[Contribution from the Chemistry Laboratory of the University of Michigan]

Reactions of Propiolic Esters. I. Addition to the Carbonyl Group of Ketones in the Presence of Sodamide

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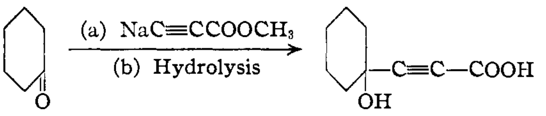
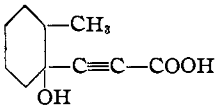
The addition of monosodium acetylide to the carbonyl group of aldehydes and ketones to form acetylenic carbinols is a well-known reaction. However, not a single example of the addition of the sodio derivative of propiolic esters, NaC≡C—COOR, to a carbonyl group has been reported. Such a reaction would prove valuable for introducing a three-carbon acid side chain at the site of a carbonyl group. Methods are available for introducing two-carbon and four-carbon acid chains by the Reformatsky reaction utilizing esters of α-bromo acids and of γ-bromocrotonic acid, respectively, but only a few instances have been reported in which a β-bromopropionic ester was employed. In the present paper we are reporting the successful addition of the sodio derivative of propiolic esters to the carbonyl group of three cyclic ketones: cyclohexanone, 2-methylcyclohexanone and 2-methyl-2-carbomethoxycyclohexanone.

The reaction with cyclohexanone was carried out by adding a solution of the ketone and methyl propiolate in ether to a suspension of sodamide in liquid ammonia. Saponification of the product yielded the known 1-hydroxycyclohexanepropiolic acid (I). In a similar manner 2-methylcyclohexanone gave crystalline 1-hydroxy-2-methylcyclohexanepropiolic acid and considerable uncrystallizable material which contained the same acid. Catalytic reduction of the acetylenic acid gave the lactone of 1-hydroxy-2-methylcyclohexanepropionic acid (III); the same lactone was obtained by catalytic reduction of the non-crystalline acidic material. The lactone reacted slowly with aqueous ammonia to form the amide (IV), which was identical with the product obtained by reduction of the amide of the propiolic acid. By opening the lactone ring with hot sodium hydroxide and treating the liberated acid immediately with diazomethane, the methyl ester of 1-hydroxy-2-methylcyclohexanepropionic acid (V) was prepared. The ester was converted by dehydration and hydrolysis to a mixture of unsaturated acids. The unsaturated acid was dehydrogenated by sulfur to the known *o*-methylhydrocinnamic acid, which was cyclized to 4-methyl-1-hydrindone. In view of the conversion of 2-methylcyclohexenepropionic acid into *cis*-8-methylhydrindanone[2] and 9-methyldecalone,[3] the present work provides a new route to these bicyclic ketones.





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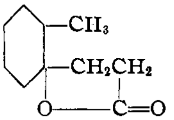

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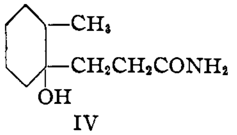

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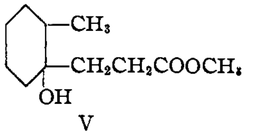
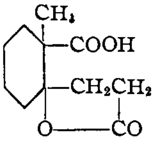


V

The substituted propiolic ester formed from the reaction of 2-methyl-2-carboethoxycyclohexanone with the sodio derivative of ethyl propiolate was reduced catalytically and the saturated hydroxy ester was hydrolyzed. From the product the crystalline lactone acid (VI) could be isolated. The hydroxydicarboxylic acid which was produced by opening of the lactone ring in alkali reverted to the lactone acid during the process of isolation. However, the dimethyl ester (VII) of the hydroxy acid could be obtained by hydrolyzing the lactone ester with one equivalent of sodium hydroxide and treating the liberated ester acid immediately with diazomethane. The diester was dehydrated and hydrolyzed to a mixture of crystalline unsaturated acids, presumably 2-methyl-2-carboxycyclohexenepropionic acid (VIII) and its isomer, from which one of them was isolated in a pure form. Catalytic reduction of the mixture of unsaturated acids gave the known *cis* 2-methyl-2-carboxycyclohexanepropionic acid (IX); none of the *trans* form was found. Pyrolysis of a mixture of lead carbonate and the dicarboxylic acid yielded *cis* 8-methylhydrindanone.



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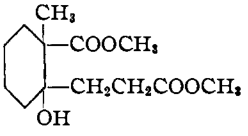

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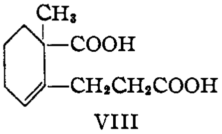
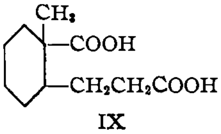


VIII



IX

Other cyclic ketones, 1-tetralone and 1-keto-

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[1] From the Ph.D. dissertation of E. K. Raunio, 1949. Present address: University of Idaho, Moscow, Idaho.

[2] Chuang, Tien and Ma, *Ber.*, **69**, 1494 (1936); Nenitzescu and Przemetsky, *ibid.*, **74**, 676 (1941).

[3] (a) Cook and Lawrence, *J. Chem. Soc.*, 1637 (1935); (b) Plentl and Bogert, *J. Org. Chem.*, **6**, 669 (1941).

1,2,3,4-tetrahydrophenanthrene, were found to undergo a Michael reaction with ethyl propiolate instead of addition to the carbonyl group. The results of these experiments will be described in a subsequent paper.

Experimental

Reaction with Cyclohexanone.—A solution of 5 g. (0.051 mole) of cyclohexanone and 4.7 g. (0.056 mole) of methyl propiolate in 20 ml. of anhydrous ether was added to a suspension of sodamide, freshly prepared from 1.3 g. of sodium and 100 ml. of liquid ammonia.[4] It was found that a less colored product was formed if a brisk stream of gaseous ammonia was passed through the sodamide suspension during the addition of the reactants. After the ammonia had evaporated (finally with the aid of a water-bath), the mixture was treated with crushed ice and 25 ml. of 5 *N* sulfuric acid, and the aqueous layer was extracted with three 30-ml. portions of ether. The combined ethereal solutions after being washed with water were extracted with 20% potassium carbonate, from which 2.56 g. of acidic product was isolated. The neutral product when refluxed with 10 ml. of 20% potassium hydroxide for ten minutes yielded 3.68 g. of acidic product. The combined acidic product when triturated with a mixture of ether and petroleum ether gave 2.44 g. of crystals. The 1-hydroxycyclohexanepropiolic acid crystallized from benzene–ethyl acetate in colorless needles; m. p. 126–127° cor. (reported,[5] 125°).

The methyl ester, prepared from the acid and diazomethane, reacted rapidly when shaken with concentrated aqueous ammonia and gave the amide; m. p. 156–157° after one recrystallization from water (reported, 157° for the amide of 1-hydroxycyclohexanepropiolic acid).

Reaction with 2-Methylcyclohexanone.—The ketone was prepared by addition of a solution of 162 g. of potassium dichromate and 140 ml. of concentrated sulfuric acid in 1 liter of water to a stirred mixture of 171 g. of 2-methylcyclohexanol (Eastman Kodak Co.) and 200 ml. of water at such a rate that the temperature remained at 35–40°; an ice-bath was used to cool the reaction mixture during the addition. After the mixture had been stirred at room temperature for two hours, the 2-methyclyclohexanone was isolated; yield, 119 g.; b. p. 55–65° at 8 mm.; $n^{25}{}_{\text{D}}$ 1.4447. The product gave the same results in the next step as the ketone (b. p. 163–166°, $n^{25}{}_{\text{D}}$ 1.4437) which was regenerated by heating its semicarbazone with *N* sulfuric acid on a steam-bath for four hours.

The reaction of 25 g. of 2-methylcyclohexanone with 20.7 g. of methyl propiolate and sodamide prepared from 5.7 g. of sodium was carried out as described for cyclohexanone. A solution of the combined acidic material (31.7 g.) in 15 ml. of benzene deposited fine colorless needles (7.1 g.) of the product immediately; petroleum ether helped to precipitate more solid. After several recrystallizations from benzene a sample of the **1-hydroxy-2-methylcyclohexanepropiolic acid** (II) melted at 135–135.5°. The analytical sample was sublimed at 90–100° and 0.1 mm. The acid reduced aqueous potassium permanganate.

Anal. Calcd. for $C_{10}H_{14}O_3$: C, 65.9; H, 7.7. Found: C, 66.1; H, 7.8.

The liquid methyl ester, prepared from II and diazomethane, reacted rapidly with concentrated aqueous ammonia. After a few minutes the **amide of 1-hydroxy-2-methylcyclohexanepropiolic acid** was extracted with ether. It crystallized from benzene–petroleum ether in thin colorless plates; m. p. 142.5–144°. It sublimed unchanged at 90–100° and 0.1 mm.

Anal. Calcd. for $C_{10}H_{15}O_2N$: C, 66.3; H, 8.3; N, 7.7. Found: C, 66.1; H, 8.2; N, 7.6.

Reduction of the Substituted Propiolic Acid.—A solution of 1 g. of the crystalline 1-hydroxy-2-methylcyclohexanepropiolic acid in 10 ml. of 95% ethanol was shaken with 50 mg. of Adams catalyst under 40 pounds pressure of hydrogen for ten minutes. The filtered solution did not reduce 1% aqueous permanganate. Evaporation of the solvent under reduced pressure on a steam-bath left a colorless liquid, undoubtedly the lactone of 1-hydroxy-2-methylcyclohexanepropionic acid (III), which was insoluble in cold 5% aqueous sodium hydroxide but reacted when heated to give the sodium salt of the acid.

The same lactone was obtained from the non-crystalline acidic product left after removal of solid II. A solution of 24.6 g. of the liquid acid in 60 ml. of acetic acid was shaken with 0.5 g. of 10% palladium on carbon under 40 pounds pressure of hydrogen. More catalyst was added each time the absorption stopped until 0.38 g. of hydrogen was absorbed. The isolated product, after being warmed on a steam-bath to ensure complete lactonization, was dissolved in ether and the solution was washed with 20% aqueous potassium carbonate. The lactone (14 g.) remaining in the ether was obtained as a colorless liquid by distillation at 148–152° and 11 mm.

A sample of the lactone was gradually converted into the crystalline amide when allowed to stand with concentrated aqueous ammonia at room temperature for two weeks. The amide (m. p. 171–174°) was identical with the amide formed by catalytic reduction at atmospheric pressure of the amide of the substituted propiolic acid in ethanol with Adams' catalyst. The **amide of 1-hydroxy-2-methylcyclohexanepropionic acid** (IV), crystallized from benzene–petroleum ether in thin colorless plates; m. p. 174–176°.

Anal. Calcd. for $C_{10}H_{19}O_2N$: C, 64.9; H, 10.3; N, 7.6. Found: C, 65.0; H, 10.4; N, 7.4.

2-Methylcyclohexenepropionic Acid.—A mixture of 4.7 g. of the lactone (III) and 30.9 ml. of *N* sodium hydroxide was warmed until a clear solution resulted. Ice (10 g.) and 25 ml. of ether were added to the cooled solution and then 30.8 ml. of *N* sulfuric acid. The mixture was shaken vigorously to transfer the liberated hydroxy acid into the ether, and the solution was immediately treated with an excess of ethereal diazomethane. The isolated colorless viscous liquid, presumably methyl 1-hydroxy-2-methylcyclohexanepropionate, was added to a solution of 15 ml. of thionyl chloride and 7.5 ml. of pyridine in 40 ml. of anhydrous ether at 0°. After one-half hour at this temperature and one-half hour at room temperature the mixture was poured onto ice. Evaporation of the ethereal extracts of the product, after washing with dilute alkali and with water, gave the ester of the unsaturated acid (or acids) (4.4 g.) as a liquid with a fruity odor and less viscous than the lactone or the hydroxy ester. The product reduced aqueous permanganate readily.

A sample of the product, mixed with concentrated aqueous ammonia, changed to an oily solid after two weeks. After recrystallization from a mixture of benzene and petroleum ether the product, presumably a mixture of the amides of isomeric unsaturated acids, melted at 90–118°. By repeated recrystallizations thin colorless plates with m. p. 135–137° were obtained. Plentl and Bogert[3b] report 135° for the **amide of 2-methylcyclohexenepropionic acid** prepared by another method.

Anal. Calcd. for $C_{10}H_{17}NO$: C, 71.8; H, 10.2; N, 8.4. Found: C, 71.9; H, 10.6; N, 8.2.

Hydrolysis of 3.8 g. of the unsaturated ester in 30 ml. of ethanol by refluxing with 15 ml. of 50% aqueous sodium hydroxide for twelve hours gave 3.4 g. of the unsaturated acid as a liquid. A mixture of 2.5 g. of the unsaturated acid and 0.5 g. of sulfur was heated under nitrogen at 220° for forty-five minutes. The product, after purification through its sodium salt, was evaporatively distilled at 15 mm. The distillate crystallized from petroleum ether in fine colorless needles; yield, 1.03 g.; m. p. 103–108°. It was identical with the acid prepared by catalytic reduction of *o*-methylcinnamic acid (4.76 g.) obtained by heating a mixture of 4 g. of *o*-tolualdehyde, 4 g. of malonic acid and 0.6 ml. of pyridine on a steam-bath for two hours and recrystallizing the acid (m. p. 177–182°) from ethanol. The *o*-methylhydrocinnamic acid after recrystallization

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[4] Nieuwland, Vaughn and Vogt, This Journal, **56**, 2120 (1934).

[5] Haynes and Jones, *J. Chem. Soc.*, 503 (1946).

melted at 106–108° (reported,[6] 102°). Cyclization of a sample of the *o*-methylhydrocinnamic acid, prepared by dehydrogenation, by means of hot sulfuric acid gave 4-methylhydrindone; m. p. 98–101° (reported, 95°, 101–102°[6]).

Reaction with 2-Methyl-2-carboethoxycyclohexanone.—Methylation of 2-carboethoxycyclohexanone was carried out according to the procedure of Chuang, Tien and Huang[7] with the modification suggested by Bachmann and Kushner.[8] From the addition of a solution of sodium methoxide from 28.3 g. of sodium and 250 ml. of methanol to 195 g. of 2-carboethoxycyclohexanone[9] and 94 ml. of methyl iodide 200 g. (93%) of 2-methyl-2-carboethoxycyclohexanone with b. p. 100–104° at 9 mm. was obtained.

The reaction mixture from 11.4 g. of 2-methyl-2-carboethoxycyclohexanone, 6.19 g. of ethyl propiolate and the sodamide from 1.6 g. of sodium, after evaporation of the ammonia, was shaken with iced dilute sulfuric acid and extracted with ether. Evporation of the ethereal solution, after being washed with 20% aqueous potassium carbonate and water, gave 14.95 g. of a viscous liquid, which reduced aqueous permanganate, rapidly decolorized a solution of bromine in carbon tetrachloride, and did not react with 2,4-dinitrophenylhydrazine.

A solution of 13 g. of the product in 50 ml. of acetic acid, shaken with 0.5 g. of Adams catalyst under 40 pounds pressure, absorbed 0.22 g. of hydrogen during fifteen hours. The product, after the removal of the solvent, was refluxed with 50 ml. of 20% potassium hydroxide for fifteen minutes and the mixture was diluted with water and extracted with ether to remove a small amount of neutral material. The acid obtained on acidification was extracted into ether and the solvent was removed on a steam-bath. Since the product was not completely soluble in cold 5% sodium hydroxide, it was dissolved in ether and the ether solution was extracted with 20% aqueous potassium carbonate. The liquid acid (8.07 g.) which was isolated from the alkaline solution was fractionated, and the fraction (3.73 g.) with b. p. 200–212° at 0.5 mm. was dissolved in an equal volume of ether and kept cool. From the solution 1.8 g. of the colorless **lactone of 1-hydroxy-2-methyl-2-carboxycyclohexanepropionic acid** (VI) (m. p. 139–144°) crystallized; neutral equivalent, 210 (calculated, 212); saponification equivalent, 105 (calculated, 106). After several recrystallizations from ethanol the lactone acid formed colorless prisms; m. p. 147–149°. It sublimed unchanged at 120–130° and 0.1 mm. If the crude product is colored, it can be decolorized by Norit in hot water; from the solution the lactone acid crystallizes in colorless rhombs. The lactone acid did not decolorize aqueous permanganate.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.2; H, 7.6. Found: C, 62.2; H, 7.7.

A solution of 0.5 g. of the crystalline lactone acid in 5 ml. of 35% aqueous potassium hydroxide was refluxed for forty minutes. The cooled solution was diluted, acidified and extracted with ether. Removal of the ether left a colorless liquid which crystallized immediately and completely when scratched. The product did not depress the m. p. of the original lactone acid.

Conversion of the Lactone Acid (VI) into *cis* 2-Methyl-2-carboxycyclohexanepropionic Acid (IX).—The liquid lactone of 1-hydroxy-2-methyl-2-carbomethoxycyclohexanepropionic acid, prepared from 3.06 g. of the lactone acid and diazomethane, was warmed with 17.5 ml. of *N* sodium hydroxide until solution was complete. The iced solution was shaken with 25 ml. of ether and 17.5 ml. of *N* sulfuric acid, and the ether solution was quickly treated with diazomethane. The product (3.55 g.), undoubtedly methyl 1-hydroxy-2-methyl-2-carbomethoxycyclohexanepropionate, a colorless viscous liquid, was dehydrated with 10 ml. of thionyl chloride and 5 ml. of pyridine in 20 ml. of ether at 0° (one hour); a copious colorless precipitate (probably pyridine hydrochloride) formed. The product, a mobile liquid which instantly decolorized aqueous permanganate, was refluxed with 10 ml. of 35% potassium hydroxide for two hours. The resulting unsaturated dicarboxylic acid or mixture of acids, isolated by means of ether, crystallized when triturated with a little benzene; yield, 2.43 g.; m. p. 134–146°; neutral equivalent, 109 (calculated 106). After repeated recrystallizations from ethanol a sample of **2-methyl-2-carboxycyclohexenepropionic acid** (VIII) or its isomer, melted at 154–158°; it sublimed unchanged at 120–130° and 0.1 mm. The acid rapidly decolorized aqueous permanganate. A mixture of the acid and the isomeric lactone acid melted below 116°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.2; H, 7.6. Found: C, 62.1; H, 7.6.

A solution of 2 g. of the unsaturated dicarboxylic acid (m. p. 134–146°) in 15 ml. of acetic acid was shaken with 0.1 g. of Adams catalyst under 50 pounds pressure of hydrogen for twelve hours. The colorless liquid after being seeded crystallized completely in the course of twelve hours; m. p. 102–110°. After several recrystallizations from benzene–petroleum ether a sample of the *cis*-2-methyl-2-carboxycyclohexanepropionic acid melted at 109–111.5° alone and when mixed with an authentic specimen prepared by hydrolysis of the dimethyl ester of Bachmann and Kushner.[8]

Pyrolysis of a mixture of 0.5 g. of the unrecrystallized acid (m. p. 102–110°) and an equal volume of basic lead carbonate at 290–300° at 15 mm. until distillation ceased (about one and one-half hours) gave a pale-yellow distillate with a camphoraceous odor which solidified. The semicarbazone (0.35 g.) melted at 221–225°, alone and when mixed with an authentic specimen of the semicarbazone of *cis*-8-methylhydrindanone.

When 9.4 g. of the crude condensation product from ethyl propiolate and 2-methyl-2-carboethoxycyclohexanone was catalytically reduced and the product (8.8 g.) was dehydrated with thionyl chloride and pyridine and saponified and again reduced, 6.5 g. of acid was obtained, from 1 g. of which 0.22 g. of the semicarbazone of *cis*-8-methylhydrindanone was obtained after cyclization.

Summary

The addition of ethyl propiolate in the presence of sodamide to the carbonyl group of cyclohexanone, 2-methylcyclohexanone, and of 2-methyl-2-carboethoxycyclohexanone to form acetylenic hydroxy esters is described. The reaction offers a method of introducing a three-carbon acid side chain at the site of a carbonyl group in certain ketones.

The application of the reactions to the synthesis of bicyclic ketones is indicated or demonstrated.

ANN ARBOR, MICHIGAN RECEIVED DECEMBER 5, 1949

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[6] Young, *Ber.*, **25**, 2102 (1892); Chakravarti, *J. Indian Chem. Soc.*, **20**, 393 (1942), *Chem. Abs.*, **39**, 516 (1945).

[7] Chuang, Tien and Huang, *Ber.*, **68**, 866 (1935).

[8] Bachmann and Kushner, THIS JOURNAL, **65**, 1963 (1943).

[9] Snyder, Brooks and Shapiro, "Org. Syntheses," Coll. Vol. II, 531 (1943).