The Synthesis of Asymmetrically Labeled 5-Norbornene-2,3-*endo*-dicarboxylic Anhydride[1]

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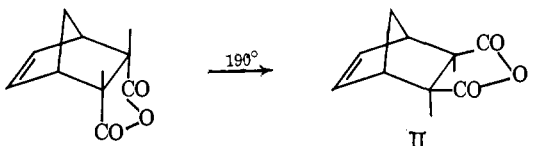
Abstract: Procedures are described for a synthesis of 5-norbornene-2,3-*endo*-dicarboxylic anhydride stereospecifically labeled with ^{14}C in one carbonyl group and for the degradation of the anhydride to determine which carbonyl group was labeled. The particular method of synthesis was found to give the labeled anhydride with ^{14}C in that carbonyl group which corresponds in position to the carboxyl group of the levorotatory 2-*endo*-norbornanecarboxylic acid.

In the course of our investigations aimed to better understanding of the mechanism of the Diels–Alder reaction[2-11] we have focused on the thermal isomerization of the cyclopentadiene–maleic anhydride adduct [5-norbornene-2,3-*endo*-dicarboxylic anhydride (I)] to the corresponding *exo* isomer (II) which takes place rather rapidly at 190°.[12] Berson and co-workers[2,3] have made a detailed study of this rearrangement and have reported that in decalin it occurs both by an "external" pathway (a retrogression of the *endo* adduct I to the addends which then recombine to give the



I II

exo isomer II) and an "internal" pathway (a direct mechanism not involving dissociation into kinetically free fragments).

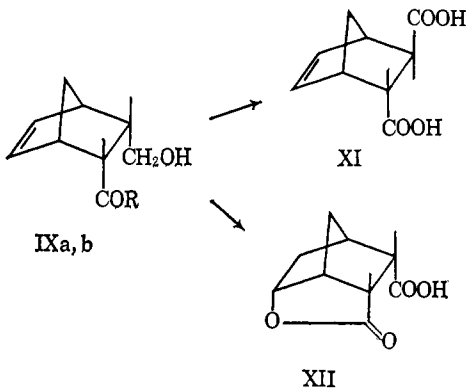
In an attempt to clarify the mechanism of the "internal" mechanism we have undertaken to synthesize the *endo* anhydride I stereospecifically labeled with carbon-14 in *one* carboxyl group. The idea was then to isomerize this substance under conditions which would allow the separation of the internal and external pathways,[13] so as to obtain a labeled *exo* anhydride II formed as nearly exclusively as possible by the "internal" mechanism. The position of the label in the rearranged product II compared with its position in the starting *endo* anhydride I would then permit a distinction between several of the possible "internal" mechanisms. In particular, it would be possible to distinguish between those mechanisms which would lead to retention of configuration (2,3-C–C bond cleavage[5]), inversion of configuration (7,5-hydrogen migration[3,5,12]), and loss of configurational integrity (a cage mechanism,[3,5,12] a mix of different mechanisms, etc.). It was after completion of the synthesis of 5-norbornene-2,3-*endo*-dicarboxylic anhydride (Ia), asymmetrically labeled with carbon-14 in one carboxyl group, and development of an appropriate degradative procedure to locate the label as described in this paper that we found[14] conclusive evidence that there is, in fact, no significant operation of an internal mechanism in the thermal interconversion of I to II in *t*-pentylbenzene and, although not proven, it seems unlikely that there is an internal mechanism in decalin either, contrary to the conclusions drawn[2,3] and uncritically accepted[11] in earlier work.

Synthesis of 5-Norbornene-2,3-*endo*-dicarboxylic Anhydride-2-^{14}C (Ia)

The plan of the finally successful synthesis of Ia is outlined in Figure 1. 3-Chloropropanediol-1,2 (III) with ^{14}C-labeled potassium cyanide gave the dihydroxynitrile IV. Hydrolysis of IV with aqueous sodium hydroxide solution followed by the dehydration of the β-hydroxylactone (V) with phosphorus pentoxide resulted in formation of carbonyl-labeled isocrotonolactone (VI) in an over-all yield of 40%.[15-17] Addition of isocrotonolactone (VI) to cyclopentadiene takes place very slowly relative to the corresponding additions of acrylic ester or substituted acrylic esters[18] which occur at 0° or room temperature. Indeed, the addition with isocrotonolactone (VI) gave reasonable yields only after 2 hr at 105°. The resulting addition product was a mixture of the *endo* and *exo* adducts (VIIa,b and VIIIa,b)

(1) Supported by the National Science Foundation.
(2) J. A. Berson and R. D. Reynolds, *J. Am. Chem. Soc.*, 77, 4434 (1955).
(3) J. A. Berson, R. D. Reynolds, and W. M. Jones, *ibid.*, 78, 6049 (1956).
(4) J. A. Berson, A. Remanick, and W. A. Mueller, *ibid.*, 82, 5501 (1960).
(5) J. A. Berson and W. A. Mueller, *ibid.*, 83, 4940 (1961).
(6) J. A. Berson and A. Remanick, *ibid.*, 83, 4947 (1961).
(7) R. B. Woodward and T. J. Katz, *Tetrahedron*, 5, 70 (1959).
(8) P. Yates and P. Eaton, *Tetrahedron Letters*, No. 11, 5 (1960).
(9) P. Yates and P. Eaton, *Tetrahedron*, 12, 13 (1961).
(10) R. C. Cookson, J. Hudec, and R. O. Williams, *Tetrahedron Letters*, No. 22, 29 (1960).
(11) J. E. Baldwin and J. D. Roberts, *J. Am. Chem. Soc.*, 85, 115 (1963).
(12) D. Craig, *ibid.*, 73, 4889 (1951).
(13) Originally, it was planned to use tetracyanoethylene as a scavenger[11] for cyclopentadiene formed by the external mechanism so that all of the II obtained would have to come by the internal pathway. The possibility of doing this was wholly vitiated by the unexpected discovery that maleic anhydride reacts with cyclopentadiene at a rate comparable to that of tetracyanoethylene above 150° in both decalin and *t*-pentylbenzene. The most reasonable alternative approach would seem to be to run the reaction in the presence of a large excess of unlabeled maleic anhydride to ensure that the II formed by the external mechanism would be essentially all unlabeled.
(14) C. Ganter, U. Scheidegger, and J. D. Roberts, *J. Am. Chem. Soc.*, 87, 2771 (1965).
(15) R. Rambaud, S. Ducher, and R. Boudet, *Bull. Soc. Chim. France*, 1419 (1956).
(16) J. W. E. Glattfeld, G. Leavell, G. E. Spieth, and D. Hutton, *J. Am. Chem. Soc.*, 53, 3164 (1931).
(17) J. W. E. Glattfeld and E. Rietz, *ibid.*, 62, 974 (1940).
(18) J. A. Berson, Z. Hamlet, and W. A. Mueller, *ibid.*, 84, 297 (1962).

in a ratio which was found to be dependent both on temperature and on the solvent. With increasing temperature, the expected relative increase in *exo* product was observed, while a larger portion of the *endo* isomer was obtained with increasing solvent polarity (80% *endo* in dimethyl sulfoxide compared to 65% *endo* in benzene).[19] The separation of the *endo* (VIIa,b) from the *exo* isomer (VIIIa,b) was achieved by repetitive column chromatography on acid-washed alumina. In the next step, the *endo* lactones (VIIa,b) were treated with *d*-(−)-desoxyephedrinemagnesium bromide,[20] forming the two diastereomeric hydroxyamides IXa + IXb in nearly quantitative yield. Their resolution was achieved by fractional recrystallization which yielded isomer A with $[\alpha]_D$ −34.1° (mp 142°) and isomer B with $[\alpha]_D$ +32.6° (mp 164°) in about equal portions. The two diastereomeric hydroxyamides were shown to be completely separated from one another by thin layer chromatography. Oxidation of the *endo* hydroxyamides IXa + IXb to the *endo* diacid X proved to be extremely delicate and sensitive to the solvent employed. Under basic conditions (pyridine, 1 *N* sodium hydroxide solution) IX partially isomerized to the unsaturated



trans diacid XI. In acidic medium, formation of the *trans* diacid XI and the lactone–acid XII was observed. A procedure was finally devised for this oxidation using dichromate and sulfuric acid with acetone as solvent and under these conditions XI and XII were formed only as minor by-products. Of the two diastereomers IXa + IXb, IXa (mp 142°) oxidized more specifically and with a better yield and, consequently, it was chosen for the continuation of the synthesis. Oxidation of IXa gave the *endo* diacid X in about 70% yield and the subsequent dehydration with acetic anhydride yielded 5-norbornene-2,3-*endo*-dicarboxylic anhydride (I) in an over-all yield of 1.1%. The pure *endo* anhydride I was then diluted with an excess of inactive material. Its final specific activity was 23.33 μcuries/mole.

The over-all approach involving as it does preparation of the two enantiomeric *endo* lactones VII and the subsequent resolution *via* the diastereomeric *endo* amides IX guaranteed that essentially 100% of the label was present in one and the same carbonyl group of the *endo* anhydride I. It remained to determine which of the two carboxyl groups in I actually was labeled, and a degradation involving the elimination of one particular carboxyl group was required to settle this question.

(19) For an excellent correlation of solvent effects on the stereoselectivities of Diels–Alder reactions, see Berson and co-workers.[18]

(20) This reaction was developed by analogy with the procedure for amidation of esters described by H. L. Bassett and C. R. Thomas, *J. Chem. Soc.*, 1188 (1954).

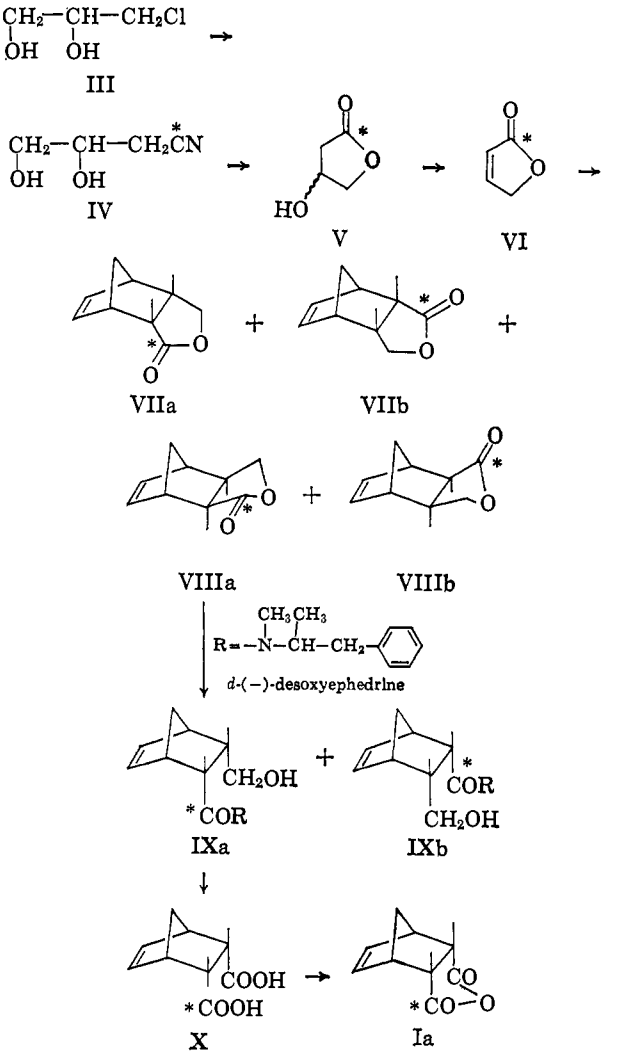


Figure 1. Synthesis of asymmetrically labeled 5-norbornene-2,3-*endo*-dicarboxylic anhydride.

Degradation of the *endo* Anhydride Ia

The following sequence was investigated as a means of locating the labeled carbonyl group in the *endo* anhydride I.

5-Norbornene-2,3-*endo*-dicarboxylic anhydride (Ia) and methanol yielded the unsaturated monoacid esters XIIIa,b which on hydrogenation gave the norbornane-2,3-*endo*-monoacid esters XIVa,b. Opening of I followed by hydrogenation was found to proceed more specifically than hydrogenation followed by esterification. Of the several methods examined to decarboxylate the *endo* acids XIVa,b, the procedure using lead tetraacetate and iodine in carbon tetrachloride[21] was by far most effective. The nmr and infrared spectra indicated the reaction product to consist of the expected iodo esters XVa,b together with the corresponding dehalogenated *endo* esters XVIa,b and the *endo* anhydride I as minor by-products.[22] The mixture of iodo esters XVa,b; was reduced with zinc and acetic acid to give the methyl 2-*endo*-norbornanecarboxylates (XVIa,b) in 60% yield and subsequent hy-

(21) D. H. R. Barton and E. P. Serebryakov, *Proc. Chem. Soc.*, 309 (1962).

(22) A similar side reaction was observed when the corresponding norbornane 2 *exo*-acid 3-*exo*-ester was decarboxylated with bromine and mercuric oxide (unpublished results).

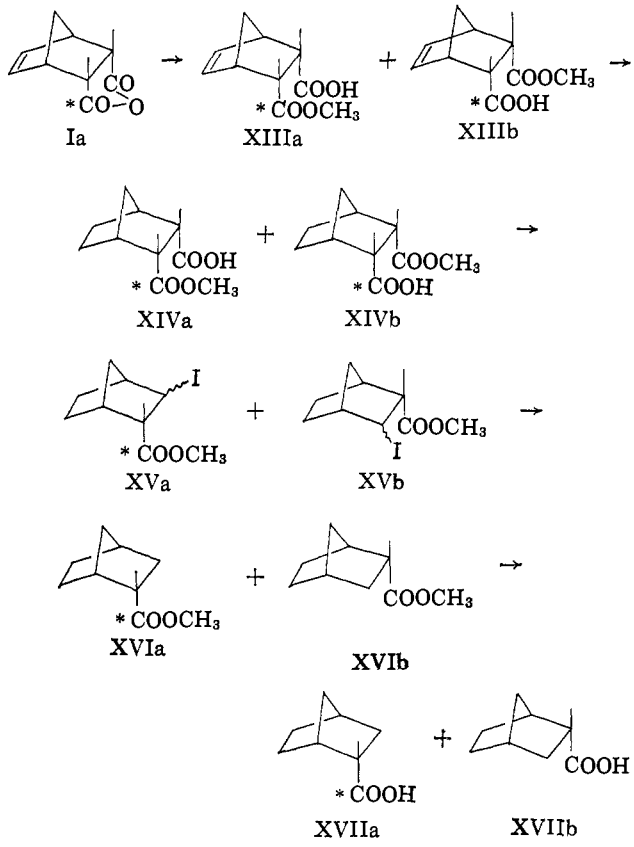
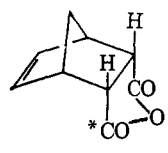


Figure 2. Sequence for degradation of the stereospecifically labeled *endo* anhydride Ia to *endo*-norbornane-2-carboxylic acid (XVII).

drolysis[23] afforded the 2-*endo*-norbornanecarboxylic acids (XVIIa,b), see Figure (2). Resolution of *endo* acids XVIIa,b was achieved by way of the cinchonidine salt.[24] Crystallization from absolute ethanol yielded the salt of the levorotatory acid XVIIa while the salt of dextrorotatory acid XVIIb was obtained from 95% alcohol. Since amounts of *endo* acid XVIIa,b on hand did not permit a complete resolution into the (−) and (+) acids in reasonable quantities, several fractions of different optical purity were prepared and both their rotations and specific activities determined. The results of these measurements are shown in Figure 3.

The results of this degradation prove that the 5-norbornene-2,3-*endo*-dicarboxylic anhydride (Ia) was in fact stereospecifically labeled with ^{14}C in that carbonyl group corresponding to the position of the carboxyl group in the levorotatory *endo*-norbornene-2-carboxylic acid. Since this acid actually has the *S* configuration,[25] the labeled anhydride is therefore Ia.



Ia

(23) K. D. Gundermann and H. Schulze, *Ber.*, **94**, 3254 (1961).
(24) J. A. Berson and D. A. Ben-Efraim, *J. Am. Chem. Soc.*, **81**, 4083 (1959).
(25) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *ibid.*, **83**, 3986 (1961).

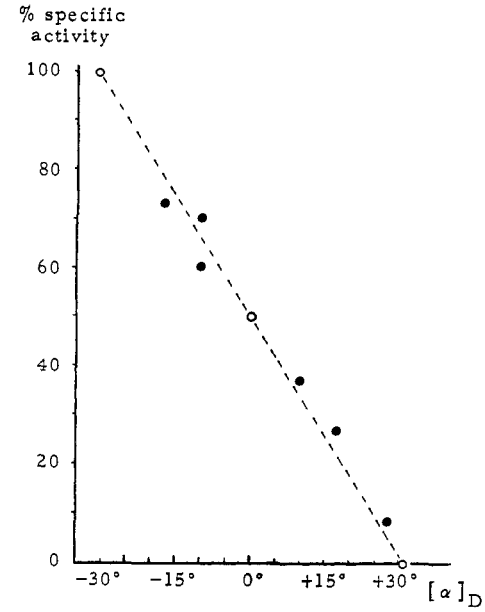


Figure 3. Optical rotation *vs.* relative ^{14}C content for mixtures of *endo*-norbornane-2-carboxylic acids (XVIIa and XVIIb) stereospecifically labeled, obtained by crystallization of the cinchonidine salts. The dotted line defined by the open circles represents the expected relationship between rotation and relative ^{14}C content if only one isomer is labeled. The filled circles are the experimental points.

Experimental Section

Unless stated otherwise, elementary analyses were carried out by Westcoast Analytical Laboratory, El Cerrito, Calif.; melting points (measured on a Büchi apparatus) and boiling points are uncorrected; optical rotations refer to the sodium D line and were taken at room temperature (23–26°) in chloroform or ethanol solutions; infrared spectra were measured with the Beckman IR-7 spectrometer; and vapor-phase chromatographic separations were effected using the Perkin-Elmer Model 154C and Model 800 instruments. Proton magnetic resonance spectra were recorded in chloroform with a Varian A-60 spectrometer at room temperature. The chemical shifts are δ values based on tetramethylsilane as an internal standard. The ^{14}C activities were determined with a Nuclear Chicago liquid scintillation counter (System 724) using toluene as the solvent.

Isocrotonolactone-1-^{14}C (VI). To a stirred solution of 55 g of 3-chloro-1,2-propanediol (0.5 mole) in 180 ml of 95% ethanol in a 500-ml, three-necked flask carrying a water-cooled condenser was added 14.1 mg of sodium cyanide-^{14}C (1.0 mcurie) and 32 g of potassium cyanide (0.49 mole) in 50 ml of water. The mixture was stirred for 1 hr at room temperature, then warmed to the boiling point over 40 min and kept at reflux for an additional 3 hr. The solution was cooled and filtered and the residue washed with 95% ethanol. After addition of 30 g of sodium hydroxide in 150 ml of water to the combined filtrates, the reaction mixture was heated under reflux for 6 hr, while a stream of purified air was passed through. The cooled reaction product was acidified with dilute hydrochloric acid (1:1) and most of the solvent removed under reduced pressure. The precipitated salts were removed by filtration, 95% ethanol was added, and the solvent removed again. This process was repeated until no further precipitation occurred. The viscous, dark brown residue was then dissolved in 120 ml of absolute dioxane and after careful addition of 25 g of phosphorus pentoxide in two portions the mixture was allowed to stand overnight at room temperature. The liquid was then decanted and the residue extracted with absolute ethanol. The combined extracts were evaporated under reduced pressure (20 mm, 70–80°) and the residual oil distilled at 3.5–4 mm. The whole sequence was carried out twice and the combined crude product distilled to give 16.0 g of pure isocrotonolactone (VI), bp 68° (3.5 mm), $n^{26}D$ 1.4556.

The infrared spectrum showed significant absorptions in chloroform at 3060, 1780, 1750, 1603, 1158, and 1041 cm^{-1} and in carbon tetrachloride at 3120, 1784, 1748, 1603, 1153, 1041, and 878 cm^{-1}.

Addition of Isocrotonolactone-1-^{14}C (VI) to Cyclopentadiene. Isocrotonolactone-1-^{14}C (VI, 5.0 g, 0.06 mole) and freshly distilled

cyclopentadiene (50 g, 0.75 mole) in 10 ml of benzene were sealed in a Pyrex tube and kept at 110° for 2 hr. The light yellow oil from three such runs was then distilled at 1 mm (bath temperature 70°) through a 30-cm Vigreux column which removed most of the dicyclopentadiene formed and also some of the unreacted isocrotonolactone VI. The residue was repetitively chromatographed on acid-washed alumina with benzene as the elutant, giving first the *exo* lactone VIIIa,b, followed by the *endo* lactone VIIa,b. From six consecutive column chromatograms, a total of 11.8 g of the *endo* lactone VIIa,b (0.084 mole), 4.4 g of the *exo* lactone VIIIa,b (0.031 mole), 3.5 g of the isocrotonolactone VI (0.042 mole), and 1.8 g of unresolved *endo–exo* mixture (0.013 mole) were isolated. The degree of separation between the *exo* and *endo* components in the various fractions was determined by thin layer chromatography.

The 5-norbornene-2-*endo*-hydroxymethyl-3-*endo*-carboxylic acid lactone[26] (VIIa,b) showed infrared absorption at 1761 cm^{-1} in chloroform.

Anal. Calcd for $C_9H_{10}O_2$: C, 71.98; H, 6.71. Found: C, 71.60; H, 6.70.

Amidation of the *endo*-Lactone VIIa,b.[26] To a stirred solution of ethylmagnesium bromide, prepared from 2.14 g of magnesium (88 mg-atom), in 100 ml of absolute ether was added 12.8 g of *d*-(−)-desoxyephedrine (86 mmoles) dissolved in 70 ml of absolute ether over a period of 5 min. The milky aminomagnesium bromide solution was then added slowly with vigorous stirring to a solution of 6.4 g of the *endo* lactone VIIa,b (43 mmoles) in 10 ml of absolute ether which was prepared in a 500-ml, three-necked flask equipped with mechanical stirrer, condenser, and dropping funnel, and after 1 hr at room temperature the reaction mixture was heated under reflux for a further 2 hr. After addition of 5 ml of water and sufficient 1 *N* hydrochloric acid to dissolve the magnesium salt, continuous extraction with ether overnight yielded 12.1 g of the crystalline mixture of the diastereomeric hydroxyamides (XIab). In a second run using 5.3 g of *endo* lactone VIIa,b (35 mmoles), 11.6 g of crude product was obtained.

The resolution of the two diastereomers was achieved by fractional recrystallization from ethyl acetate until the melting points were constant. The course of the resolution could also be followed conveniently by thin layer chromatography (silica gel G, developed with 70:30 hexane–acetone).

The yield of the **hydroxyamide IXa**[26] was 6.55 g, mp 142–142.5° and $[\alpha]^{25}D$ −34.1° (*c* 3.2 in chloroform). The infrared spectrum in chloroform showed significant absorptions at 3640, 3440, 3030, and 1626 cm^{-1}.

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.00; H, 8.47; N, 4.80.

The yield of the **hydroxyamide IXb**[26] was 6.85 g, mp 164–164.5° and $[\alpha]^{25}D$ +32.6° (*c* 2.9 in chloroform). The infrared spectrum in chloroform showed significant absorptions at 3630, 3410, 3030, and 1630 cm^{-1}.

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 75.80; H, 8.35; N, 4.91.

5-Norbornene-2,3-*endo*-dicarboxylic Acid (X).[27] In three successive runs, a total of 6.5 g of the hydroxyamide isomer IXa (mp 142–142.5°, $[\alpha]D$ −34.1°, 21.8 mmoles) was dissolved in 800 ml of acetone and, after addition of 46 ml of a solution made up from 60 g of sodium dichromate, 80 g of concentrated sulfuric acid, and 270 g of water, stirred at room temperature for 3 days. Water and sufficient potassium bicarbonate was added to neutralize the acid, most of the acetone was removed on the steam bath, and the residue extracted with ether. The ether fraction contained mainly *d*-(−)-desoxyephedrine. The aqueous phase was carefully acidified with 1 *N* hydrochloric acid, saturated with sodium chloride, and extracted continuously with ether. The crude product (4.5 g) was stirred overnight in 60 ml of 1 *N* hydrochloric acid at room temperature. Continuous ether extraction of the mixture gave a total of 2.3 g of 5-norbornene-2,3-*endo*-dicarboxylic acid (X).

5-Norbornene-2,3-*endo*-dicarboxylic Anhydride (Ia).[27] The *endo* diacid X (2.3 g, 12.8 mmoles) was dissolved in 25 ml of acetic anhydride and left overnight at room temperature. The solvent was stripped off at 0.5 mm (bath temperature 40–50°) and the brown crystalline residue taken up in benzene and decolorized by filtration through Super-Cel. The product was then recrystallized from benzene until constant activity was observed. The resulting *endo* anhydride Ia (850 mg, mp 163–164°, 1.790 mcuries/mole) was diluted with 65 g of freshly recrystallized unlabeled anhydride and twice recrystallized from benzene to give 33 g of 5-norbornene-2,3-*endo*-dicarboxylic anhydride (I) with an activity of 23.22 μcuries/mole. The residue left by evaporation of the mother liquid of the second recrystallization had the same ^{14}C activity.

Methyl Hydrogen 5-Norbornene-2,3-*endo*-dicarboxylate (XIIIa, b).[27] 5-Norbornene-2,3-*endo*-dicarboxylic anhydride (I, 7.0 g, 42.6 mmoles) was heated under reflux in 70 ml of absolute methanol for 20 hr. The solvent was removed, and the residue (8.3 g) was crystallized from carbon tetrachloride; mp 100.5–101.0°. The infrared spectrum in carbon disulfide showed significant absorption at 3400–2600, 3090, 1749, and 1713 cm^{-1}. The specific activity was 21.26 μcuries/mole.

Methyl Hydrogen Norbornane-2,3-*endo*-dicarboxylate (XIVa,b).[27] A solution of 8.4 g of methyl hydrogen 5-norbornene-2,3-*endo*-dicarboxylate (XIIIa,b, 42.9 mmoles) in 80 ml of ethyl acetate was shaken with hydrogen in a Parr bomb for 2 hr over 800 mg of platinum oxide. The solution was filtered and the filtrate freed of solvent in a rotatory evaporator. The residual methyl hydrogen norbornane-2,3-*endo*-dicarboxylate (XIVa,b) was recrystallized from carbon tetrachloride to give 7.6 g of material with mp 84.5–85°. The infrared spectrum in carbon disulfide showed significant absorption at 3300–2800, 1748, and 1713 cm^{-1}. The specific activity was 21.66 μcuries/mole.

Decarboxylation of Methyl Hydrogen Norbornane-2,3-*endo*-dicarboxylate (XIVa,b).[27] To a refluxing solution of 16.8 g of freshly dried lead tetraacetate (38 mmoles) in 20 ml of carbon tetrachloride in a three-necked flask equipped with condenser and dropping funnel and illuminated with a tungsten lamp was added 7.55 g of methyl hydrogen 2,3-*endo*-norbornanedicarboxylate (XIVa,b, 38 mmoles) in 50 ml of carbon tetrachloride. After 5 min, a solution of 9.6 g of iodine (38 mmoles) in 400 ml of carbon tetrachloride was added in small portions, the addition being continued as soon as the reaction mixture was substantially decolorized. After the addition was complete the reaction mixture was refluxed for a further 2 hr. Most of the solvent was then removed in a rotatory evaporator, the residue taken up in ether, and the solution washed with aqueous sodium thiosulfate solution, potassium bicarbonate solution, and water. The ethereal part was dried with sodium sulfate and, after removal of the solvent, there was left 10.1 g of crude, oily 2,3-*endo*-iodocarbomethoxynorbornane (XVa,b). The infrared spectrum in carbon disulfide showed strong absorption at 1722 cm^{-1}.

Methyl 2-*endo*-Norbornanecarboxylate (XVIa,b).[28] A solution of 9.6 g of the *endo*-iodo ester XVa,b (34.3 mmoles) in 100 ml of glacial acetic acid was heated with 10 g of zinc dust on a steam bath for 2 hr. The mixture was then poured on ice, neutralized with cold potassium hydroxide solution, and extracted with ether, and the ether layer washed with water. Removal of the solvent gave 4.0 g of an oil, which was distilled under reduced pressure to give 3.11 g of methyl 2-*endo*-norbornanecarboxylate (XVIa,b); bp 81–83° (32 mm) [lit. 81° (67 mm),[29] 80–82° (12 mm),[30] 52–53° (1.8 mm)[31]]; $n^{30}D$ 1.4621 (lit. $n^{26}D$ 1.4625,[29] $n^{17}D$ 1.4670[31]). The infrared spectrum in carbon disulfide showed absorption at 1741 cm^{-1}. The specific activity was 11.43 μcuries/mole.

2-*endo*-Norbornanecarboxylic Acid (XVIIa,b).[28] Methyl 2-*endo*-norbornanecarboxylate[28] (XVIa,b, 3.1 g, 20.1 mmoles) was heated in 40 ml of a 1:1 hydrochloric acid–glacial acetic acid mixture for 5 hr on the steam bath. The reaction mixture was then poured on ice, neutralized with cold dilute sodium hydroxide solution, and washed with ether. The aqueous layer was acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the ether gave 2.8 g of crude product which was twice recrystallized from acetonitrile. The resulting 2-*endo*-norbornanecarboxylic acid[28] (XVIIa,b, 2.0 g) had mp 63–64° (lit. 64–66°,[24] 65°[32]). The infrared spectrum in carbon disulfide showed significant absorption at 3300–2800 and 1708 cm^{-1}. The specific activity was 11.42 μcuries/mole.

Resolution of 2-*endo*-Norbornanecarboxylic Acid (XVIIa,b). The racemic 2-*endo*-norbornanecarboxylic acid (XVIIa,b, 2.0 g, 14.3 mmoles) and 4.2 g of cinchonidine (14.3 mmoles) were dis-

(26) This compound is labeled with ^{14}C in the carboxyl position.

(27) This compound is labeled asymmetrically with ^{14}C in one of the two carboxyl positions.

(28) One enantiomer of the racemic mixture is labeled with ^{14}C in the carboxyl position.

(29) C. F. Wilcox and R. R. Craig, *J. Am. Chem. Soc.*, **83**, 3866 (1961).
(30) K. Alder, K. Heimbach, and R. Reubke, *Ber.*, **91**, 1516 (1958).
(31) H. Kwart and G. Null, *J. Am. Chem. Soc.*, **81**, 2765 (1959).
(32) K. Alder, G. Stein, M. Liebmann, and E. Rolland, *Ann.*, **514**, 197 (1934).

Table I

Fraction	$[\alpha]_D$, deg	Specific activity, μcuries/mole
1	−10.4	13.68
2	−10.4	16.08
3	−17.8	16.73
4	+9.4	8.51
5	+17.4	6.25
6	+27.2	1.99

solved in 10 ml of absolute ethanol, heated until the solution became clear, and then allowed to crystallize in a refrigerator. The resolution of the two cinchonidine salts was achieved using absolute ethanol to crystallize the levorotatory acid and 95% ethanol to obtain the dextrorotatory acid.[24] The cinchonidine salts were then converted to the free acids by treatment with 1 *N* hydrochloric acid and extraction with chloroform. The crude acids so obtained were purified by filtration of an ether solution through silicic acid followed by distillation or crystallization from acetonitrile. Six fractions of different optical purity were isolated (see Table I). The results show that the enantiomer XVIIa with $[\alpha]_D$ −30.6°[24] is labeled with carbon-14 at the carboxyl position.

Mechanisms of Elimination Reactions. VII. Rates of Elimination of Some Deuterated Cyclohexyl Tosylates[1]

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Abstract: *trans*-Cyclohexanol-2-*d* was prepared by opening epoxycyclohexane with lithium aluminum deuteride, and *cis*-cyclohexanol-2-*d* resulted from deuterioboration of cyclohexene. Exchange of cyclohexanone with deuterium oxide followed by reduction yielded cyclohexanol-2,2,6,6-d_4. Cyclohexanol-1-*d* was obtained by treating cyclohexanone with lithium aluminum deuteride. These alcohols, along with undeuterated cyclohexanol, were converted to the tosylates. Rates of reaction of the tosylates with ethoxide in ethanol and *t*-butoxide in *t*-butyl alcohol at 50° were determined. The over-all reaction is at least 98% elimination. The rate data provide primary isotope effects for β deuteration, and secondary isotope effects for both α and β deuteration. The β-deuterium primary effect (4.5 in ethanol and 7.5 in *t*-butyl alcohol) resembles that previously noted for 2-phenylethyl-2,2-d_2 tosylate, and the α-deuterium secondary effect is of normal size (1.14 in ethanol and 1.15 in *t*-butyl alcohol). The β-deuterium secondary effect is considerably larger than expected (1.33 in ethanol and 1.52 in *t*-butyl alcohol). The nature of the transition state for elimination is discussed in the light of these findings.

Our interest in the structure of the transition state in E2 reactions[2,3] has led us to study deuterium isotope effects in elimination reactions of specifically deuterated cyclohexyl tosylates. This system provides an unusual opportunity to observe the primary β-deuterium effect and both α- and β-deuterium secondary effects. Previous studies had revealed that β-deuterium primary isotope effects in the 2-phenylethyl-2,2-d_2 series[4] vary considerably as the leaving group and base are changed. The correlation of these results with other evidence on transition-state structure has been discussed in a recent reinterpretation.[3]

Syntheses of the desired deuterated cyclohexanols were readily accomplished. Cyclohexanol-1-*d* resulted from reduction of cyclohexanone with lithium aluminum deuteride by the procedure of Streitwieser, *et al.*, for cyclopentanone.[5] Exchange of cyclohexanone with deuterium oxide[6] followed by reduction with lithium aluminum hydride gave cyclohexanol-2,2,6,6-d_4.

trans-Cyclohexanol-2-*d* was obtained by the action of lithium aluminum deuteride on cyclohexene epoxide. Although there seemed no reason to question the stereochemistry of this process,[5] subsequent work[7] demonstrated a small irregularity. Another sample of *trans*-cyclohexyl-2-*d* tosylate was converted to the *cis*-cyclohexyl-2-*d*-trimethylammonium salt by treatment with trimethylamine in nitromethane. To check the stereochemistry of the substitution, a Hofmann degradation was performed on the quaternary ammonium salt. Examination of the resulting cyclohexene in a mass spectrometer revealed *ca.* 4–5% of *dideuterated* material in addition to the monodeuterated material predicted for substitution with inversion.

A precedent for this result is to be found in the reduction of 4-*t*-butylcyclohexene epoxide with lithium aluminum deuteride,[8] which gives 11% of dideuterated product. The authors explain the result by invoking hydride abstraction by aluminum deuteride on the alkoxide intermediate, followed by reduction of the resulting ketone with more lithium aluminum deuteride. Evidently this side reaction is less important with our unsubstituted cyclohexene oxide, and the few per cent of dideuterated material having the hydroxyl *cis* to the 2-deuterium would not significantly change the measured isotope effect. There is, however, an evident need for caution in using epoxide opening as a route to stereospecifically deuterated products.

cis-Cyclohexanol-2-*d* was obtained by the deuterioboration method.[9-11] Although there is ample evi-

(1) This work was supported by the National Science Foundation.
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(7) Unpublished results of Dr. T. A. Ashe in these laboratories.
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