column (20°, 70 cc/min) yielded 62.1 mg of 5,5,5-d_3-pentyl methyl ether. The labeled pentyl methyl ether was placed with an excess of anhydrous hydrogen iodide in a 1-ml sealed tube and allowed to stand for 24 hr at 0°. Due to the small amount of product, the reaction mixture was refluxed with an excess (0.5 ml) of hexamethyldisilazane and one drop of chlorotrimethylsilane until no more ammonia was evolved. The 5,5,5-d_3-pentan-1-ol trimethylsilyl ether was collected by gas–liquid partition chromatography (10% GE SF-96 column) and the mass spectrum revealed the following isotopic composition: 87% d_3, 7% d_2, 6% d_1.

1,1-d_2-Dihydrocinnamyl Alcohol.—Reduction of 100 mg of dihydrocinnamic acid with lithium aluminum deuteride yielded 85.0 mg of 1,1-d_2-dihydrocinnamyl alcohol whose mass spectrum revealed an isotopic composition of 100% d_2.

2,2-d_2-Dihydrocinnamyl Alcohol.—Using the above-described procedures, 2.3 g of phenylacetic acid was reduced with lithium aluminum deuteride and the resulting 1,1-d_2-β-phenylethanol converted to its bromide. The bromide was subjected to a Grignard carbonation, followed by a lithium aluminum hydride reduction to yield 697 mg of 2,2-d_2-dihydrocinnamyl alcohol whose mass spectrum revealed an isotopic composition of 100% d_2.

3,3-d_2-Dihydrocinnamyl Alcohol.—Reduction of 500 mg of benzoic acid with lithium aluminum deuteride and conversion of the resulting 1,1-d_2-benzyl alcohol to its bromide were carried out by previously described procedures. A malonic ester condensation, followed by hydrolysis, decarboxylation, and reduction with lithium aluminum hydride yielded 339 mg of 3,3-d_2-dihydrocinnamyl alcohol whose mass spectrum indicated the following isotopic composition: 98% d_2, 2% d_0.

1,1,1,3,3-d_5-Pentan-2-ol.—Utilizing a procedure similar to that of Seibl and Gaümann,[28] pentan-2-one was exchanged under acid-catalyzed conditions. Preparation of the labeled acid catalyst was accomplished by slowly dissolving 4.0 g of dry phosphorus pentachloride in 16 ml of deuterium oxide in a nitrogen atmosphere. The solution was then diluted with another 16 ml of deuterium oxide and stored in a tightly stoppered flask. A mixture of 1.0 g of pentan-2-one and 10 ml of 10% deuteriophosphoric acid in deuteriochloric acid solution was heated under reflux for 12 hr. Extraction with deuterium oxide washed ether was followed by neutralization of the combined aqueous–ethereal layers with potassium carbonate. After extracting three more times with ether, the solvent was stripped on a rotary evaporator. The exchange procedure was repeated three more times and the final ethereal extract dried over anhydrous magnesium sulfate. After filtration, a lithium aluminum hydride reduction of the ethereal solution yielded 247 mg of 1,1,1,3,3-d_5-pentan-2-ol whose mass spectrum indicated the following isotopic composition: 73% d_5, 24% d_4, 2% d_3 and 1% d_2.

p-d_3-Methoxybenzyl Alcohol.—In 5 ml of acetone was placed 270 mg of p-hydroxybenzyl alcohol and 276 mg of potassium carbonate. To the mixture 284 mg (0.14 ml) of d_3-methyl iodide was rapidly added and the mixture heated under reflux for 8 hr using a Dry Ice condenser. The solution was cooled, diluted with 5 ml of water, and extracted twice with ether. The ethereal extracts were washed twice with water and dried over anhydrous magnesium sulfate. Filtration followed by evaporation of the ether on a rotary evaporator yielded 267 mg of p-d_3-methoxybenzyl alcohol whose mass spectrum showed the isotopic composition to be 100% d_3.

Registry No.—II, 14629-45-9; III, 14629-46-0; IV, 14629-47-1; V, 14629-48-2; VI, 14629-49-3; VII, 14629-50-6; VIII, 1825-67-8; IX, 14629-51-7; X, 14629-52-8; XII, 14642-79-6; XIII, 14629-53-9; XIV, 14629-54-0; XV, 14856-73-6; XVI, 14629-55-1; XVII, 14856-74-7; XVIII, 14629-56-2; XIX, 14856-75-8; XXI, 14629-57-3; XXII, 14629-59-5; XXIII, 14629-58-4; XXIV, 14629-60-8; XXV, 14856-76-9; XXVI, 14629-61-9; XXVII, 14856-77-0; XXVIII, 14629-62-0; XXIX, 2290-40-6; XXX, 14856-79-2; XXXI, 14629-63-1; XXXII, 10433-33-7; XXXIII, 14629-65-3; XXXIV, 14884-70-9; XXXV, 14629-66-4; XXXVI, 14629-67-5; XXXVII, 14856-80-5; XXXVIII, 3459-80-1; 2,2-d_2-pentan-1-ol, 14856-81-6; 3,3-d_2-pentan-1-ol, 14629-68-6; 4,4-d_2-pentan-1-ol, 14629-69-7; 1,1,1,3,3-d_5-pentan-2-ol, 14629-70-0; p-d_3-methoxybenzyl alcohol, 14629-71-1.

Control of Lithium Aluminum Hydride Reduction of Cyclic Dicarboxylic Acid Anhydrides to Produce γ-Lactones or Diols[1]

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The reduction of *cis*- and *trans*-1-methylcyclohex-4-ene-1,2-dicarboxylic acid anhydride, **1** and **3**, and of their saturated derivatives, **5** and **7**, by lithium aluminum hydride in tetrahydrofuran at −55° produced γ-lactones with reduction at the more hindered carbonyl as the sole product in yields of 89, 75, 78–82, and 85%, respectively. Similar treatment of methyl and phenyl succinic anhydride, **14** and **15**, produced mixtures of lactones in 69 and 72% yields. Five other symmetrical anhydrides also gave lactones in 70–80% yields. A mechanism involving 1,4-hydride addition is invoked to account for the high stereoselectivity observed in these reductions. Diols are produced in excellent yield when anhydrides are reduced with excess lithium aluminum hydride in refluxing tetrahydrofuran.

The reduction of mono- or dicarboxylic acid anhydrides by lithium aluminum hydride has been very infrequently used for the production of alcohols.[3] If a cyclic anhydride is reduced, the expected product is a diol. Our main interest in this area has been in the synthesis of 1,4-diols as intermediates in a broader program.[4–6] When reductions were carried out in diethyl ether, besides the expected diol, a frequently encountered product was a γ-lactone. This result is annoying when diols are desired, but there is a precedent for it.[3b,7,8]

Our interest in developing a lactone synthesis, without concurrent formation of diol, was spurred by several

(3) (a) W. G. Brown, *Org. Reactions*, **6**, 469 (1951); (b) N. G. Gaylord, "Reductions with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956, pp 373–379.
(4) J. J. Bloomfield and P. V. Fennessey, *Tetrahedron Letters*, 2273 (1964).
(5) J. J. Bloomfield and A. Mitra, *Chem. Ind.* (London), 2012 (1966).
(6) J. J. Bloomfield, *J. Org. Chem.*, in press.
(7) V. Parrini, *Gazz. Chim. Ital.*, **87**, 1147 (1957).
(8) D. G. Farnum and J. P. Snyder, *Tetrahedron Letters*, 3861 (1965).
(9) R. Granger and H. Techer, *Compt. Rend.*, **250**, 142 (1960).
(10) G. Snatzke and G. Zanati, *Chem. Ber.*, **648**, 62 (1965).
(11) H. C. Brown, P. M. Weissman, and N. M. Yoon, *J. Am. Chem. Soc.*, **88**, 1458 (1966).
(12) H. C. Brown and N. M. Yoon, *ibid.*, **88**, 1464 (1966).

papers. In one, it was reported that *cis*-1-methyl-cyclohex-4-ene-1,2-dicarboxylic acid anhydride (1) gave only the lactone 2, resulting from reduction of the more
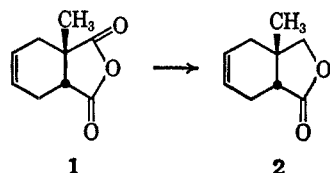
hindered carbonyl group.[9] In another paper, the oxidation of 9,10-bis(hydroxmethyl)decalin to the lactone was described.[10] Inasmuch as the diol was obtained by reduction of the related anhydride, it seemed to us that a one-step preparation of the lactone from the anhydride would be of value.

Recently, Brown and his co-workers have pointed out that lactones generally can be produced by reduction of anhydrides with lithium tri-*t*-butoxyalumino-hydride (LTBA),[11,12] but the steric course of these reductions is not known.

Discussion

Brown, *et al.*,[11,12] prefer the use of tetrahydrofuran (THF) as solvent for hydride reductions. Our experience indicates that this solvent is superior to diethyl ether regardless of the hydride reduction under consideration. Brown[11,12] further suggests that LTBA should be used to reduce anhydrides to lactones or to reduce other functional groups in the presence of carboxylic acid groups. In contrast, we have found that operating for a short time at low temperatures, about $-55°$, with 0.5 mole of $LiAlH_4$ per mole of anhydride is a very effective procedure for the partial reduction of a variety of anhydrides. The ease of this procedure and the cheapness of $LiAlH_4$ relative to LTBA makes it, we feel, the preferred one for lactone synthesis. However, the same procedure proved unsatisfactory for the partial reduction of the corresponding half-esters.

The complete reduction of anhydrides requires a rather prolonged reflux period, in most cases 24–48 hr. In fact, even the reductions of the diesters, especially when ether is the solvent, are best conducted at reflux for as long as 48 hr.

The conversion of 1 in to 2[9] seems contrary to the expectation that reduction should occur at the least hindered carbonyl group. Nevertheless, we have confirmed Granger and Techer's[9] result with 1 (obtaining 2 in 88.6% yield) and with the related *trans* isomer 3 as well as the saturated derivatives 5 and 7 (Scheme I). All four lactones are crystalline solids. There may be small amounts of the isomeric lactones present, but we were unable to detect their presence with several different gas chromatography columns. The nmr spectra of the CH_2O region of the lactones are most revealing. All spectra were determined on the crude distillate and on the recrystallized lactones. Examination of these spectra indicated that the isomeric lactones, if present at all, were produced in amounts less than 5%. Lactones 2 and 6, at 60 MHz,[13] show a triplet (for CH_2O-) with the outlying peaks separated from the central peak by 9 Hz and having about 0.05 times the peak height at

Scheme I
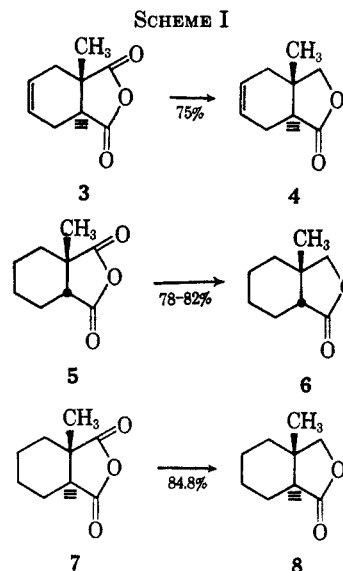
half-height. At 100 MHz[14] the spectrum of 2 shows a splitting of the central peak into two peaks separated by 2 Hz. Lactone 6 at 100 MHz shows a similar split of the central peak, but in this case the splitting is only 0.5 Hz. These nmr results are expected on the basis of structures 2 and 6 and not for the isomeric lactones; this is shown clearly by the spectrum of the isomer of 2, lactone 10, produced from 9a by reduction with $LiAlH_4$. This lactone shows a very complex multiplet consisting of a four-peak pattern (1 H) centered at δ 4.25, with peak separations of 8.0, 2.0, and 8.0 Hz and a three-peak pattern (1 H) centered at δ 3.80 with peak separations of 8.0 Hz.

9a, R = CH_3; R′ = H
b, R = C_2H_5; R′ = H
c, R = R′ = C_2H_5
d, R = C_2H_5; R′ = n-C_4H_9
e, R = R′ = CH_3
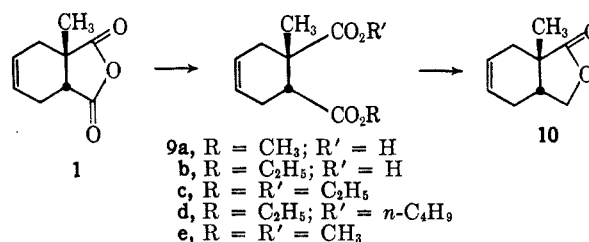
The nmr spectrum of crude 2 from the very early attempts at lactone preparation shows evidence of 10 to the extent of less than 5%. The spectra of crude 2, prepared when the reduction technique had been perfected, and of crude 6 show no evidence of isomeric lactone.

The *trans*-lactones 4 and 8 both show quartets in the CH_2-O region, centered at δ 4.00 and 3.90, respectively, with $J = 8.0$ Hz. The 100-MHz spectra confirm the simplicity of the pattern and the value of J. An attempt to prepare lactone 13 (isomeric with 4) was only partially successful because the mixture of esters (11 and 12) was not separable. The crude mixture of esters (prepared by partial esterification of 3) was reduced and 13 was purified by tedious preparative gas–liquid partition chromatography. The nmr spectrum of crude 13 and the glpc purified product show complex spectra around δ 4.0 which is not resolvable because of the presence of contaminants.

11   **12**

3

13   + 4
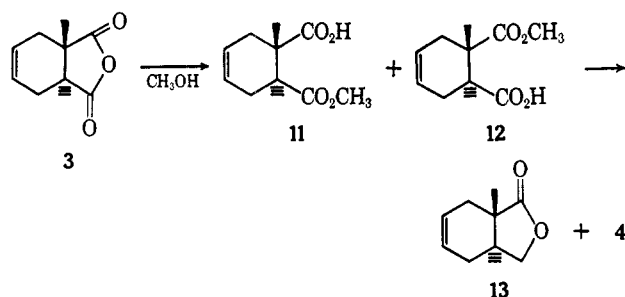
Several other anhydrides were also reduced. Methyl and phenyl succinic anhydrides, **14** and **15**, in contrast to the anhydrides described above, gave mixtures consisting of two lactones in a 1:2.2 and 3:2 ratio, respectively. A lactone mixture containing **17b** was prepared

14, R = CH₃   16a, R = CH₃   16b, R = CH₃
15, R = C₆H₅   17a, R = C₆H₅   17b, R = C₆H₅
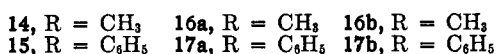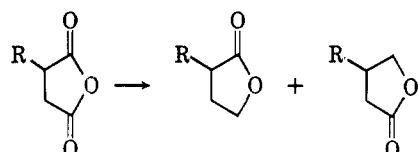
by the reaction of malonic ester anion with styrene oxide.[15,16] Gas chromatographic comparison of the mixtures of lactones prepared by the condensation route and by reduction of phenyl succinic anhydride showed that **17b** was the major component of the reduction reaction.

18   **17b**
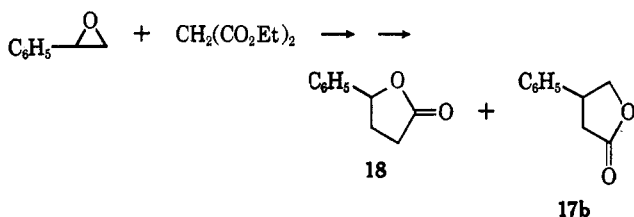
In order to explain this result and the high specificity described above, we suggest that the less hindered carbonyl oxygen interacts (complexes) with a solvated cation. In the process this site becomes the more hindered one. Attack at the other carbonyl by an aluminohydride ion produces an aldehyde which is
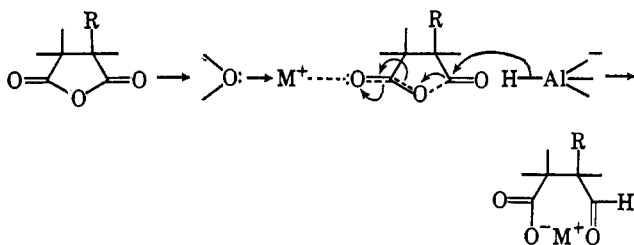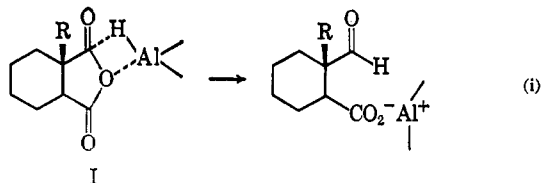

subsequently rapidly reduced. This amounts to a 1,4-hydride addition to the O=C—O—C=O system.[17–19]

(15) G. H. DePuy, F. W. Breitbeil, and K. L. Eilers, *J. Org. Chem.*, **29**, 2810 (1964).
(16) We are indebted to R. A. Martin for preparing this lactone mixture.
(17) An alternative mechanism, suggested by a referee, involves a four-center transition state between >AlH and anhydride. Thus mechanism i


I   (i)

A similar result occurs in the hydride reduction of free diacids. Noyce and Denney[20] and Marvel and Fuller[21] have observed that the LiAlH₄ reduction of a diacid leads to a mixture of diol and lactone. In the one instance where the lactone structure was determined[20] the reduction occurred at the more hindered carbonyl, in marked contrast, as these authors noted, to the result of monoesterification of hindered diacids. If LiAlH₄ can convert short-chain diacids into the anhydrides, these results are in accord with our observations and our suggested mechanism.

The anhydrides in Scheme II were also reduced in good yield, as indicated.

SCHEME II

19   75%   **20**

21   70.4%   **22**

23   72.8%   **24**

25   79–83%   **26**

27   70.5%   **28**
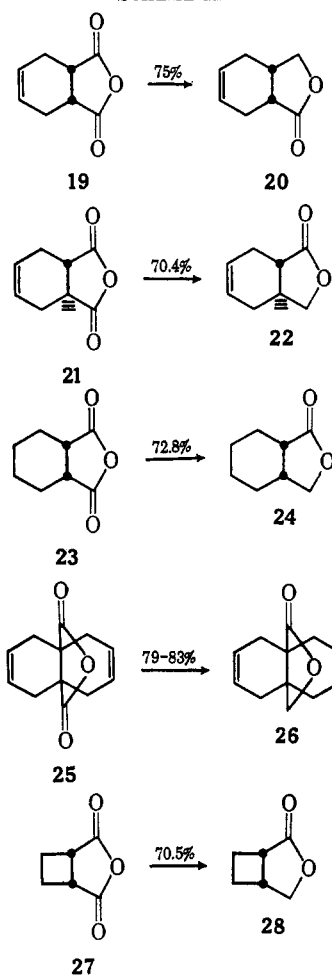
produces a less hindered carboxylate than ii.

II   (ii)
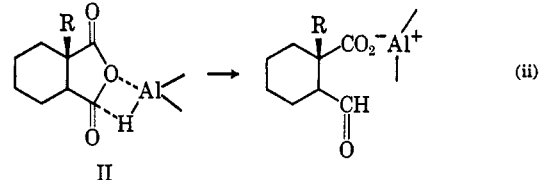
The implication is that product development control[18] leads to the less hindered product. There is, at this point, no experimental evidence for either mechanism, but it seems to us that the high basicity of the carbonyl oxygen as opposed to the central oxygen, plus the exothermic character of the reduction, predict a transition state closer to reactants than to products.[19] For the mechanism described in this reference, sizeable amounts of reduction in both directions should be found, because there seems to be little difference between transition states I and II.

(18) See W. G. Dauben, G. J. Fonken, and D. S. Noyce, *J. Am. Chem. Soc.*, **78**, 2579 (1956).
(19) See G. S. Hammond, *ibid.*, **77**, 334 (1955).
(20) D. S. Noyce and D. B. Denney, *ibid.*, **72**, 5743 (1950).
(21) C. S. Marvel and J. A. Fuller, *ibid.*, **74**, 1506 (1952).

The nmr spectra of **20** and **24** in the CH_2–O region are similar, showing an AB quartet further split by the proton at the bridgehead.

In **20**, $J_{AB} = 8.8$ Hz, $J_{BX} = 3.8$ Hz; $J_{AX} = 1.4$ Hz. In **24**, $J_{AB} = 8.6$ Hz, $J_{BX} = 2.2$ Hz; $J_{AX} = 0$. The related region of the spectrum of **22** is broad and not well resolved.

Anhydrides **1**, **3**, and **25** have been converted into diols in high yield using excess LiAlH$_4$ in refluxing THF (Scheme III). When the reduction of **19** to the diol

SCHEME III
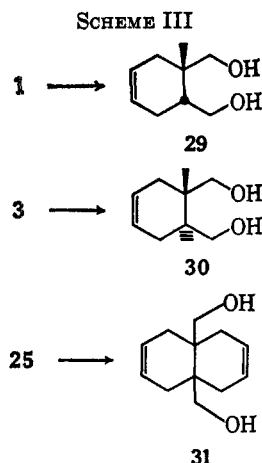
32 was conducted in either (before THF was used for all LiAlH$_4$ reductions in our laboratories), the yields varied from 45 to 85% depending on the length of the reflux period and on the work-up procedure. With THF as solvent, the yields are 85% and up. For production of **32** and the related *trans*-diol **33**, when ether is the solvent, the esters are better starting materials. For synthesis of *trans*-1,2-bishydroxymethylcyclohex-4-ene (**33**), the acid chloride **36** (prepared from butadiene and fumaryl chloride) was a quite satisfactory precursor.

34 (*cis*), R = OC$_2$H$_5$ **32** (*cis*)
35 (*trans*), R = OC$_2$H$_5$ **33** (*trans*)
36 (*trans*), R = Cl
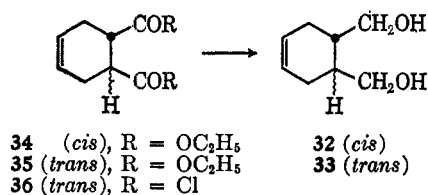
Experimental Section[22]

Lactones.—The following general procedure for the lactone synthesis was used throughout. A 500-ml three-necked round-bottom flask was fitted with a reflux condenser, a Hershberg addition funnel, and a Trubore[23] stirrer, with an inlet for maintaining a slight positive pressure of dry, oxygen-free nitrogen. To 200 ml of tetrahydrofuran, which was freshly distilled from lithium aluminum hydride, was added 2.2 g of LiAlH$_4$ and this mixture was stirred under reflux for 30 min. The condenser was removed, replaced by a low-temperature thermometer, and the

mixture was cooled with stirring to −55° (Dry Ice–acetone bath). Then 0.1 mole of the anhydride dissolved in 150 ml of THF was added at a rate to maintain the temperature at −55 ± 5°, usually 30 min. When the anhydride was all added the solution was allowed to warm to 0° over 90 min, stirred at 0° for 10–20 min (ice bath), then cooled to −15° (Dry Ice–acetone bath), and 40 ml of 6 N hydrochloric acid was added over 5–15 min. Then, after the cold bath was removed, stirring was continued for 10–20 min. At this point the mixture was either immediately worked up by separating layers, extracting the aqueous layer with ether, and drying the combined organic solutions over anhydrous sodium sulfate, or allowed to stand for several hours before this work-up. The drying agent was removed by filtration, the solvent was stripped on a rotary evaporator, and the residue was distilled.

Diols.—With all the 1,4-diols the work-up procedure is critical. The preferred procedure involves hydrolysis of the reaction mixture with water, followed by filtration of the mixture. The resulting filter cake is then leached with ether. However, some of the diols, **32** and **33** particularly, form a marshmallowlike syrup which is totally intractable. In these instances the reaction mixture is dissolved with *cold* 4–9 N sulfuric acid. Continuous extraction with ether is necessary to recover the diol from the aqueous solution. In any case when acid is used in the work-up procedure, a base wash of the organic layer (or drying over potassium hydroxide) is necessary in order to avoid conversion of a large part of the diol into the tetrahydrofuran derivative.

trans-**4-Cyclohexene-1,2-dicarbonyl Chloride (36).**—Fumaryl chloride (Distillation Products Industries, 517 g, 3.38 moles, directly from the bottle) in 250 ml of anhydrous ether at −25° was added to a solution of butadiene (dried by passage through a column of Linde 4A Molecular Sieve, 260 g, 4.8 moles) in 600 ml of anhydrous ether at −50°. The combined solution was rapidly poured into the glass liner of a 2-l. Parr[24] stirred autoclave. The top of the bomb was rapidly fastened and the stirrer was started; at this point the temperature was −25°. The temperature then rose rapidly, reaching 132° 11 min after the bomb was sealed. The cooled bomb was opened and the product was distilled[22] at 0.1 mm, bp 66–70°, to give **36**, 649 g, 92.9%.[25]

trans-Δ^4-**Tetrahydrophthalic Anhydride (21).**—An old sample of acid chloride was treated with water and the acid was then heated with acetic anhydride at 90° for several hours. The anhydride separated from the cooled solution and was crystallized from benzene and dried under vacuum: mp 176–177° (lit. mp 183.5–184.5°,[25] 186°,[26] 187.5–189°[27]); infrared (KBr disk) ν_{max} 1787, 1840 cm^{-1}.

trans-**1,2-Bis(hydroxymethyl)cyclohex-4-ene (33).**—Diacid chloride **36**, 649 g (3.14 moles), was added dropwise (over 4 hr) through a Hershberg addition funnel to a stirred solution of LiAlH$_4$, 180 g (4.5 moles), in 3 l. of tetrahydrofuran under a nitrogen atmosphere. After the mixture was stirred an additional 12 hr, the flask was placed in a cold bath at 0° and with continued vigorous stirring 700 ml of 9 N sulfuric acid was added over 2.5 hr. The mixture was filtered and the residue was treated with an additional 1300 ml of 9 N sulfuric acid. The aqueous solution was then continuously extracted with ether for 6 days and the combined organic extracts were dried over potassium carbonate. Evaporation of the solvent and distillation[22] at 0.1 mm, bp 106°, gave the diol, 379 g (85%),[28] which solidified in the receiver. Similar results were obtained when the acid chloride was converted into the diethyl ester which was then reduced essentially as described above.

cis-**1-Methylcyclohex-4-ene-1,2-dicarboxylic Acid Anhydride (1).**—Butadiene gas was passed through a column of Linde 4A Molecular Sieve and then condensed by passage through a glass spiral immersed in a Dry Ice–acetone bath. The liquid, 490 g (9 moles), was added to citraconic anhydride (Matheson Coleman and Bell, 450 g, 4 moles) and hydroquinone (5 g) contained in the glass liner of a 2-l. Parr[24] stirred autoclave. The bomb was sealed and heated, with stirring, at 123° for 12 hr. The reaction mixture was distilled at aspirator pressure to remove vinyl-

(22) All melting points were taken with NBS calibrated Anschütz thermometers. Analyses were performed by the Monsanto Analytical Laboratory and by Alfred Bernhardt, Mikroanalytisches Laboratorium, Mülheim (Ruhr). Distillations (unless indicated otherwise) were through a 25-cm vacuum-jacketed vigreux column fitted with a total reflux, partial take-off head. Nmr spectra were taken in carbon tetrachloride solution, with internal tetramethylsilane as standard, on Varian A-60, A-56/60, and HA-100 instruments. Infrared spectra were determined on Beckman IR-4, IR-5, or IR-8 instruments.

(23) Trademark, Ace Glass Co.

(24) Parr Series 4500, stainless steel. Parr Instrument Co., Moline, Ill.

(25) *Cf.* M. E. Bailey and E. D. Amstutz, *J. Am. Chem. Soc.*, **78**, 3828 (1956).

(26) K. Alder, M. Schumacher, and O. Wolff, *Ann.*, **564**, 79 (1949).

(27) F. V. Brutcher, Jr., and D. D. Rosenfeld, *J. Org. Chem.*, **29**, 3154 (1964).

(28) *Cf.* D. C. Ayres and R. A. Raphael, *J. Chem. Soc.*, 1779 (1958).

cyclohexene and then at 0.1 mm, bp 82–85°,[22] to produce 625 g (93.8%) of the anhydride, lit.[29] bp 113–115 (4 mm).

cis-1-Methylcyclohexane-1,2-dicarboxylic Acid Anhydride (5).—The unsaturated anhydride, 1, was reduced with 5% palladium on carbon in benzene under 4 atm of hydrogen. The product was crystallized from carbon tetrachloride–hexane at −19°, mp 60–62° (lit.[29a,c] mp 72°). The infrared spectrum, in chloroform, showed bands for anhydride at 1780 and 1830 cm⁻¹.

cis-1-Methyl-2-carbomethoxycyclohex-4-ene-carboxylic Acid (9a).—The anhydride, 1, dissolved in twice its volume of methanol was boiled until the volume was reduced by 50%. Cooling gave a crystalline solid, recrystallized from benzene–hexane, mp 116–118°. *Anal.* Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: 60.67; H, 7.14.

Similar treatment of the anhydride with ethanol gave the corresponding half-ethyl ester, **9b**, which was crystallized three times from hexane and then from ethyl acetate–hexane at −80° to give the analytical sample, mp 87.0–88.1°. *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.45; H, 7.58.

Diesters of 1, 9c, and 9d.—The anhydride was also converted into the diethyl ester, **9c**, by prolonged reflux (24 hr) with a mixture of absolute ethanol and ethyl orthoformate in the ratio of 2:1 by volume, in the presence of 1% p-toluenesulfonic acid. The product (31.8%) was distilled through a 2-ft Nester–Faust stainless steel spinning band-column at 0.01 mm: bp 62°; $n^{25}D$ 1.4600. *Anal.* Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.05; H, 8.08.

The residue from this reaction was refluxed with a large excess of n-butyl alcohol and 1% p-toluenesulfonic acid to produce a mixture of mono-n-butyl monoethyl and di-n-butyl[29b] esters. The mono-n-butyl monoethyl ester, **9d**, was distilled through the Nester–Faust column at 0.02 mm: bp 77°; $n^{25}D$ 1.4599. *Anal.* Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.02. Found: C, 66.86; H, 9.00.

Dimethyl cis-1-Methylcyclohex-4-ene-1,2-dicarboxylate (9e). —The dimethyl ester, **9e**, was prepared by refluxing for 40 hr a mixture of 41.5 g of anhydride 1, 0.5 g of p-toluenesulfonic acid, 35 g of methyl orthoformate, and 20 g of methanol. The solvent was then slowly distilled off until the pot temperature reached 160°. The residue, after a base wash, was distilled at 0.01 mm to give the crude product: bp 71 ± 3°; yield, 41.4 g (78.2%). Redistillation through the Nester–Faust column gave a middle fraction: bp 96° (1.2 mm); $n^{25}D$ 1.4700. *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.24; H, 7.60. Found: C, 62.32; H, 7.60.

cis-1-Methyl-1,2-bis(hydroxymethyl)cyclohex-4-ene (29).—The cis-anhydride 1, 365 g (2.2 moles), was added over 45 min to a solution of LiAlH₄ in 1.5 l. of tetrahydrofuran (from a freshly opened bottle of Fisher certified reagent). After the reaction mixture had stirred under reflux for 42 hr (nitrogen atmosphere), 400 ml of water was added and the thick slurry was filtered through a coarse sintered disk funnel. The filtrate was concentrated and the precipitate in the funnel was washed with the recovered solvent and with 2 l. of ether. Concentration of all the organic filtrates gave a pale yellow oil which was mixed with 150 ml of benzene and 300 ml of petroleum ether (bp 30–75°). The crystalline diol was collected and air dried to give 315 g (91.9%), mp 64.8–68.4°. In other instances, the product was distilled at 0.1 mm, 100°,[22] to give yields ranging from 73 to 98%. The analytical sample was recrystallized three times from benzene–hexane, mp 65–66.5°. *Anal.* Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.31; H, 10.25.

cis-1-Methyl-2-hydroxymethylcyclohex-4-ene Carboxylic Acid γ-Lactone (10).—The half-ester, **9a**, 9.9 g (0.05 mole), in 150 ml of tetrahydrofuran was added to 1.65 g of lithium aluminum hydride at −55° as in the general lactone synthesis. The reaction mixture was worked up in the same manner except, since the reduction was not complete under these conditions, a bicarbonate wash was necessary to remove starting acid. The final yield was about 0.3 g (4%). Recrystallization several times from hexane at 0° gave the analytical sample, mp 46.8–47.6°. Admixture with 2 gave a liquid at room temperature: infrared (CHCl₃) $ν_{max}$ 1777 cm⁻¹; nmr, δ 5.72 d (2 H), 4.0 m (seven

peaks, 2 H), 2.7–2.35 m (1 H), 2.35–1.90 m (4 H), 1.2 s (3 H). *Anal.* Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.21; H, 7.78.

trans-1-Methylcyclohex-4-ene-1,2-dicarboxylic Acid Anhydride (3).—Mesaconyl chloride was prepared according to the method of Kyrides for the synthesis of fumaryl chloride[30] from citraconic anhydride (Eastman or Matheson Coleman and Bell) on 1–5.6-mole scales in yields ranging from 72 to 85%. The product was distilled from phthaloyl chloride through a 27-in. helix-packed column at a reflux ratio of 10–12 to 1 at 9 mm with a head temperature of 65° and a pot temperature of 135°. In a typical run the freshly distilled acid chloride, 680 g (4.05 moles), 1 g of t-butyl catechol, 350 g of dry butadiene, and 500 ml of dry ether were placed in the liner of the Parr 2-l. autoclave[24] and the bomb was sealed. The reaction mixture was allowed to stand for 8 hr. Then the temperature was gradually raised to 60° over 5 hr and maintained at 60° for 18 hr. After an additional 11 hr the bomb was opened, the contents were filtered, and the ether was distilled off. The residue was then distilled[22] at 0.6 mm to give a small forerun, bp 48–70°, 19.2 g, and the major fraction at 0.15 mm, 65–70°, 851 g (94.5%).

The anhydride was prepared from the acid chloride either by hydrolysis followed by treatment of the diacid with acetyl chloride or by treatment of the acid chloride (17.6 g) with acetic acid (10.0 g) which gave the anhydride directly on distillation. The first method usually produced a slightly better product because recrystallized acid was used. In the second process, the crystalline trans-anhydride was usually contaminated by the liquid cis-anhydride. The cis-anhydride was readily removed by crystallizing the mixture from carbon tetrachloride–hexane at −20°. The product so produced had mp 77.5–78.7° (lit.[29a] mp 78–79°). The acid prepared from the acid chloride had mp 181.0–183.5° (lit.[29a] mp 180–181°).

trans-1-Methylcyclohexane-1,2-dicarboxylic Acid Anhydride (7).—Reduction of 5 was performed to give 7 as described in the preparation of 3 from 1. The product had mp 86.0–86.5° after crystallization from benzene–hexane and acetyl chloride in the ratio of 2:8:1 at −8° (lit.[29a] mp 87–88°).

trans-1-Methyl-1,2-bis(hydroxymethyl)cyclohex-4-ene (30).— The trans-anhydride, 3, was reduced according to the procedure described for the preparation of 29 from 1 to produce yields ranging from 83 to 92%. The analytical sample was distilled through the Nester–Faust column: bp 107–108° (0.1 mm); $n^{25}D$ 1.5020. *Anal.* Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.00; H, 10.36.

trans-1-Methyl-2-hydroxymethylcyclohex-4-ene Carboxylic Acid γ-Lactone (13).—A liquid mixture of monomethyl esters was prepared by treating 3 with methanol. This crude mixture was reduced with LiAlH₄ as described for 10. The neutral fraction was separated into four parts by preparative gas chromatography on a 6-ft, 0.25-in. column packed with 20% SE-30 on 110/120 mesh Anakrom ABS at 120°.[31] The fourth fraction[31] contained 97% of one component according to the analytical glpc results.[31] The infrared spectrum of this sample showed a C=O band at 1790 cm⁻¹. The nmr spectra exhibited the expected degree of complexity in the CH₂–O region showing six peaks centered at δ 4.15, but the methyl group peak appeared as a doublet, indicating that the sample was still not pure and further efforts to obtain a pure sample of 13 were abandoned.

cis-1-Methyl-1-hydroxymethylcyclohex-4-ene Carboxylic Acid γ-Lactone (2).—Following the general procedure the lactone was obtained in 88.6% yield, bp[22] 68–72° (0.1 mm). The analytical sample was recrystallized from petroleum ether and had mp 48.8–49.8° (lit.[9] mp 46°); infrared (CHCl₃) $ν_{max}$ 1778 cm⁻¹; nmr, δ 5.68 s, br (2 H), 3.88 t (2 H), 2.52–2.26 m (3 H), 2.12–1.90 m (2 H), 1.17 s (3 H). *Anal.* Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.06; H. 7.78.

trans-1-Methyl-1-hydroxymethylcyclohex-4-ene carboxylic acid γ-lactone (4) was obtained in 75% yield: bp[22] 99–103° (3 mm); $n^{25}D$ 1.4890. The sample solidified on cooling and after recrystallization from petroleum ether the analytical sample had mp 41.8–42.6; infrared (CHCl₃) $ν_{max}$ 1780 cm⁻¹; nmr, δ 5.82 s, br (2 H), 4.00 q (2 H), 2.82– 2.40 m (1 H), 2.40–2.00 m (4 H),

(29) (a) I. N. Nazarov and V. F. Kucherov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 289 (1952); *Chem. Abstr.*, **47**, 5363c (1953); (b) *cf.* B. Phillips and P. S. Starcher, U. S. Patent 2,794,030 (May 28, 1957); *Chem. Abstr.*, **51**, 16556b (1957); (c) *cf.* B. Bailey, R. D. Haworth, and J. McKenna, *J. Chem. Soc.*, 967 (1954).

(30) L. P. Kyrides, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 422.

(31) The mixture showed two peaks on 0.063 in. × 10 ft column packed with 3% SE-30 on Aeropak 30 (Varian Aerograph) but on the preparative column these came over as one broad peak from which samples were cut at four different places.

1.02 s (3 H). *Anal.* Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.23; H, 7.83.

cis-1-Methyl-1-hydroxymethylcyclohexane carboxylic acid γ-lactone (6) was obtained in 82% yield, bp²² 51–61° (0.07 mm). The compound solidified in the receiver and in the head during distillation. The analytical sample, from petroleum ether, had mp 49.8–50.6° (lit.⁹ mp 43°); infrared (CHCl₃) ν_max 1770 cm⁻¹; nmr, δ 3.80 t (2 H), 2.18 d (1 H), 2.05–1.80 m (1 H), 1.80–1.30 m (5 H), 1.20 s (3 H). *Anal.* Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.09. Found: C, 70.08; H, 9.20.

trans-1-Methyl-1-hydroxymethylcyclohexane carboxylic acid γ-lactone (8) was obtained as a liquid, which rapidly solidified, in 85% yield, bp²² 116–125° (5 mm). The analytical sample, from petroleum ether, had mp 38–39°; infrared (CHCl₃) ν_max 1775 cm⁻¹; nmr, δ 3.90 q (2 H), 2.2–1.2 complex multiplet (7 H), 1.01 s (3 H). *Anal.* Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.09. Found: C, 70.41; H, 8.84.

α and β-Methyl-γ-butyrolactone (16a, b).—Distilled methyl succinic anhydride (an ancient commercial sample of unknown origin) was reduced according to the general procedure to produce a 69% yield of the mixed lactones, bp²² 80° (9 mm). The nmr spectrum showed two sets of methyl doublets centered at δ 1.18 (minor constituent) and 1.10 (major constituent). Gas–liquid partition chromatography on a 0.25-in., 10-ft column packed with 18% Carbowax 20M and 1% silver nitrate at 165° showed two peaks in the ratio of 1:2.2.

α and β-Phenyl-γ-butyrolactone (17a, b).—Reduction of phenyl-succinic anhydride³²,³³ gave a mixture of 17a and 17b in 72% yield, bp²² 113–122° (0.1 mm). Gas–liquid partition chromatography on a 0.25-in., 10-ft 20% Carbowax 20M (containing 1% CuCl₂) column at 230° showed two peaks in the ratio of 6:4. The first peak overlapped with one of the peaks produced by a mixture of β- and γ-phenylbutyrolactone,¹⁵,¹⁶ indicating that reduction occurred predominately at the more hindered carbonyl.

cis-Δ⁴-Tetrahydrophthalide (20) was obtained from 19 in 75% yield: bp²² 85° (0.1 mm); n²⁵D 1.4998; infrared (smear) 1778 cm⁻¹; nmr, δ 5.75 sextet (2 H), 4.30 q (1 H), 2.95–1.85 very complex multiplet (6 H). *Anal.* Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 68.98; H, 7.22.

trans-Δ⁴-Tetrahydrophthalide (22).—Reduction of 21 produced a crystalline solid, mp 100–102°, in 70.4% yield. Recrystallization from benzene–hexane gave the analytical sample: mp 102.0–

102.8°; infrared (CHCl₃) ν_max 1780 cm⁻¹; nmr, δ 5.75 m (2 H)t 4.68–4.36 m (1 H), 4.15–3.75 m (1 H), 2.75–1.80 br with mos, of area centered at 2.28 (6 H). *Anal.* Calcd for $C_8H_{10}O_2$: C, 69.54; H, 7.30. Found: C, 69.40; H, 7.28.

cis-Hexahydrophthalide (24) was produced in 72.8% yield: bp²² 72–77° (0.5 mm) (lit. bp 134–138 (25 mm),³⁴ 120° (5 mm)⁷); infrared (smear) ν_max 1778 cm⁻¹; nmr, δ 4.18 q (1 H), 3.88 d (1 H), 2.75–2.30 m (2 H), 2.1–1.0 very complex multiplet (8 H).

10-Hydroxymethyl-Δ²,⁶-hexalin-9-carboxylic Acid γ-Lactone (26).—The anhydride, 25,³⁵ was reduced on the 0.1-mole scale described above in 82.7% yield and by the same procedure on a 1.0-mole scale in 79.5% yield. The analytical sample, crystallized from cyclohexane–chloroform, had mp 80.6–81.8°; infrared (CHCl₃) ν_max 1770 cm⁻¹; δ 5.65 m (4 H), 3.97 s (2 H), 2.8–1.7 complicated ABX multiplet (8 H). *Anal.* Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.71; H, 7.57.

9,10-Bis(hydroxymethyl)-Δ²,⁶-hexalin (31).—The reduction of the anhydride, 25,³⁵ was carried out on 2.1–3.5-mole scale as described above using 100–180 g of LiAlH₄ in 2–3 l. of Fisher certified tetrahydrofuran (from a freshly opened bottle) with yields of 85–94%.³⁶

cis-2-Hydroxymethylcyclobutane Carboxylic Acid γ-Lactone (28).—Reduction of 27³⁷ produced lactone 28 in 70.4% yield: bp²² 109–113° (15 mm); n²⁵D 1.4687; infrared (smear) ν_max 1762 cm⁻¹ (with a very weak shoulder at 1848 cm⁻¹ which suggested the presence of a small amount of anhydride). The nmr spectrum was very complicated showing multiplets at δ 4.5–4.0 (2 H), 3.5–2.85 (2 H), 2.8–1.8 (4 H). *Anal.* Calcd for $C_6H_8O_2$: C, 64.28; H, 7.36. Found: C, 64.01; H, 7.42.

Registry No.—2, 14679-25-5; 4, 14679-26-6; 5, 14679-27-7; 6, 14723-44-5; 8, 14679-28-8; 9a, 14679-29-9; 9b, 14679-30-2; 9c, 14679-31-3; 9d, 14679-32-4; 9e, 14679-33-5; 10, 14679-34-6; 16a, 1679-47-6; 16b, 1679-49-8; 17a, 6836-98-2; 17b, 1008-73-7; 20, 14679-39-1; 21, 13149-03-6; 22, 14679-41-5; 24, 14764-51-3; 26, 14679-43-7; 28, 14764-52-4; 29, 14679-45-9; 30, 14679-46-0.

(32) Prepared by treatment of phenylsuccinic acid³³ with acetyl chloride.
(33) C. F. H. Allen and H. B. Johnson, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 804.

(34) A. Windaus, F. Klänhardt, and G. Reverey, *ibid.*, **55B**, 3981 (1922).
(35) K. Alder and K. H. Backendorf, *ibid.*, **71**, 2199 (1938).
(36) See J. J. Bloomfield and J. R. S. Irelan, *J. Org. Chem.*, **31**, 2017 (1966).
(37) E. R. Buchman, A. O. Reims, T. Skei, and M. J. Schlatter, *J. Am. Chem. Sci.*, **64**, 2696 (1942).

Oxidative Coupling of Alkylbenzenes by Nitric Acid

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o-Xylene, o-diethylbenzene, and hemimellitene react with nitric acid to give biphenyls. Reactive intermediates can be preferentially intercepted by a more basic alkylbenzene to produce unsymmetrical alkylbiphenyls. At low temperatures the rate of nitration is slow compared with that of the coupling reaction. Yields are in some cases 30% at about 40% hydrocarbon conversion. The mechanism was investigated by use of deuterionitric acid.

Nitrative coupling and cross coupling of alkylbenzenes to form alkyl homologs of nitrobiphenyl is a preparatively significant side reaction during nitration.¹ The reaction proceeds in two steps;² polyalkylbiphenyls are formed by oxidative coupling, and then are nitrated. Nitration of the coupled products is slower at low temperatures than the coupling itself, consequently, it appeared possible to use this procedure as a preparative method for polyalkylbiphenyls. The purpose of the present study was to optimize the reaction conditions, to isolate and identify the polyalkylbiphenyls, and to elucidate the reaction mechanism.

(1) I. Puskas and E. K. Fields, *J. Org. Chem.*, **31**, 4204 (1966).
(2) I. Puskas and E. K. Fields, *ibid.*, **32**, 589 (1967).

Results

Table I summarizes the experiments aimed at the preparation of polyalkylbiphenyls, which, with one exception, were restricted to methyl compounds. Although o-xylene can couple with itself, mixtures of o-xylene with more basic methylbenzenes gave predominantly cross coupled products; the small amounts of homo-coupled products were usually nitrated. The cross couplings are the preparatively important reactions.

Above the optimal temperature ranges the coupled products nitrated fast to nitropolyalkylbiphenyls.² With o-xylene–pseudocumene and o-xylene–prehnitene