presumed to be formed from further hydroboration of 4-chloro-1-butene. This was prevented by hydroborating at −25 to −30° over 12 hr. and hydrolysis of the reaction mixture before warming to room temperature. Under identical conditions, 2,5-dichloro-2,5-dimethyl-3-hexene gave 5-chloro-2,5-dimethyl-2-hexene while 3,6-dibromocyclohexene was transformed to 4-bromocyclohexene. The relatively lower yield (12%) of the latter olefin may be attributed to the fact that bromine is a better leaving group than chlorine and may undergo more elimination during hydroboration.

Experimental

4-Chloro-1-butene.—Diborane was generated by adding over 5 hr. 3.1 g. (0.076 mole) of sodium borohydride (Callery Chemical) in 50 ml. of diglyme (purified by distillation over sodium) to 27.0 g. (0.20 mole) of redistilled Eastman boron trifluoride in 25 ml. of diglyme. It was fed through a delivery tube to a reaction flask, previously flushed with nitrogen, which was kept at −30° and contained 18.6 g (0.15 mole) of the 55–55° (20 mm.) fraction of Eastman 1,4-dichloro-2-butene dissolved in 50 ml. of diglyme. After borohydride addition was complete, the generator was warmed for 10 min. at 70° and the reaction mixture kept at −25 to −30° for 7 hr. and then hydrolyzed with 25 ml. of water followed by 25 ml. of 1.0 *M* aqueous sodium bicarbonate. After the mixture had come to room temperature, the upper layer was separated, dried over anhydrous sodium sulfate, and distilled at 74–75° (761 mm.) through a Vigreux column to give 4.5 g. of a liquid that was identified by its b.p. of 74–75°, d^{20}_4 0.918, n^{20}_D 1.4192° (lit.[6] b.p. 75°, d^{20}_4 0.9211, n^{20}_D 1.4205°), mol. wt. by Dumas 93.0 (calcd. 90.5), and infrared spectrum with peaks at 6.1 (C=C stretching), 7.1 (terminal C=C), and 15.5 μ (C—Cl stretching). Hydroboration followed by oxidation gave 4-chloro-1-butanol which formed a phenylurethane, m.p. 56°, lit.[7] 54°.

5-Chloro-2,5-dimethyl-2-hexene.—2,5-Dimethyl-2,4-hexadiene (Tennessee Eastman) was purified by distillation and then treated with an equimolar amount of chlorine by the method of Skvarchenko[8] to form 2,5-dichloro-2,5-dimethyl-3-hexene. An 18.5-g. (0.10 mole) sample of the latter was hydroborated by the procedure described above and the product distilled to give 4.1 g. of a liquid, b.p. 67–68° (25 mm.) which was identified as 5-chloro-2,5-dimethyl-2-hexene by the 0.5 min. required for reaction with alcoholic silver nitrate as compared with immediate precipitation with 2,5-dichloro-2,5-dimethyl-2-hexene, infrared peaks at 6.1 (C=C stretching) and medium intensity at 14 μ (C—Cl stretching), and its formation of a Grignard reagent which was hydrolyzed to 2,5-dimethyl-2-hexene, b.p. 110–111°, d^{20}_4 0.7244, n^{20}_D 1.4133 (lit.[8] b.p. 112.2°, d^{20}_4 0.720, n^{20}_D 1.4140).

Anal. Calcd. for $C_8H_{15}Cl$: C, 65.6; H, 10.2; Cl, 24.2. Found: C, 65.2; H, 9.93; Cl, 24.4.

4-Bromocyclohexene.—Wohl–Zeigler[9] bromination of cyclohexene gave 3-bromocyclohexene which was dehydrohalogenated with quinoline to 1,3-cyclohexadiene. Addition of an equimolar amount of bromine to this diolefin by the method of Crossley and Haas[10] gave 3,6-dibromocyclohexene; 25.0 g. (0.10 mole) of this product was hydroborated by the procedure above. Hydrolysis and separation of the reaction product gave 1.9 g. of 4-bromocyclohexene, b.p. 53–55° (15 mm.), d^{20}_4 1.3772, n^{21}_D 1.5188 (lit.[11] b.p. 48° (12 mm.), d^{20}_4 1.3779, n^{20}_D 1.5168).

Anal. Calcd. for C_6H_9Br: Br, 49.5. Found: Br, 49.9.

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An Improved Laboratory Method for the Preparation of Diacetylene

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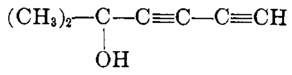
Diacetylene is a highly reactive bifunctional building block for the synthesis of a variety of polyacetylenic derivatives.[1,2] However, due to its instability, it has never been deliberately prepared on a commercial scale, and is consequently not readily available as a synthesis intermediate. It polymerizes rapidly above 0°, and in the presence of air can be readily detonated in vapor concentrations of 20–25% by a suitable ignition source.

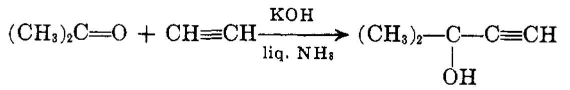
The presently accepted method of preparing free diacetylene at the bench-scale level is the dehydrohalogenation of 1,4-dichlorobut-2-yne with either sodium hydroxide[3,4] or with sodamide in liquid ammonia. The latter method utilizes 3 moles of sodamide/mole of dichloride and forms the disodium diacetylide *in situ*, while the former method yields free diacetylene in 60% conversion

Although the base-catalyzed cleavage of 1,4-acetylenic diols[5] to acetylene is well known, the analogous cleavage of 1,3-diyne-1,6-diols to diacetylene and ketone has been studied only by Zalkind and Aizikovich.[6] In their cursory investigation, they employed large amounts of base (alkali metal carbonates and alkaline earth hydroxides) and obtained from 2,7-dimethylocta-3,5-diyne-2,7-diol low conversions to diacetylene, besides the semicleavage product, 2-methylhexa-3,5-diyn-2-ol.



$$(CH_3)_2\underset{\substack{|\\ OH}}{C}—C≡C—C≡CH$$

During the course of work at this laboratory it was necessary conveniently to prepare free diacetylene as a starting material. Consequently, the above diynediol (B), readily available from acetone and acetylene *via* the following catalytic reactions,[1,2,7] was considered an excellent starting material for diacetylene preparation. Under optimum conditions the conversions to A and B, respectively, average 95–100%.



$$(CH_3)_2C=O + CH≡CH \xrightarrow[\text{liq. NH}_3]{\text{KOH}} (CH_3)_2—\underset{\substack{|\\ OH}}{C}—C≡CH \quad (1)$$

A

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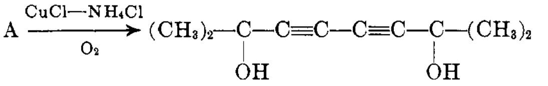

$$\mathrm{A} \xrightarrow[\mathrm{O_2}]{\mathrm{CuCl{-}NH_4Cl}} (\mathrm{CH_3})_2{-}\underset{\mathrm{OH}}{\mathrm{C}}{-}\mathrm{C{\equiv}C{-}C{\equiv}C}{-}\underset{\mathrm{OH}}{\mathrm{C}}{-}(\mathrm{CH_3})_2 \qquad (2)$$

B

$$\mathrm{B} \xrightarrow[\text{xylene}]{\text{KOH or NaOH}} \mathrm{HC{\equiv}C{-}C{\equiv}CH} + (\mathrm{CH_3})_2\mathrm{C{=}O} + \mathrm{KOH} \qquad (3)$$

We have found that the successful base-catalyzed cleavage of B is highly dependent upon the concentration of sodium or potassium hydroxide used as catalyst as shown in Table I.

TABLE I

DIACETYLENE FROM DIMETHYLOCTADIYNEDIOL[a]

Base, g.	% conversion to	
	Diacetylene	Acetone
KOH, 0.02	0	0
KOH, 0.07	74	88
KOH, 0.10	71	80
NaOH, 0.13	80	83
KOH, 0.23	61	83

[a] 0.10 mole of diynediol in 100 ml. of xylene.

Amounts of potassium hydroxide larger than 0.23 g. result in increased amounts of dark, polymeric residues and lower diacetylene conversions. Sodium hydroxide, however, yields less polymer and higher diacetylene conversions at equivalent concentrations. The above diacetylene conversions are minimum values since a presently undetermined amount of diacetylene complexes with or dissolves in the acetone as it is condensed. Similar complex formation of diacetylene with N-methylpyrrolidone has been reported by Shachat.[8] Diacetylene, however, can be separated from acetone solutions by water scrubbing,[9] if higher conversions are required.

Other solvents such as mineral oil, pyridine, dioxane, or water gave inferior results due to either foaming, sublimation, polymerization, or difficulty of separation. Xylene functioned efficiently, since it was a good solvent for the diynediol at 80–100°, and while refluxing on the sides of the flask minimized its sublimation. It also does not complex strongly with diacetylene, thereby allowing the latter to have a short residence time in the cleavage medium which in turn minimizes polymerization. Alkali metal carbonates and alkaline earth hydroxides were found to be inferior cleavage catalysts, yielding negligible amounts of diacetylene at the above catalyst concentrations.

When the above cleavage is carried out in an atmosphere of nitrogen and the diacetylene rapidly is condensed and stored below $-30°$, no danger of detonation or exothermic polymerization is incurred. An advantage of the present method is that small amounts of diacetylene can be generated and used as needed, using the stable dimethyloctadiynediol as starting material. In this way the hazardous storage of diacetylene for prolonged periods of time can be avoided. In fact, it is preferable to lead the evolved gas directly into the desired reaction medium.

The cleavage is always performed under nitrogen, and the diacetylene is used within several hours after preparation. Overnight storage at Dry Ice temperature under a nitrogen atmosphere can be employed but is not recommended as common practice. The operator should at all times be protected with a face shield and the apparatus used in an efficient hood equipped with a Plexiglas (or similar type) shield or window.

If diacetylene, either as the pure liquid (b.p. 10.3°) or in organic solutions, is allowed to stand at 0° or above for more than 1 hr., pronounced darkening followed by the rapid precipitation of polymer is observed. At 10° the discoloration is rapid and solutions containing 10% diacetylene in acetone or xylene will set to a porous gel on standing overnight. However, no discoloration or polymer formation was noted for diacetylene stored at -20 to $-35°$ under nitrogen during 4 hr. Polymer derived from diacetylene has been found to be stable to impact, friction, and slow heating, and when thrown on a hot plate at 200° disappears quietly in a puff of smoke. Attempts to stabilize solutions of diacetylene with pyridine, hydroquinone, phenyl-β-naphthylamine, or diphenylpicrylhydrazyl were ineffective. The best inhibitor system was refrigeration below $-30°$ and the careful exclusion of air. A sample of diacetylene which had been stored, in one instance, over the weekend at Dry Ice temperature in the absence of a nitrogen blanket on redistillation decomposed in the distillation vessel with a mild explosion and the formation of much finely divided carbon. It is believed that unstable peroxides were the cause.

Using the conditions described for this cleavage, no significant amounts of the partial cleavage product 2-methylhexa-3,5-diyn-2-ol are obtained. However, this diynol derivative can be obtained in an impure condition in 52–56% conversions, together with 30–38% diacetylene, by cleavage in the presence of sodium or potassium carbonates (0.20 g. of carbonate/0.10 mole of diynediol) using mineral oil (Nujol) as solvent. This high boiling product (137° at 70 mm.) is relatively unstable and polymerizes both during and after distillation. It was noted that a sample in a vial expanded on polymerizing to a hard dark red-brown glossy mass and cracked the vial. The instability of this compound agrees with earlier observations.[6,10]

Experimental

3-Methyl-1-butyn-3-ol.—This material (b.p. 104°) is available commercially[11] or it can be prepared catalytically in liquid ammonia[7] or stoichiometrically at atmospheric pressure using powdered potassium hydroxide in ether or acetal solvents.[5]

2,7-Dimethylocta-3,5-diyne-2,7-diol.—This product is conveniently prepared[1,2] by the oxidative coupling of 3-methyl-1-butyn-3-ol in aqueous solution using a catalytic amount of cuprous chloride solubilized by excess ammonium chloride. Oxygen is considerably more effective than air as oxidant, although the latter can be employed. The resulting diynediol is sparingly soluble in water, and is readily freed of cuprous chloride by washing with concentrated ammonium chloride solution, then water, followed by recrystallization from xylene, and air drying the product (m.p. 132–133°).

Base-Catalyzed Cleavage of 2,7-Dimethylocta-3,5-diyne-2,7-diol to Diacetylene.—The diynediol, if not recrystallized, should be clarified (Nu-char) and filtered in hot xylene solution (commercial *ortho–para* mixture) from residual copper salts to avoid the later possibility of forming copper diacetylene complexes or acetylides which may initiate the exothermic decomposition or polymerization of diacetylene.

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(11) Air Reduction Chemical and Carbide Co., 150 East 42nd St., New York 17, N. Y.

The apparatus for base-cleavage and separation of diacetylene from xylene and acetone consists principally of a decomposition flask (A), an acetone–xylene condensation receiver (B), a graduated diacetylene trap (C), and a reactor flask (D).

Flask A is a 500-ml., 29/42 standard taper, three-necked flask equipped with a thermometer well or joint. One neck is equipped with a gas inlet tube for introduction of nitrogen while the furthest neck is equipped with a 10-in. Vigreux column (29/42 joints, 1-in. o.d.). The middle neck is equipped with a Tru-bore stirrer and mineral oil seal to minimize possible loss of diacetylene. The top of the Vigreux column is equipped with a standard distillation head, which condenses acetone (water cooling below 25°) yet allows the major part of the evolved diacetylene to be swept (nitrogen) into C or D. The condensed acetone can be allowed to reflux or led directly to B.

Collection flask B is a 250-ml., three-necked flask equipped with a 0.5-in. (o.d.) delivery tube leading from the distillation head of A into receiver B. A stopcock (0.25-in. bore) located 2 in. above the neck of B serves to isolate B from A and collect acetone. The furthest neck of B is fitted with a 10-in. packed (stainless steel 0.25-in. Podbielniak) column, the top of which is equipped with a total return condenser for acetone, but allows diacetylene gas to be collected in C or D. The receiver is kept at a temperature 55–60° to minimize diacetylene solubility in acetone.

Diacetylene–nitrogen sweep gas lines (0.25-in. i.d., Pyrex) leading from distillation head (A) and total return condenser (B) meet at a T-connection prior to leading into the diacetylene trap (C). Trap C (1-in. i.d.) is graduated to 0.20-ml. accuracy and has a capacity of about 50 ml. It is equipped with an entrance tube ending approximately at the 20-ml. mark, and an exit tube used to vaporize the diacetylene slowly under a slow nitrogen current into the cooled reactor (D) containing an appropriate solvent. Trap C is cooled to approximately −50 to −70° by the use of Dry Ice and alcohol, and by immersing the trap up to the 20-ml. mark. However, care must be exercised to avoid freezing (−36°) the diacetylene in the entrance line and causing a plug. The bath is lowered somewhat if crystallization is noted, otherwise a bath temperature of −30 to −35° can be used safely for several hours if the diacetylene is to be used in a reaction.

The generation of diacetylene is started by first adding to flask A, 100 ml. of xylene, 0.10 mole (16.6 g.) of 2,7-dimethylocta-3,5-diyne-2,7-diol, and 0.10 g. of powdered 90–98% potassium or sodium hydroxide (latter preferred). The reaction system previously well purged with nitrogen is now purged again with nitrogen for 10 min. using a moderate flow through a mineral oil bubble counter. The reaction slurry is stirred at a speed sufficient to maintain good mixing, but to prevent splashing, as the reaction slurry is heated.

As the reaction temperature approaches 90° some gradual volatilization of possibly acetone and diacetylene is noted. With the use of constant heat input, the reaction temperature rises to 92–94° and then falls to 87–88° whereupon active distillation of both acetone and diacetylene is observed. When approximately 50% (by volume) of the expected amounts of products have been collected in B and C, the rate of distillation decreases as the reaction temperature increases. By the time the boiling point of xylene (139°) is reached, distillation of acetone and condensation of diacetylene have essentially ceased. Slowing the rate of heating after distillation starts has been observed to be detrimental to the conversion to diacetylene. The acetone collection chamber is kept at 60° to minimize solubility of diacetylene in acetone. Both flasks A and B are swept with slow currents of nitrogen during the cleavage and for 15 min. after heating was halted. The nitrogen sweep for both A and B can be operated independently of each other. The conversion to diacetylene is measured directly by noting the volume of liquefied gas (d^0_4 0.7364) or by weighing the cold tared trap. If stored overnight, it should be cooled to −70 to −80° under a nitrogen atmosphere. Exposure to air and alkali must be avoided at all times, and a safety face shield should be worn when handling this material. A well-ventilated hood with a sliding glass or Plexiglas window should be used. It is preferable to lead the diacetylene directly into reaction vessel (D) or shortly after (within several hours) it is collected in C to vaporize it slowly into D using a current of nitrogen and a water bath at 5–10°. Recommended solvents for dissolving diacetylene and for carrying out the reactions are methylal, dioxane, liquid ammonia, N-methylpyrolidone, and dimethyl sulfoxide. The diacetylene collected on redistillation leaves no residue and boils at 9–10°.

The physical constants are diacetylene,[12] b.p. 10.3° (760 mm.); m.p. −36 to −35°; d^0_4 0.7364; vapor pressure 1.6 mm. (−78°), 93.5 (−35.5°), 519 (0°).

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α-Methyldopa. Resolution and Configuration

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The hypotensive activity of 3-(3,4-dihydroxyphenyl)-2-methylalanine (α-methyldopa) resides in the optical isomer with a negative rotation,[1] $[\alpha]^{25}_D$ −4° (*c* 2, 0.1 *N* hydrochloric acid).

The same isomer inhibits the decarboxylation of L-3,4-dihydroxyphenylalanine (L-dopa) by mammalian decarboxylase while the other isomer is totally inactive.[2] This suggests that the biologically active isomer has the L configuration. The rotatory dispersion curve for (−)-α-methyldopa (Fig. 1) supports this sug-

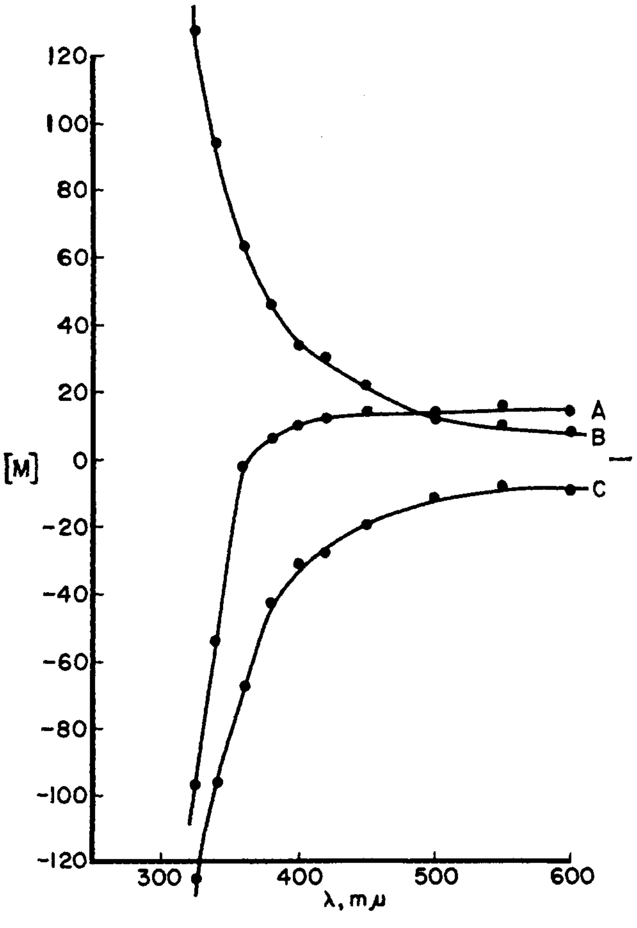

Fig. 1.—Rotatory dispersion curves: A, D-dopa; B, L-α-methyldopa; C, D-α-methyldopa. Measurements were made at 25° on 1% solutions of the amino acids in 6 *N* hydrochloric acid.

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