

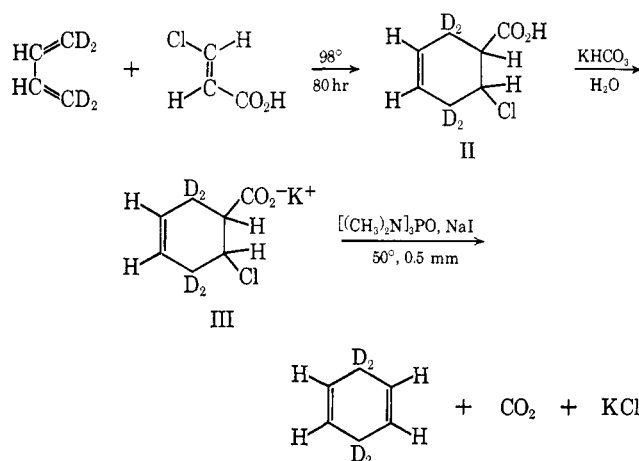
Preparation of 3,3,6,6-*d*₄-Cyclohexa-1,4-diene

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3,3,6,6-*d*₄-Cyclohexa-1,4-diene (I) was required in connection with some hydrocarbon pyrolysis studies. The well-known methods of preparing 1,4-cyclohexadiene by reduction of benzene¹ were not applicable in this case nor were the methods² used for the preparation of some other deuterated 1,4-cyclohexadienes. Therefore, a new 1,4-cyclohexadiene synthesis was devised. Its generality has not been investigated, but by proper choice of substituents on the butadiene or the β-chloroacrylic acid the preparation of a variety of substituted



1,4-cyclohexadienes should be possible. One reason that this synthetic route was chosen is because 1,1,4,4-*d*₄-buta-1,3-diene is readily available,³ and the reaction conditions are sufficiently mild so that hydrogen scrambling is unlikely.

Optimum reaction conditions were first established using unlabeled butadiene. The progress of the first step (Diels-Alder reaction) was followed with nmr. In the last step of the reaction it was found, by using a high-boiling polar solvent, that the reaction occurred at a reasonable temperature and that the 1,4-cyclohexadiene could be removed under reduced pressure as fast as it was generated, practically eliminating any disproportionation and oxidation. Sodium iodide was added because the reaction in the last step proceeds only to about 25% completion without it. This may mean that III is a mixture of *cis* and *trans* isomers (with respect to Cl and CO₂H) and since the *trans* isomer is the one that undergoes elimination⁴ then the *cis* isomer remains unreacted. Iodide would displace chloride of the *cis* isomer giving a *trans* isomer which would then eliminate iodide and carbon dioxide. This problem

(1) R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *J. Org. Chem.*, **28**, 1094 (1963), and references therein.

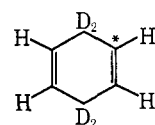
(2) 1,4-*d*₂, 1,3,3,4,6,6-*d*₆, and 1,2,3,3,4,5,6,6-*d*₈-cyclohexa-1,4-dienes were prepared by dehydration of the appropriately deuterated 1,4-cyclohexanediols: M. I. Gorfinkel and V. A. Koptyug, *Izv. Sib. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk*, 109 (1967).

(3) Available from Isotopic Products, Merck, Sharp & Dohme of Canada Ltd.

(4) S. J. Cristol and W. P. Norris, *J. Amer. Chem. Soc.*, **75**, 632 (1953).

was not pursued further since the addition of iodide effectively solved the problem of production of 1,4-cyclohexadiene.

The over-all yield of I based on 1,1,4,4-*d*₄-buta-1,3-diene (neglecting recovered starting material) was 45%. The product after one trap-to-trap distillation was about 98% I as judged from nmr and vpc data. There was about 0.1% of *d*₂-benzene (probably 1,4-*d*₂-benzene), and the remainder of the impurities were higher boiling materials including some hexamethylphosphoramide. There was no 1,3-cyclohexadiene detected by vpc or nmr. Purification by vpc eliminated the impurities within the detection limits of the vpc. The nmr spectrum of I shows a single vinylic proton peak at τ 4.36 and a very small peak (about 1% of the vinylic proton peak) at 7.40, the position of the peak for methylene protons of 1,4-cyclohexadiene. This is equivalent to the isotropic purity of the 1,1,4,4-*d*₄-buta-1,3-diene starting material. Hence, no hydrogen exchange at the methylene positions occurred. The vinyl



* = ¹³C (natural abundance)

proton-¹³C interaction gives $J_{H^{13}C} = 158$ Hz and, for the *cis* vinyl protons, $J_{1,2} = 10$ Hz. The mass spectrum of I shows a strong parent ion peak at m/e 84.

Experimental Section

2-Chlorocyclohex-4-ene-1-carboxylic Acid.—A mixture of 11.7 g (0.11 mol) of *trans*-β-chloroacrylic acid and 5.4 g (0.10 mol) of 1,3-butadiene was degassed and sealed in a glass ampoule on a vacuum line. The ampoule was heated in a bomb (partially filled with liquid trichlorofluoromethane to act as a heat-transfer medium and to pressurize the outside of the ampoule) to 98 ± 2° for 80 hr.⁵ The ampoule was opened on the vacuum line and 0.014 mol of gaseous material was evolved, at least 75% of which was butadiene (by nmr analysis). The other volatile constituents were not identified. There was 15.8 g of solid remaining in the ampoule. The solid was added to 50 ml of H₂O containing 11 g of KHCO₃, filtered to remove small amount of polymer, and extracted with two 50-ml portions of ether. The aqueous phase was acidified with 6 N HCl; the crystalline solid was filtered off, washed with 20 ml cold water, and dried on the filter by drawing air through the filter for 1 hr. This gave 11 g (68% yield) of acid, mp 104–108°. Two recrystallizations from *n*-hexane gave 6.5 g of 2-chlorocyclohex-4-ene-1-carboxylic acid, mp 110–112°.

Anal. Calcd for C₇H₉ClO₂: C, 52.35; H, 5.65; Cl, 22.08. Found: C, 52.16; H, 5.64; Cl, 22.02.

1,4-Cyclohexadiene.—2-Chlorocyclohex-4-ene-1-carboxylic acid (5.2 g, 0.032 mol), mp 104–108°, was combined with 2.7 g of NaHCO₃ in 2.5 ml of water. After the acid was neutralized, the water was removed under reduced pressure keeping the temperature below 25°. The dry salt along with 4.9 g (0.032 mol) of NaI was added to 50 ml of vacuum-distilled [(CH₃)₂N]₃PO in a 250-ml round-bottomed flask and heated to 70° at 1 mm pressure for 4 hr and then to 75° for 1 hr while stirring with a magnetic stirrer. The flask was connected to the vacuum pump through a trap cooled with Dry Ice and acetone. Two trap-to-trap distillations under vacuum gave 1.8 g (70% yield) of 1,4-cyclohexadiene of about 98% purity. The impurities, benzene and higher boiling materials, were removed by vpc using a 3/8-in.

(5) The optimum conditions for the reaction were determined by sealing equimolar amounts of the reactants into 5-mm standard walled-glass tubing and observing the change of the nmr spectrum with respect to time and temperature. The temperature was kept as low as practicable to minimize scrambling of hydrogens of the reactants or the product.

(6) Either the sodium or the potassium salt may be used.

by 20-ft aluminum column packed with 20% Apiezon L on Chromosorb W. Helium was used as the carrier gas. The infrared absorption spectrum of the gaseous product shows bands in μ at 3.2 ($>CH-$), 3.4 and 3.45 ($>CH_2$), 6.1 ($>C=C<$), and 6.9 ($>CH_2$) with two broad and complex bands centered at 10.2 and 11.2. The nmr spectrum shows a triplet due to vinyl protons at τ 4.36 and a triplet due to methylene protons at 7.26 with $J = 1$ Hz. The mass spectrum gives a strong parent ion peak at m/e 80. An authentic sample of 1,4-cyclohexadiene gives the same values as above.

Preparation of 3,3,6,6- d_4 -Cyclohexa-1,4-diene (I).—1,1,4,4- d_4 -Buta-1,3-diene (0.10 mol) and *trans*- β -chloroacrylic acid (0.11 mol) were reacted, and the product was worked up in the same manner as with the unlabeled material, except that the product was not recrystallized from hexane. 3,3,6,6- d_4 -2-Chlorohex-4-ene-1-carboxylic acid (11.7 g, 0.071 mol) was neutralized with 7.1 g of $KHCO_3$ dissolved in 50 ml of water. The water was removed under reduced pressure, and the dried salt along with 11 g of NaI was added to 100 ml of vacuum-distilled hexamethylphosphoramide. The system was evacuated through a Dry Ice-acetone trap to 0.5-mm pressure and heated to 50° for 4 hr. One trap-to-trap distillation under vacuum of the volatile material gave 3.8 g (45% based on butadiene) of I of about 98% purity as shown by vpc and nmr analysis. There was about 0.1% d_2 -benzene (presumably 1,4- d_2 -benzene), and the remainder of the impurities were higher boiling materials. Final purification was effected with preparative vpc using the column and the conditions used for the purification of unlabeled I in the previous experiment. The infrared absorption spectrum of I (gas phase) shows bands in μ at 3.25 ($>CH-$), 4.62 and 4.76 ($>CD_2$), 6.1 ($>C=C<$), and a poorly resolved triplet centered at 9.3 ($>CD_2$), with two broad bands centered at 10.4 and 11.3. There is no detectable methylene ($>CH_2$) absorption at 3.4 or 6.9 μ as there is in the unlabeled compound. The nmr spectrum shows a singlet at τ 4.36 due to the vinyl protons and at 7.25, the methylene proton region, there is a peak of about 1% the area of the vinyl proton peak.⁷ Hence there is no detectable exchange of hydrogen at the 3,3,6,6-positions during the synthesis. The mass spectrum shows a molecular ion peak, which is the base peak, at m/e 84.

Registry No.—I, 17791-27-4; 2-chlorocyclohex-4-ene-1-carboxylic acid, 17791-28-5; 1,4-cyclohexadiene, 628-41-1.

(7) The manufacturer (ref 3) claimed at least 98% isotopic purity, and a check by nmr indicated that the 1,1,4,4 positions of the labeled butadiene had about 1% 1H .

The Selective Oxidation of Large-Ring Organoboranes with Chromic Acid. The Synthesis of Macrocyclic Musk Compounds

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The C_{16} musk compound, 8-cyclohexadecen-1-one (5),¹ was obtained in very low yield (ca. 5%) by pyrolytic cyclization of the yttrium salt of the corresponding C_{17} diacid.² The saturated ketone, cyclohexadecanone (9), was obtained in a slightly higher yield (ca. 16%) by cyclization (twofold condensation) of the dichloride of azelaic acid, followed by reduction

(1) E. H. Rodd, "Chemistry of Carbon Compounds," Vol. II, part A, Elsevier Publishing Co., New York, N. Y., 1953, p 277.

(2) L. Ruzicka, M. Stoll, W. Scherrer, H. Schinz, and C. F. Seidel, *Helv. Chim. Acta*, **15**, 1459 (1932); L. Ruzicka, M. Stoll, and H. Schinz, *ibid.*, **9**, 249 (1926).

of one of the carbonyl groups.³ Both ketones were recently⁴ formed by an acyloin cyclization of aleuritic acid in about 5% yield. The odors of both ketones were reported as musklike.

The disadvantages of ring-closure methods to give unsaturated ketones have been realized for some time. Recently, the synthesis of a large-ring, unsaturated compound has been demonstrated by the olefin metathesis reaction⁵ of cyclo olefins, which suggests the present approach, in which a large ring is used as the starting material. The macrocyclization of cyclooctene provides a mixture of large-ring compounds.⁶ Under suitable conditions⁷ the reaction can be directed to appreciable (ca. 20%) amounts of the dimer, 1,9-cyclohexadecadiene (1), which occurs as a mixture of the *cis,cis* (35%), *cis,trans* (53%), and *trans,trans* (12%) isomers.

The conversion of the large-ring diene by hydroboration into the C_{16} musk compound seemed especially attractive, if a reasonable amount of monohydroboration would occur. The addition of 1 equiv of diborane ($^1/6B_2H_6$) was expected to give approximately 50% mono- and 25% dihydroborated compounds if the reaction went to completion. The cyclic diene (1) was treated with diborane (Scheme I) generated *in situ* by the addition of boron trifluoride etherate to sodium borohydride in diglyme.⁸ The distribution of alkylboranes varied with the proportions of diborane. The unsaturated intermediate 2, may be formed by addition of boron to either end of the double bond. The dihydroborated intermediates, 3 and 4, may form in equal amounts if not affected by conformational preferences. The possibly of boron-bridged intermediates (from 3 and 4) is presently under investigation.

Oxidation of organoboranes to the corresponding ketones with aqueous chromic acid added to ethyl ether has been reported.^{9,10} This type of chromic acid oxidation, which is known to be selective for secondary alcohols in the presence of carbon-carbon double bonds¹¹ was found in this work to be selective as well for the alkylborane group in the presence of a carbon-carbon double bond, as is shown by the desired unsaturated ketone 5 (Scheme I). Oxidation also gives the diketones 8 and 10, from the dihydroborated compounds, but in much lower yield (Table I) than initially predicted for addition of 1 equiv of diborane to the diene. This may be attributed to the insolubility of the dialkylborane which precipitates and resists further alkylation.

Gas chromatographic and ir analyses of recovered starting materials showed that when the diene was treated with 2 or 3 equiv of diborane the *cis,cis* isomer had always reacted to a greater extent than the *trans-*

(3) A. T. Blomquist, J. Prager, and J. Wolinsky, *J. Amer. Chem. Soc.*, **77**, 1804 (1955); A. T. Blomquist and J. Wolinsky, *ibid.*, **77**, 5423 (1955).

(4) H. H. Mathur and S. C. Bhattacharyya, *Tetrahedron*, **21**, 1537 (1955).

(5) K. W. Scott, N. Calderon, E. A. Ofstead, W. A. Judy, and J. F. Ward, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, No. L54; *Advances in Chemistry Series*, in press.

(6) N. Calderon, E. A. Ofstead, and W. A. Judy, *J. Polymer Sci.*, **5**, 2209 (1967).

(7) N. Calderon and E. A. Ofstead, unpublished data.

(8) H. C. Brown and P. A. Tierney, *J. Amer. Chem. Soc.*, **80**, 1552 (1958).

(9) H. C. Brown and C. P. Garg, *ibid.*, **83**, 2951 (1961).

(10) H. C. Brown and C. P. Garg, *ibid.*, **83**, 2952 (1961).

(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946); P. Bladon, J. M. Fabian, H. B. Henbest, H. P. Koch, and G. W. Wood, *ibid.*, 2402 (1951).