

Anal. Calcd. for $C_{18}H_{18}O_3N_2S$: N, 8.24; S, 9.41.
Found: N, 8.00, 8.17; S, 9.36, 9.69.

Summary

1. Diethyl oxalo-phenoxyacetate, the hitherto uncharacterized intermediate in the Koelsch-Whitney synthesis of coumarone-2,3-dicarboxylic acid, has been isolated, purified and characterized.

2. Cleavage of this ester at the unsaturated

linkage of its enolic form has been shown to occur under various conditions.

3. The analogous diethyl oxalo-(S-phenylmercapto)-acetate is so sensitive to this type of cleavage and also loses carbon monoxide so readily that extension of the Koelsch-Whitney method to the preparation of thianaphthene-2,3-dicarboxylic acid derivatives is impracticable.

CAMBRIDGE, MASSACHUSETTS RECEIVED APRIL 8, 1948

[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Substitution Products of 5-Cyclopentyl-5-oxopentanoic Acid and 6-Cyclohexyl-6-oxohexanoic Acid¹

BY J. ENGLISH, JR., G. W. BARBER AND L. J. LAPIDES²

In the course of an investigation of methods applicable to the synthesis of compounds related in structure to those proposed by Kögl³ for the plant growth hormones, auxin-a and auxin-b, we have had occasion to prepare and examine the two analogous hydroxy keto lactones, 5-(1-hydroxycyclopentyl)-5-oxo-4-hydroxypentanoic acid γ -lactone and 6-(1-hydroxycyclohexyl)-6-oxo-5-hydroxyhexanoic acid δ -lactone (XIV and XV, Fig. 1). As starting materials, 5-cyclopentyl-5-oxopentanoic acid and 6-cyclohexyl-6-oxohexanoic acid were utilized. These acids were first prepared by Wallach by hydrogenation and subsequent oxidation of cyclopentylidenecyclopentanone⁴ and cyclohexenylcyclohexanone,⁵ respectively. We have prepared these same keto acids also by an aluminum chloride condensation, as indicated in Fig. 1, obtaining products identical with those prepared by Wallach's method. The older method, however, is shorter and gives better yields. An analogous keto acid, 5-cyclohexyl-5-oxopentanoic acid, has also been synthesized by the aluminum chloride condensation, but has not been investigated further.

The keto acids, VII and X, reacted rapidly at room temperature with two moles of bromine, yielding in each case a crystalline dibromo keto acid which was readily hydrolyzed by dilute aqueous sodium hydroxide. The hydrolysis products were, respectively, the lactone, 5-(1-hydroxycyclopentyl)-5-oxo-4-hydroxypentanoic acid γ -lactone (XIV), and the acid, 6-(1-hydroxycyclohexyl)-6-oxo-5-hydroxyhexanoic acid (XIII). The latter was readily converted to a corresponding lactone (XV) by refluxing in benzene with a trace of iodine. The following considerations serve to establish the structures of these two lactones.

Bromination of keto acids of this type is to be

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(3) Kögl and Erzleben, *Z. physiol. Chem.*, **235**, 181 (1935).

(4) Wallach, *Ann.*, **329**, 180 (1912).

(5) Wallach, *ibid.*, **321**, 95 (1911).

expected only in the positions adjacent to the keto or carboxyl groups, and bromine atoms in these positions would be expected to be readily removed by hydrolysis. The two dibromo keto acids, XI and XII, in fact rapidly consumed three moles of alkali when titrated in hot 50% alcohol with dilute sodium hydroxide. A fleeting end-point corresponding to the consumption of one equivalent of alkali was observed in a cold solution with XII, but not with XI. The hydrolysis products, XIII, XIV and XV, readily reduced Fehling solution when heated, a behavior characteristic of α -ketols. None of the three compounds gave with ferric chloride the positive color test expected of an alpha hydroxy acid,⁶ and a quantitative analysis for this group⁷ confirmed the absence in any of the three compounds of an hydroxyl adjacent to a carboxyl group. This conclusion is further verified by the results of periodic acid titration of XIII, XIV and XV.

In a periodic acid titration⁸ of the dihydroxy keto acid (XIII), two moles of periodate was consumed in eighteen hours at room temperature. On titration of the lactones XIV and XV, however, only one mole of periodate was consumed in twenty-four hours, and three days were required to consume a second mole. When the lactones were first converted to the sodium salts and titrated with periodic acid, two moles of periodate were consumed in twenty-four hours. The lactone rings in XIV and XV are therefore fairly stable to periodic acid (0.2 *N*). Treatment of XIV and XV with slightly less than one equivalent of periodic acid gave, on steam distillation, cyclopentanone and cyclohexanone, respectively, which were identified as the 2,4-dinitrophenylhydrazones.

Experimental⁹

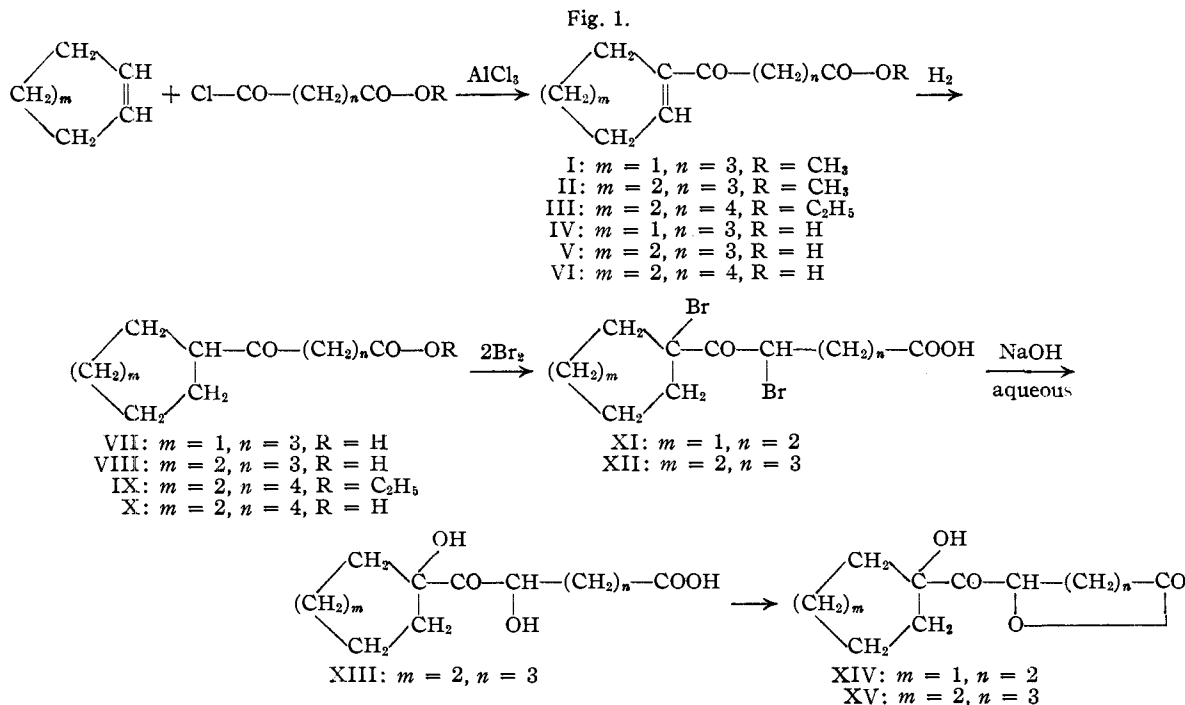
Acid Chlorides of Methyl Hydrogen Glutarate and Ethyl Hydrogen Adipate.—Methyl hydrogen glutarate was prepared from glutaric anhydride and methanol in a

(6) Berg, *Bull. soc. chim.*, [3] **11**, 883 (1894).

(7) Mitchell, *et al.*, *THIS JOURNAL*, **62**, 1776 (1940).

(8) E. L. Jackson, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 361.

(9) All melting points have been corrected.



manner similar to the preparation of methyl hydrogen succinate.¹⁰ Ethyl hydrogen adipate was prepared according to "Organic Syntheses."¹¹ The mono esters were heated on the steam-bath with a 20% excess of thionyl chloride until there was no further evolution of hydrogen chloride. On vacuum distillation, the acid chlorides were obtained in 90–95% yields: γ -carbomethoxybutyryl chloride, b. p. 108–110 (17 mm.), n_D^{25} 1.4438; δ -carbomethoxyvaleryl chloride, b. p. 90–91° (3 mm.).

5-(Δ^1 -Cyclopentenyl)-5-oxopentanoic Acid (IV).—To a stirred solution of 4 g. (0.059 mole) of cyclopentene and 7.6 g. (0.046 mole) of γ -carbomethoxybutyryl chloride in 15 cc. of nitrobenzene maintained at 0° was added slowly a solution of 7 g. (0.052 mole) of aluminum chloride (Mallinckrodt analytical reagent) in 35 cc. of nitrobenzene. After stirring for twenty-four hours at room temperature, the viscous red mixture was poured onto ice. The nitrobenzene layer was separated and added to an ether extract of the water layer. The combined extracts were washed with sodium bicarbonate and water, dried over anhydrous sodium sulfate and distilled. The methyl ester of 5-(Δ^1 -cyclopentenyl)-5-oxopentanoic acid boiled at 153–155° (3 mm.). The yield of light yellow oil was 3.5 g. (39%). Two grams (0.012 mole) of the methyl ester was saponified by refluxing for two hours with a solution of 1.4 g. (0.025 mole) of potassium hydroxide in 7 cc. of 95% ethanol. The solution was diluted with water, extracted with ether, acidified and again extracted with ether. This second extract was dried and distilled. The 5-(Δ^1 -cyclopentenyl)-5-oxopentanoic acid was thus obtained as a viscous yellow oil, b. p. 178–181° (0.7 mm.).

The yield was 1.4 g. (75%). Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_5$: neut. equiv., 182. Found: neut. equiv., 180.

Anal. Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_5$: C, 65.9; H, 7.74. Found: C, 65.4; H, 7.55.

5-(Δ^1 -Cyclohexenyl)-5-oxopentanoic Acid (V).—The methyl ester was prepared from 23 g. (0.14 mole) of γ -carbomethoxybutyryl chloride, 13 g. (0.16 mole) of cyclohexene and 18.5 g. (0.14 mole) of aluminum chloride, in the same manner as the methyl ester of 5-(Δ^1 -cyclopentenyl)-5-oxopentanoic acid.

(10) "Organic Syntheses," **25**, 19 (1945); Bachmann, *THIS JOURNAL*, **64**, 977 (1942).

(11) "Organic Syntheses," **19**, 45 (1939).

tenyl)-5-oxopentanoic acid. Eight and two-tenths grams (29%) of ester boiling at 132° (2 mm.) was obtained, n_D^{25} 1.4880. This was saponified as before to give, after recrystallization from water, 6.5 g. (85%) of 5-(Δ^1 -cyclohexenyl)-5-oxopentanoic acid as white crystals, m. p. 92°. Calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_5$: neut. equiv., 196. Found (in 50% ethanol): neut. equiv., 197.

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{O}_5$: C, 67.3; H, 8.22. Found: C, 67.5; H, 7.96.

6-(Δ^1 -Cyclohexenyl)-6-oxohexanoic Acid (VI).—The ethyl ester was prepared from 19.3 g. (0.1 mole) of δ -carbomethoxyvaleryl chloride, 25 g. (0.3 mole) of cyclohexene and 13.3 g. (0.1 mole) of aluminum chloride. The method was the same as that described above for the methyl ester of 5-(Δ^1 -cyclopentenyl)-5-oxopentanoic acid, except that the reaction mixture was stirred at room temperature for only three hours, and after decomposing the aluminum chloride addition product with ice, the nitrobenzene solution was refluxed for three hours with 23 g. (0.25 mole) of diethylaniline. The diethylaniline was then removed by washing with 6 *N* hydrochloric acid and water. On distillation, 12.5 g. (53%) of colorless ethyl 6-(Δ^1 -cyclohexenyl)-6-oxohexanoate, b. p. 155–160°, was obtained; n_D^{20} 1.4852; d_{20} 1.0276. This material darkens rapidly on standing. Semicarbazone, m. p. 100° (recrystallized from dilute ethanol). Calcd. for $\text{C}_{16}\text{H}_{26}\text{O}_5\text{N}_2$: N, 14.2. Found: N, 14.5.

Eleven grams of the ethyl ester was saponified and the acid product distilled to give 6 g. (62%) of colorless oil boiling at 172–175° (1.5 mm.). This oil solidified on standing and was recrystallized from benzene-petroleum ether (b. p. 60–100°). Colorless prisms of 6-(Δ^1 -cyclohexenyl)-6-oxohexanoic acid melting sharply at 74.5° were finally obtained: semicarbazone, m. p. 194–195°. Wallach prepared this acid by oxidation of 1-(Δ^1 -cyclohexenyl)-cyclohexanol-2 with dilute permanganate,⁵ and reported a melting point of 74–75°.

5-Cyclopentyl-5-oxopentanoic Acid (VII).—One gram of 5-(Δ^1 -cyclopentenyl)-5-oxopentanoic acid in 10 cc. of methanol was hydrogenated at 40 pounds pressure using Adams platinum oxide catalyst. Removal of the solvent

(12) The larger excess of the more readily available cyclohexene was used to compensate for its polymerization, which was extensive.

under reduced pressure left a colorless oil which was distilled, b. p. 155° (1.5 mm.). The distillate solidified when cooled to a white crystalline solid, m. p. 23–25°. This same 5-cyclopentyl-5-oxopentanoic acid, m. p. 23–25°, was also prepared from cyclopentanone by Wallach's method⁴ in an over-all yield of 28% of the theoretical. Wallach reported this compound only as an oil, and characterized it by its semicarbazone, m. p. 181–183°. We have prepared this semicarbazone, m. p. 181–182°, after recrystallization from ethanol.

5-Cyclohexyl-5-oxopentanoic Acid (VIII).—Four grams of 5-(Δ^1 -cyclohexenyl)-5-oxopentanoic acid was hydrogenated at 40 pounds pressure using Adams platinum catalyst. Removal of the solvent under vacuum left a solid mass of 5-cyclopentyl-5-oxopentanoic acid, which was recrystallized from petroleum ether (b. p. 30–60°) to give 3.7 g. (92%) of white plates, m. p. 55°.

Anal. Calcd. for $C_{11}H_{18}O_3$: C, 66.6; H, 9.15. Found: C, 66.6; H, 9.13.

6-Cyclohexyl-6-oxohexanoic Acid (X).—Twenty-four grams (0.1 mole) of the ethyl ester of 6-(Δ^1 -cyclohexenyl)-6-oxohexanoic acid (III) was hydrogenated and the product distilled, yielding 23 g. (95%) of colorless liquid, b. p. 137–140° (2.5 mm.); n_D^{20} 1.4628. Eleven grams of this hydrogenated ester (IX) was refluxed for one hour with methyl alcoholic potassium hydroxide. The solution was diluted with water, extracted with ether, acidified with hydrochloric acid and cooled. The crude 6-cyclohexyl-6-oxohexanoic acid thus obtained was recrystallized from petroleum ether (b. p. 60–100°) to give 3.5 g. (36%) of colorless needles, m. p. 56°. This same acid was also prepared from cyclohexanone by Wallach's method,⁵ colorless needles melting at 57° being obtained in an over-all yield of 31% (from cyclohexanone). A mixed melting point of samples prepared by the two different routes was 56–57°.

Bromination of the Keto Acids (VII and X).—In each case, two moles of bromine was added gradually to a stirred solution of one mole of keto acid in carbon tetrachloride. Decoloration was rapid, and was accompanied by evolution of hydrogen bromide. The solvent was then removed under vacuum, leaving a yellow solid residue which was recrystallized from a mixture of chloroform and petroleum ether (b. p. 60–100°). From 4 g. (0.022 mole) of 5-cyclopentyl-5-oxopentanoic acid (VII) was obtained 6.8 g. (91%) of 5-(1-bromocyclopentyl)-5-oxo-4-bromopentanoic acid (XI) as colorless needles, m. p. 79°. This material decomposed slowly at room temperature with evolution of hydrogen bromide. Calcd. for hydrolysis of both bromines: neut. equiv., 114. Found (in hot 50% ethanol): neut. equiv., 117.

Anal. Calcd. for $C_{10}H_{14}O_3Br_2$: C, 35.1; H, 4.13; Br, 46.7. Found: C, 35.5; H, 4.15; Br, 46.4.

From 30 g. (0.14 mole) of 6-cyclohexyl-6-oxohexanoic acid (X) was obtained 47 g. (90%) of 6-(1-bromocyclohexyl)-6-oxo-5-bromohexanoic acid (XII) as a white crystalline powder, m. p. 108°. Neut. equiv.: calcd., 370; found (at room temp.), 369; calcd. for hydrolysis of both bromines, 123.4; found (in hot 50% ethanol), 124. This compound, in contrast to the above analog, showed no tendency to decompose at room temperature, even after standing for two years.

Anal. Calcd. for $C_{12}H_{18}O_3Br_2$: Br, 43.2. Found: Br, 43.4.

Hydrolysis of the Dibromo Keto Acids (XI and XII).—The dibromo compounds were suspended in hot water and titrated to a permanent phenolphthalein end-point with sodium hydroxide (0.2–2.0 *N*). Three equivalents of alkali were consumed in each case. The solution was then acidified with hydrochloric acid and exhaustively extracted with ether. After drying over anhydrous sodium sulfate, the ether was removed under vacuum to give the lactone, XIII, and the acid, XIV, respectively.

From 6 g. (0.0176 mole) of 5-(1-bromocyclopentyl)-5-oxo-4-bromopentanoic acid, an oil was obtained which did not solidify and could not be distilled. A pseudo-

benzylthiuronium salt was prepared and recrystallized from alcohol to give 2.5 g. of colorless crystals, m. p. 131–132°. On shaking this salt with ether and 6 *N* hydrochloric acid, and evaporating the ether layer, a colorless oil was obtained. After drying thoroughly in vacuum, this oil solidified and was recrystallized from *n*-butyl alcohol to give colorless crystals of 5-(1-hydroxycyclopentyl)-5-oxo-4-hydroxypentanoic acid γ -lactone, m. p. 66°. On titration with alkali, this material behaved as a lactone. Calcd. for the lactone (XIII): neut. equiv., 198. Found: neut. equiv., 201.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.6; H, 7.12. Found: C, 60.4; H, 6.69.

From 37 g. (0.1 mole) of 6-(1-bromocyclohexyl)-6-oxo-5-bromohexanoic acid, a pale yellow oil was obtained, which solidified after cooling for several days in Dry Ice. Recrystallization from benzene gave 15.5 g. (63%), m. p. 86°. Several more recrystallizations from benzene raised the melting point of pure 6-(1-hydroxycyclohexyl)-6-oxo-5-hydroxyhexanoic acid to 87.5°. Calcd. for the acid (XIV): neut. equiv., 244.3. Found: neut. equiv., 244.2.

Anal. Calcd. for $C_{12}H_{20}O_5$: C, 59.0; H, 8.25. Found: C, 59.1; H, 8.24.

δ -Lactone of 6-(1-Hydroxycyclohexyl)-6-oxo-5-hydroxyhexanoic Acid (XV).—Two grams of the dihydroxy keto acid (XIV) and a trace of iodine were dissolved in 50 cc. of benzene. The solution was refluxed for two hours in a Soxhlet apparatus containing phosphoric anhydride in the cup. Removal of the benzene under vacuum left the δ -lactone of 6-(1-hydroxycyclohexyl)-6-oxo-5-hydroxyhexanoic acid as a white solid which was recrystallized from benzene to give 1.2 g. of shining white flakes, m. p. 122°. Calcd. for the lactone (XV): neut. equiv., 226. Found (in hot solution): neut. equiv., 225.

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.7; H, 8.02. Found: C, 63.6; H, 8.21.

Analysis for α -Hydroxy Acid Group.—A Zerewitinoff tube¹³ containing a weighed sample (10–20 mg.) in one leg and 2 cc. of concentrated sulfuric acid in the other was used. After flushing with carbon dioxide, the sulfuric acid was added to the sample and heated at approximately 100° while a slow stream of carbon dioxide was maintained. The evolved carbon monoxide was collected in a nitrometer over 50% potassium hydroxide. Heating was continued for one hour after apparent completion of carbon monoxide evolution. A blank was determined and subtracted from the observed volumes of carbon monoxide. The following values were obtained. Malic acid: calcd. % CO, 20.9; found, 20.8. Compound XIII: calcd. % CO, 11.5; found, 0.28. Compound XIV: Calcd. % CO, 14.1; found, 0.99. Compound XV: Calcd. % CO, 12.4; found, 0.14.

Periodate Cleavage of Lactones.—Suspensions of the lactones (XIV and XV) in aqueous solution of slightly less than one equivalent of periodic acid were stirred for one and a half hours. The mixtures were then steam distilled and the distillates collected in an excess of a 0.1% solution of 2,4-dinitrophenylhydrazine in 6 *N* hydrochloric acid. The yellow precipitate was recrystallized from alcohol in each case, and mixed melting points taken with authentic samples of the 2,4-dinitrophenylhydrazones of cyclopentanone and cyclohexanone, respectively.

In this manner, a yellow 2,4-dinitrophenylhydrazone melting at 143–144° was obtained from the γ -lactone of 5-(1-hydroxycyclopentyl)-5-oxo-4-hydroxypentanoic acid. An authentic sample of the 2,4-dinitrophenylhydrazone of cyclopentanone melted at 146°. The mixed melting point was 145–146°.

From the δ -lactone of 6-(1-hydroxycyclohexyl)-6-oxo-5-hydroxyhexanoic acid, there was obtained a yellow derivative melting at 157–159°. An authentic sample of the 2,4-dinitrophenylhydrazone of cyclohexanone melted at 159–160°, and the mixed melting point was 158–159°.

(13) Pregl-Grant, "Quantitative Organic Microanalysis," The Blakiston Co., Philadelphia, Pa., 1946, p. 136.

Summary

The keto acids, 5-cyclopentyl-5-oxopentanoic acid and 6-cyclohexyl-6-oxohexanoic acid, have been synthesized by a new method. Bromination of these keto acids gives dibromo keto acids which are readily hydrolyzed to give the γ - and δ -lactones, respectively, of 5-(1-hydroxycyclopentyl)-

5-oxo-4-hydroxypentanoic acid and 6-(1-hydroxycyclohexyl)-6-oxo-5-hydroxyhexanoic acid. The structures of the latter have been established by periodic acid titration and cleavage with one mole of periodate to give cyclopentanone and cyclohexanone, respectively.

NEW HAVEN, CONNECTICUT RECEIVED APRIL 27, 1948

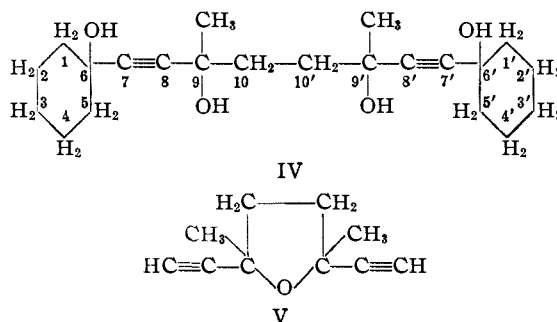
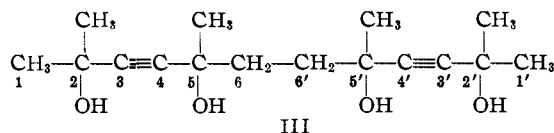
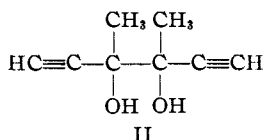
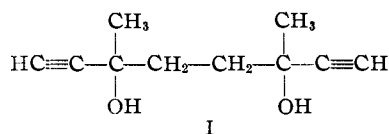
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Synthesis of Diethynyl Glycols and their Condensation with Ketones

BY NICHOLAS A. MILAS, ROBERT J. BROWN¹ AND OLIVERIO PHILLIPS²

With the exception of diacetylene³ and dipropargyl,⁴ no true diacetylenes are known in which each acetylene group bears a reactive hydrogen atom. Diacetylene has been used in this Laboratory⁵ for the synthesis of certain carotenoids containing twelve carbon atoms between two β -ionone nuclei. In the present investigation, the synthesis of diethynyl glycols in which the acetylene groups are separated by two or more carbon atoms was undertaken to provide intermediates in the synthesis of carotenoids containing longer chains between the two β -ionone nuclei. When acetylacetone or diacetyl was allowed to react with sodium acetylide in liquid ammonia, 3,6-dimethyl octa-1,7-diyndiol-3,6 (I) and 3,4-dimethyl hexa-1,5-diyndiol-3,4 (II) were formed, respectively. A condensation of these diethynyl glycols via the Grignard reaction with excess acetone or cyclohexanone yielded compounds of the type III and IV.

The tetrol (IV) was obtained in two isomeric crystalline forms which may be the *meso* and race-



mic modifications. The yield of the tetrols was somewhat low possibly because of the unfavorable solubility properties of the Grignard derivatives of the glycols.

Wilson and Hyslop⁶ prepared the diphenyl derivative of the glycol (I) from phenylacetylene and acetylacetone. When heated with 60% sulfuric acid in a sealed tube this derivative yielded a substituted tetrahydrofuran. Similarly in an attempt to dehydrate the diethynyl glycol (I) at 290–300° over aluminum phosphate on pumice⁷ the diethynyl substituted tetrahydrofuran (V) was mainly formed.

Experimental

3,6-Dimethyl-octa-1,7-diyndiol-3,6 (I).—Into a 5-liter 3-necked round-bottomed flask equipped with a Hershberg stirrer was condensed 2 liters of ammonia. The liquid ammonia was then saturated with dry acetylene and while the latter was allowed to bubble through the solution with stirring, 50.6 g. (2.2 g.-atoms) of sodium was added slowly in the course of five hours. When the blue color of the solution had completely disappeared, 114 g. (1 mole) of acetylacetone dissolved in an equal volume of ether was added dropwise in the course of three hours. Stirring was continued overnight while the temperature was allowed to rise slowly. The ammonia was then removed and to the residue was added 500 cc. of ether and the mixture cooled to 0° and acidified with a tartaric acid solution (250 cc.) containing 165 g. of tartaric acid. The ether layer was separated and the aqueous layer extracted with 3 × 100 cc. of ether, whereby a pale yellowish solid (127.2 g., 77% yield) separated out. This was further purified either by vacuum sublimation or by recrystallization from a 2:1 mixture of *n*-heptane and benzene; m. p. 92–92.5°.

(6) Wilson and Hyslop, *J. Chem. Soc.*, **125**, 707 (1924).

(7) Milas, MacDonald and Black, *THIS JOURNAL*, **70**, 1829 (1948).

(1) M. S. Thesis, Massachusetts Institute of Technology, June, 1946.

(2) B. S. Thesis, Massachusetts Institute of Technology, January, 1948.

(3) Noyes and Tucker, *Am. Chem. J.*, **19**, 128 (1897); Straus and Kollek, *Ber.*, **59**, 1672 (1926).

(4) Iotsitch, *J. Russ. Phys.-Chem. Soc.*, **38**, 656 (1906); *Bull. soc. chim.*, **4**, 1208 (1908).

(5) Rivers, Ph.D. Thesis, Massachusetts Institute of Technology, 1941.