylcyclobutanone (XIV) Mixture.—The first fraction of the ketonic mixture obtained from the acid hydrolysis of XII described above was dissolved in 1 ml. of 95% ethanol and was hydrogenated over platinum dioxide at low pressure. After removal of the catalyst by centrifugation, the solution was treated with aqueous 2,4-dinitrophenylhydrazine reagent and afforded 0.1 g. of a solid with m.p. 108–109°, after 3 recrystallizations from *n*-hexane. The m.p. was not depressed on admixture with the derivative obtained from procedure A above.

PASADENA, CALIF.

[CONTRIBUTION NO. 2350 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Small Ring Compounds. XXII. Ring Opening of Halogenated 3-Phenylcyclobutenones in Acetic Acid and Aqueous Sodium Hydroxide[1a]

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Ring-opening reactions of a number of halogen-substituted 3-phenylcyclobutenones in acetic acid and in aqueous sodium hydroxide have been investigated and the resulting carboxylic acids identified. The course of reaction in acetic acid can be rationalized by a mechanism involving vinylketene intermediates. The base-induced ring-opening reaction appears to follow a course dependent on the number and location of the halogen atoms but is generally similar to the haloform reaction.

In earlier work,[2,3] alkali-induced ring-opening reactions of two chlorine-substituted 3-phenylcyclobutenones were studied as an aid to the structure proof of the starting materials. It was found that 2,4-dichloro-3-phenylcyclobutenone (I) and 2,2-dichloro-3-phenylcyclobutenone (II) react with aqueous sodium hydroxide to yield 2,4-dichloro-3-phenyl-3-butenoic acid (III) and 4,4-dichloro-3-phenyl-2-butenoic acid (IV), respectively.

It was suggested[2] that these base-induced ring-openings proceed by a mechanism resembling that of the cleavage step of the haloform reaction,[4] although no explanation was presented for the ex-

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(4) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 295.