[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Resolution, Stereochemial Correlation and Maximum Rotations of the Norbornane- and 5-Norbornene-2-carboxylic Acids. Isotope Dilution as an Aid in the Determination of Optical Purity[1]

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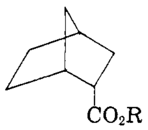
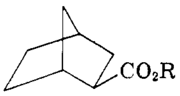
endo-Norbornanecarboxylic acid (Ia) has been resolved *via* the cinchonidine salt. The active acid has been stereochemically correlated with the *exo* isomer and with *endo*- and exo-5-norbornene-2-carboxylic acids. The optical purities of Ia and the other three acids have been established by application of the isotope dilution technique of Graff, Rittenberg and Foster.

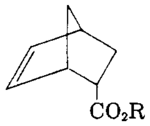
As a basis for some stereochemical studies[2] in the norbornane series, it was necessary to establish the optical rotations of enantiomerically pure *endo*- and *exo*-norbornane-2-carboxylic acids (Ia and IIa). The present paper describes experiments by means of which the required information was obtained. These experiments also established the rotations of enantiomerically pure *endo*-5-norbornene-2-carboxylic acid (IIIa) and *exo*-5-norbornene-2-carboxylic acid (IVa), and correlated the configurations of these two acids with those of Ia and IIa.



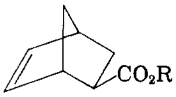
Ia, R = H
b, R = CH_3



IIa, R = H
b, R = CH_3



IIIa, R = H
b, R = CH_3



IVa, R = H
b, R = CH_3

Resolution and Stereochemical Correlation of the Norbornane- and 5-Norbornene-2-carboxylic Acids (Chart I).—The mixture of racemic unsaturated acids IIIa and IVa obtained[3] in the Diels–Alder addition of cyclopentadiene to acrylic acid had been converted[4] virtually quantitatively, by application of the iodolactone method,[5] to a readily separable mixture of the pure *exo*-unsaturated acid IVa and the iodolactone of the *endo*-unsaturated acid IIIa. Treatment of the iodolactone with zinc in acetic acid has now given the pure *endo*-unsaturated acid IIIa, whose properties corresponded to those of material obtained[4] by recrystallization of the mixed acids from the diene addition. Hydrogenation of each of the unsaturated acids gave the corresponding saturated acids in epimerically pure form.

Although crystalline salts of all four acids with a number of alkaloids formed readily, the cinchonidine salt of the *endo*-saturated acid Ia seemed to be particularly suitable for resolution. The resolution was facilitated greatly by the sensitivity of the fractionation to the solvent composition. Recrystallization of the mixed salts from absolute ethanol resulted in preferential precipitation of a salt of the levorotatory acid, whereas recrystallization from aqueous ethanol concentrated a salt of the enantiomer. The two crystalline salts did not appear to be truly diastereomeric. Elementary analyses indicated the approximate composition base:acid:0.5 ethanol for the salt of the (+)-acid and base:2 acid: ethanol for that of the (−)-acid. The melting points, however, were vague, and it is uncertain that these salts were definite chemical substances.

In a large scale systematic resolution, proper manipulation of solvents gave the enantiomers, (+)-Ia, $[\alpha]^{26}_{\mathrm{D}}$ +30.1°, m.p. 25–26.5°, and (−)-Ia, $[\alpha]^{26}_{\mathrm{D}}$ −30.6°, m.p. 25.5–26.5°. The properties of both acids were invariant with further recrystallization of the salts.

Partially resolved *endo*-unsaturated acid IIIa, $[\alpha]_{\mathrm{D}}$ −70.4°, obtained by fractionation of the cinchonidine salt from acetone, gave upon catalytic hydrogenation the *endo*-saturated acid Ia, $[\alpha]_{\mathrm{D}}$ −14.9°. Similarly, IIIa of the opposite sign of rotation, $[\alpha]_{\mathrm{D}}$ +59.7°, gave Ia of $[\alpha]_{\mathrm{D}}$ +12.7°. The ratios of the rotations IIIa:Ia, 4.72 for the (−)-series and 4.71 for the (+)-series, were thus identical within experimental error. To prevent optical fractionation, recrystallizations of the partially resolved free acids were avoided, chemical purifications being effected by distillation. Control experiments with the racemic acids showed that this procedure afforded materials identical in m.p., mixed m.p. and infrared spectra with those of the corresponding recrystallized racemic acids. In the optically active series, where m.p. was of no value as a criterion of purity, the identity of materials was checked by elemental analysis and infrared spectrum.

Conversion with diazomethane of partially resolved *endo*-unsaturated acid, $[\alpha]_{\mathrm{D}}$ −55.4°, to the methyl ester IIIb, epimeric equilibration with absolute methanolic sodium methoxide, and saponification gave a mixture of IIIa and the *exo*-unsaturated isomer IVa, from which epimerically pure IVa, $[\alpha]_{\mathrm{D}}$ −6.58°, was obtained by the iodolactone separation followed by distillation. Since these manipulations could not have affected the absolute configurations or enantiomeric purities, (−)-IVa of $[\alpha]_{\mathrm{D}}$ −6.58° is configurationally related to and of

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[1] This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command under contract No. AF 18 (600)-1544. Reproduction in whole or in part is permitted for any purpose of the United States Government.

[2] (a) J. A. Berson and S. Suzuki, THIS JOURNAL, **81**, 4088 (1959); (b) J. A. Berson and D. A. Ben-Efraim, *ibid.*, **81**, 4094 (1959).

[3] (a) K. Alder, G. Stein, M. Liebmann and E. Rolland, *Ann.*, **514**, 197 (1934); (b) J. D. Roberts, E. R. Trumbull, Jr., W. Bennett and R. Armstrong, THIS JOURNAL, **72**, 3116 (1950).

[4] C. D. ver Nooy and C. S. Rondestvedt, *ibid.*, **77**, 3583 (1955).

[5] (a) J. Bougault, *Ann. chim. phys.*, **14**, 145 (1908); **15**, 296 (1908); (b) E. E. van Tamelen and M. Shamma, *ibid.*, **76**, 2315 (1955).

the same degree of resolution as (−)-IIIa of [α]D −55.4°. Hydrogenation of IVa, [α]D −6.58°, gave the *exo*-saturated acid IIa, [α]D −10.7°. The correlation establishes that the four acids I, II, III and IV of the same sign of rotation have the same absolute configuration. This applies also to the corresponding methyl esters (see Table I and Experimental).

TABLE I

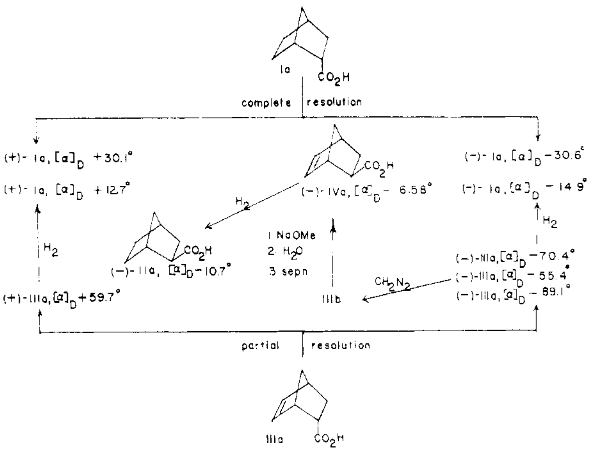
MAXIMUM OPTICAL ROTATIONS OF THE NORBORNANE- AND 5-NORBORNENE-2-CARBOXYLIC ACIDS AND THEIR METHYL ESTERS[a]

Acids	[α]D (degrees)[b]	Esters	[α]D (degrees)[b]
Ia	30.6	Ib	19.8
IIa	27.8	IIb	34.2
IIIa	144	IIIb	141
IVa	17.1	IVb	26.5

[a] In all cases, the methyl ester had the same sign of rotation as its parent acid. [b] Rotations in 95% ethanol solvent, at concentrations of about 1–3%.

The maximum rotations given in Table I were calculated from the data of Chart I on the assumption of [α]D 30.6° for enantiomerically pure Ia, an assumption that is supported by the isotope dilution experiments reported below. The maximum rotation of the *exo*-saturated acid IIa, calculated from that of enantiomerically impure but chemically pure IIa, could be different from that given in Table I only if the IIa sample were contaminated with the epimer Ia. This point was investigated by infrared analysis. An empirical calibration curve derived from spectra of known mixtures of pure *recrystallized* racemic Ia and IIa in carbon disulfide allowed detection of as little as 5% of Ia in IIa. Mixtures of the corresponding racemic methyl esters could be analyzed as liquid films for as little as 2% of Ib in IIb. Since the [α]D values for optically pure Ia and IIa were very similar (30.6° and 27.8°, respectively), optically active IIa would have had to be contaminated with about 20% of Ia in order for the [α]D value for IIa to be different from 27.8° by an amount greater than the polarimetric experimental error. The infrared spectra of optically active IIa and the derived methyl ester IIb showed no evidence (<5% and <2%, respectively) of the presence of *endo* materials. The value [α]D 27.8° for IIa is therefore reliable.

CHART I



Independent evidence of the reliability and internal consistency of the data for the unsaturated acids IIIa and IVa was provided by a study of the alkaline epimerization of the derived methyl esters. The unsaturated *endo*-methyl ester IIIb, prepared from acid IIIa of [α]D −55.4° (38.5% optically pure) was equilibrated with boiling sodium methoxide (24 hours). The resulting mixture of esters had [α]D −30.7°, which corresponds to 47% *endo*-(IIIb) and 53% *exo*-(IVb). Saponification and iodolactone separation indicated (gravimetrically) 46% *endo* material and 53% *exo* material, with a total recovery of 99%. A separate experiment with racemic material (18 hours) gave 48% *endo* and 54% *exo* material, with a total recovery of 102%. The gravimetric data imply that epimeric equilibrium was reached in these experiments. (ver Nooy and Rondestvedt[4] reported a distribution of 42% *endo* and 61% *exo* after epimerization.) The close correspondence between the gravimetric and polarimetric determinations of the equilibrium ester composition are reasonable only if the rotations given in Table I for IIIa, IIIb, IVa and IVb are correct relative to [α]D 30.6° for Ia.

Non-Polarimetric Confirmation of Enantiomeric Purity by Isotope Dilution Analysis.—The observation that the optical rotations of (+)- and (−)-Ia obtained in the above "complete" resolution reached constant and approximately equal values satisfies necessary but insufficient criteria of enantiomeric purity. Although these criteria are frequently the only ones applied in optical resolution work, it is easy to imagine complex phase behavior of diastereomeric salts or partially resolved materials that would appear to satisfy them and yet would provide only spurious evidence of complete resolution. An example of such behavior is given in the following paper.[2a] Of course, the probability of these anomalies is sharply reduced if resolutions of a given substance through two or more diastereomeric derivatives give identical results. However, this is frequently tedious and difficult, and a non-polarimetric confirmation of enantiomeric purity is desirable. This has been done for several amino acids by application of an appropriate stereospecific enzyme system, *e.g.*, L-aminoacid oxidase from cobra or rattlesnake venoms and D-aminoacid oxidase from hog kidney are capable of demonstrating the presence of 0.1% of contaminating enantiomer.[6] A less accurate but potentially more general method consists of direct analysis for one enantiomer by isotope dilution. Although the essentials were first pointed out and used by Graff, Rittenberg and Foster[7] as long ago as 1940 in a determination of the D-glutamic acid content of tumor tissues, the technique does not seem to have been applied in the non-polarimetric determination of optical purity in resolutions, or elsewhere. When a sample of weight B of a solid substance whose optical purity is to be determined is mixed with racemic isotopic carrier (of the same chemical species) of activity or atom % excess C_0 and weight x, the

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[6] (a) A. Meister, L. Levintow, R. B. Kingsley and J. P. Greenstein, *J. Biol. Chem.*, **192**, 535 (1951); (b) D. Rudman, A. Meister and J. P. Greenstein, THIS JOURNAL, **74**, 551 (1952).

[7] S. Graff, D. Rittenberg and G. L. Foster, *J. Biol. Chem.*, **133**, 745 (1940).

specific radioactivity or atom % excess (C_+) of all the (+)-material after mixing is given by equation 1 and that (C_-) of all the (−)-material by equation 2, where R is the weight of racemate in B and E is the weight of excess enantiomer—arbitrarily (+)—in B. By definition, $B = R + E$, and % optical purity $= 100\,E/B$.

$$C_{\pm} = \frac{xC_0}{2} \bigg/ \left(E + \frac{x+R}{2}\right) \qquad (1)$$

$$C_{-} = \frac{xC_0}{2} \bigg/ \frac{x+R}{2} \qquad (2)$$

Racemic material in the mixture is a chemical racemate but not an isotopic racemate, *i.e.*, it contains equal weights of enantiomers but these have different specific radioactivities. Thus, $C_{\pm}$, the specific radioactivity of the racemate, is given by a weighted average of the activities of the enantiomers, the weighting factor being $^1/_2$ (equation 3).

$$C_{\pm} = \frac{1}{2}\left[\frac{xC_0}{2} \bigg/ \left(E + \frac{x+R}{2}\right)\right] + \frac{1}{2}\,\frac{xC_0}{2} \bigg/ \frac{x+R}{2} \qquad (3)$$

Recrystallization of the mixture will, in general, cause optical fractionation. If the rotation of optically pure B is known, the enantiomeric purity of the starting B can be calculated from the rotations and isotopic compositions of two fractions obtained from the recrystallization,[7] or from the isotopic composition alone if the pure enantiomer can be isolated from the mixture. If the rotation of optically pure B is unknown, which is the case in optical resolution work, the analysis requires the separation of the pure racemate from the mixture. Although this may sometimes be difficult, there is usually no ambiguity about its accomplishment, which is signified by (in addition to zero optical rotation and characteristic melting point) an isotopic composition that is invariant with further recrystallization. Solution of (3) for the unknowns E and R then gives the enantiomeric purity of B. The method should be useful as well in mechanism studies where determination of the degree of retention of optical purity in a product contaminated with other chemical species frequently is required.[8] As is the case with conventional isotope dilution, the position and type of the isotopic label and the yield in the fractionation are immaterial in principle and can be adjusted for convenience. The accuracy of the method is limited by the accuracy of the isotopic assay technique, which varies with the type of isotope. Mass spectrometric assay of ^{15}N, used by Graff, Rittenberg and Foster,[7] was sufficiently accurate to afford enantiomeric purities to about 1–2%. In our work with ^{14}C tracer reported below and in the following paper, mounting effects limited the accuracy of the assays to about 0.7–1.0%, resulting in a relative uncertainty of about 3–5% in the enantiomeric purities. This error could doubtless be reduced if desired, with only a slight increase in inconvenience, by the use of combustion assays or liquid scintillation counting.

Methyl acrylate-2,3-^{14}C reacted with cyclopentadiene to give, after purification *via* the iodolactone, *endo*-5-norbornene-2-carboxylic acid-2,3-^{14}C, which was hydrogenated to *endo*-norbornane-2-carboxylic acid-2,3-^{14}C (Ia). A known quantity of this material was mixed with a known quantity of partially resolved Ia, $[\alpha]_D$ +16.7°. Three recrystallizations of the mixture from acetonitrile afforded the pure racemate, assay of which indicated, by application of (3), that Ia with $[\alpha]_D$ +16.7° contained 54.4% (+)-Ia and 45.6% racemic Ia. The rotation of optically pure Ia calculated from these data was 30.6°, in agreement with the polarimetric value found by resolution. The experimental error in the isotope dilution experiment produced an absolute error of about 2.6% in the weight of enantiomer. This places an upper limit of 32.1° on the rotation of optically pure material and, consequently, the optical resolution was at least 95% complete.

Experimental[9]

Racemic *endo*-5-Norbornene-2-carboxylic Acid (IIIa).—The crude iodolactone (443 g.), m.p. 55–58°, reported[4] m.p. 58–59°, obtained from 292.5 g. of a distilled cyclopentadiene–acrylic acid reaction mixture, was dissolved in 700 ml. of glacial acetic acid, cooled to 15°, stirred vigorously and treated during 10 minutes with 215 g. of zinc dust. More acetic acid (250 ml.) was added, the reaction mixture was stirred another 3.5 hours at 15° and then 2 hours at room temperature. The mixture was filtered, the insoluble residue washed with more acetic acid and water and the combined filtrates diluted with water. Ether extraction, drying with magnesium sulfate and distillation (Vigreux) gave 157 g. (60%) of IIIa, b.p. 134° (16 mm.), which crystallized in the receiver as colorless needles, m.p. 44–45.5°. Recrystallization from pentane did not change the m.p., reported[4] m.p. 45.7–46.2°, reported[10] m.p. 44–45°. This material depressed the m.p. of the *exo* epimer IVa m.p. 44–45°, prepared according to ver Nooy and Rondestvedt,[4] reported[4] m.p. 44–45°, reported[10] m.p. 45–46°.

Racemic IVa was obtained in pure form (m.p., mixed m.p. and infrared spectrum) from an iodolactone separation[4] followed by several successive bulb-to-bulb distillations of the crude acid without recrystallization. Its properties were identical with those of a recrystallized sample. The major contaminants in the crude acid, easily separated by recrystallization but difficult to remove by distillation, appeared to be a trace of iodolactone, the presence of which was indicated by a weak absorption band at *ca.* 5.6 μ and by a positive Beilstein test, and a trace of iodine or iodine-producing impurity, possibly iodohydrin,[11] which imparted a faint pink color to the distillate. Iodolactone was readily removed by re-partitioning the acid between ether and aqueous bicarbonate, and the pink color was removed by three successive bulb-to-bulb distillations.

Racemic *endo*-(Ia)- and *exo*-(IIa)-Norbornanecarboxylic Acids.[12]—Hydrogenation of pure IIIa (palladium–charcoal in ethyl acetate or platinum oxide in acetic acid) produced Ia. After bulb distillation, the acid had m.p. 64–66°;

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[8] In this case, a knowledge of the amount of B in the product is also required. It should also be noted that optically active carrier, which will sometimes be conveniently preparable from a natural product, can also be used. When (+)-carrier is added and pure (+)-enantiomer is isolated from the fractionation, $C_+ = xC_0/(x + E + R/2)$. When (+)-carrier is added and racemic material is isolated, $C_{\pm} = \frac{xC_0}{2} \Big/ (x + E + R/2)$.

[9] Melting points are corrected. Analyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, Calif. Optical rotations, unless otherwise indicated, were measured in 95% ethanol, in jacketed tubes cooled with circulating water from a thermostat, with a Rudolf model 80 high precision polarimeter. Infrared spectra were measured in carbon disulfide with a Perkin–Elmer Infracord spectrometer using NaCl optics, unless otherwise indicated. Refractive index measurements (Abbé) were thermostatically controlled. Small quantities of liquids or low-melting solids were conveniently manipulated by bulb-to-bulb distillations *in vacuo* using air-bath heating, a technique used for many years in the Zürich laboratories and recently described by K. Ronco, B. Prijs and H. Erlenmeyer, *Helv. Chim. Acta*, **39**, 2088 (1956).

[10] W. R. Boehme, E. Schipper, W. G. Scharpf and J. Nichols, THIS JOURNAL, **80**, 5488 (1958).

[11] *Cf.* S. Beckmann and R. Mezger, *Chem. Ber.*, **90**, 1559 (1957), and ref. 10.

[12] We are indebted to Dr. S. Suzuki for collaboration in this experiment.

m.p., mixed m.p., and infrared spectrum of the distilled sample were identical with those of a sample recrystallized from acetonitrile and also with those of a sample prepared according to Alder[3a] by direct recrystallization of the mixed acids obtained by hydrogenation of a diene addition mixture. Alder[3a] reports m.p. 65°; Boehme[13] reports m.p. 65–66°.

Hydrogenation of the *exo*-unsaturated acid IVa in methanol over platinum oxide gave IIa, m.p. 58–58.5°, from aqueous methanol.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.31; H, 8.74.

A sample of IIa purified by distillation only showed identical properties (m.p., mixed m.p. and infrared spectrum). Alder[14] reports m.p. 56–57° for a preparation obtained from *exo*-2-cyanonorbornane.

Resolution of Ia.—Crystalline salts of Ia were obtained with quinine, brucine and cinchonidine. The quinine and brucine salts fractionated slowly, and attention was given to the cinchonidine salt. Fractionation occurred from benzene, ethyl acetate or ethanol. After a number of preliminary experiments, a large scale separation was run.

To a mixture of 1115 g. of cinchonidine in 2700 ml. of boiling absolute ethanol was added 530 g. of pure Ia. The resulting clear solution was allowed to cool and then was seeded with a few crystals of cinchonidine salt obtained from an earlier experiment; 580 g. of salt gradually precipitated. A small sample of this material was converted with 2 *N* sulfuric acid and a chloroform extraction to free acid of $[\alpha]\mathrm{D}$ −12.9°, m.p. 48–62°. The main body of the salt (crop 1), was recrystallized from absolute ethanol to give crop 1A and mother liquor 1A. The mother liquor from the original precipitation of the salt was concentrated to give crop 2 and mother liquor 2. Crop 2 was recrystallized from mother liquor 1A, while the head fraction (crop 1A) was recrystallized from fresh absolute ethanol. The tail fraction (mother liquor 2) was concentrated further to give mother liquor 3 and crops 3 and 4. Crops 2, 3 and 4 and the appropriate mother liquors were submitted to systematic triangular fractionation. The head fraction 1C, which gave acid of $[\alpha]\mathrm{D}$ −30.8°, was combined with two other fractions from a late stage of the triangle scheme, which gave acids of $[\alpha]\mathrm{D}$ −29.7°, −30.7° and −30.1°. Recrystallization of the last salt fraction from ethyl acetate and regeneration gave acid of $[\alpha]\mathrm{D}$ −30.1°. Further salt crops from the mother liquors gave acid of $[\alpha]\mathrm{D}$ −30.3°. An analytical sample of the completely resolved acid was prepared by distillation. It had m.p. 25.5–26.5°, infrared spectrum identical with that of authentic racemic material, $[\alpha]^{26}\mathrm{D}$ −30.6° (*c* 1.2, *l* 4). A total of 17 g. of optically pure levorotatory material was obtained.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.42; H, 8.59.

The cinchonidine salt of optically pure material had m.p. 143–153°.

Anal. Calcd. for $C_{19}H_{22}ON_2 \cdot 2C_8H_{12}O_2 \cdot C_2H_6O$: C 71.58; H, 8.44; N, 4.51. Found: C, 71.86; H, 7.99; N, 4.83.

Mother liquor 3 from the triangle scheme above was treated with enough water to bring the alcohol concentration to 95%, whereupon a salt of dextrorotatory acid crystallized. Regeneration of a small portion gave material of $[\alpha]\mathrm{D}$ +17.7°. Triangular crystallization from 95% ethanol gave 3.15 g. of (+) −Ia, $[\alpha]^{26}\mathrm{D}$ +30.1° (*c* 1.3, *l* 4), m.p. 25.0–26.5°, infrared spectrum identical with that of the racemate.

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.44; H, 8.71.

The cinchonidine salt had m.p. 133–150°.

Anal. Calcd. for $C_{19}H_{22}ON_2 \cdot C_8H_{12}O_2 \cdot {}^1/_2C_2H_6O$: C, 73.49; H, 8.15; N, 6.12. Found: C, 73.68; H, 8.01; N, 5.68.

The methyl ester Ib of (+)-Ia was prepared from Ia of $[\alpha]\mathrm{D}$ +18.2° with diazomethane. It was a colorless liquid which after distillation had $[\alpha]^{25}\mathrm{D}$ +11.8° (*c* 2.7, *l* 4), $n^{25}\mathrm{D}$ 1.4626. Its infrared spectrum (neat in 0.025-mm. cell) was identical with that of racemic Ib,[10] which had $n^{25}\mathrm{D}$ 1.4625; Bode[15] reports $n^{20}\mathrm{D}$ 1.4649.

Infrared Analyses of Ia–IIa and Ib–IIb Mixtures.—An empirical curve of optical density *vs.* concentration for mixtures of acids Ia and IIa in carbon disulfide was obtained from measurements in a cell of approximately 0.125-mm. path length at fixed total concentration on the basis of relative intensities at 13.10 and 13.70 μ. The latter band is of medium intensity and is present in Ia and absent in IIa. The former is weak and is present in IIa and absent in Ia. No quantitative significance is attached to the absolute magnitudes of the optical densities, since the path length was not calibrated. The data (% *endo* in solute/optical density) were: 0.0/0.0306; 4.9/0.0338; 11.8/0.0382; 20.0/0.0437; 100/0.1761.

Mixtures of methyl esters Ib and IIb (neat) were examined in a cell of approximately 0.025-mm. path length at 13.25 μ, where Ib has a medium strong band and IIb is virtually transparent. The data were: 0.0/0.141; 4.9/0.173; 10.0/0.189; 16.0/0.206.

Partial Resolution of IIIa.—To a boiling mixture of 42.6 g. of cinchonidine in 2750 ml. of acetone was added 20.0 g. of pure IIIa in 250 ml. of acetone. An additional 100 ml. of acetone was added to complete solution. Cooling the reaction mixture produced 62 g. of salt. Recrystallization of this material from 4200 ml. of acetone gave 38.5 g. of salt which gave acid IIIa of $[\alpha]\mathrm{D}$ −43.0°. Two further recrystallizations and regeneration gave acid of $[\alpha]\mathrm{D}$ −89.1°. Regeneration of acid from an intermediate fraction and distillation gave acid of m.p. 46.5–48.0°, infrared spectrum identical with that of the racemate, $[\alpha]^{26}\mathrm{D}$ −70.4° (*c* 1.4, *l* 4).

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.55; H, 7.29. Found: C, 69.62; H, 7.18.

The dextrorotatory form was obtained by removing two successive crops of salt from the combined mother liquors by concentration. The third crop of salt was decomposed to the acid in the usual manner to give material of m.p. 44–47°, $[\alpha]^{29}\mathrm{D}$ +60.3° (*c* 1.4, *l* 4).

The methyl ester IIIb, prepared from IIIa of $[\alpha]^{25}\mathrm{D}$ −52.1° (*c* 2.2, *l* 4), was a liquid, $[\alpha]^{25}\mathrm{D}$ −50.9° (*c* 0.5, *l* 1).

Configurational Correlations. (See Chart I) A. IIIa → Ia.—Hydrogenation (10% palladium-on-charcoal, ethyl acetate) of 0.66 g. of partially resolved IIIa, $[\alpha]^{26}\mathrm{D}$ −70.4° (*c* 1.4, *l* 1), followed by distillation, gave 0.61 g. of Ia m.p. 52.5–57°, $[\alpha]^{27}\mathrm{D}$ −14.9° (*c* 2.5, *l* 1), $[\alpha]^{27}\mathrm{D}$ −15.3° (*c* 1.4, *l* 1), infrared spectrum identical with that of the racemate, inert to cold aqueous permanganate. Similarly, 0.65 g. of IIIa, $[\alpha]^{29}\mathrm{D}$ +59.7° (*c* 2.5, *l* 4) gave after hydrogenation and distillation 0.58 g. of Ia, m.p. 55–58.5°, $[\alpha]^{28}\mathrm{D}$ +12.7° (*c* 2.5, *l* 1), infrared spectrum identical with that of the racemate, inert to cold aqueous permanganate.

B. IIIa → IVa.—A solution of 10.0 g. of IIIa, $[\alpha]^{26}\mathrm{D}$ −55.4° (*c* 2.6, *l* 1) in 50 ml. of ether was treated at 0–5° with excess ethereal diazomethane. After 30 minutes at 5°, the excess diazomethane was destroyed with acetic acid, the reaction mixture was washed with aqueous bicarbonate and water and dried over magnesium sulfate. Evaporation of the ether left 10.0 g. of an oil which was taken up in 38 ml. of absolute methanol, treated with a solution of sodium methoxide (from 2.6 g. of sodium) in 25 ml. of absolute methanol and heated at reflux for 24 hours. Most of the methanol was distilled off and a small portion of the residue was worked up for ester by pouring it onto ice, extracting with ether, washing the ethereal layer with saturated brine, drying over magnesium sulfate and distilling. The resulting ester mixture had $[\alpha]^{29}\mathrm{D}$ −30.7° (*c* 2.4, *l* 1). The bulk of the above methoxide solution was treated with 25 ml. of water and the mixture was boiled for 9 hours. The resulting solution was washed with ether, neutralized with 5 *N* sulfuric acid and extracted with ether. The ether extract, after being washed with water and dried over magnesium sulfate, was evaporated to give 6.8 g. of a mixture of acids which was liquid at room temperature but crystallized in ice.

The acid mixture was dissolved in a solution of 14.4 g. of sodium bicarbonate in 228 ml. of water and treated dropwise during 30 min. with 65 ml. of a solution of 12.6 g. of iodine and 26 g. of potassium iodide in 149 ml. of water. After 30 minutes, an additional 15 ml. of the iodine solution was added. At this point, there was a permanent excess of iodine. The precipitated brown oil was extracted with ether, the ether layer was decolorized by shaking with two portions of 10% sodium thiosulfate solution, washed with

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(13) W. R. Boehme, THIS JOURNAL, **80**, 4740 (1958).

(14) K. Alder, K. Heimbach and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958).

(15) H. Bode, *Ber.*, **70**, 1167 (1937).

water, dried over magnesium sulfate and evaporated to give 5.93 g. of crude crystalline iodolactone.

The aqueous layer from the iodolactone separation was decolorized with 10% sodium thiosulfate and carefully brought to *p*H 2–3 with 205 ml. of *N* sulfuric acid. (Over-acidification results in the separation of sulfur.) The mixture was extracted with ether, the extract was washed with water and dried over magnesium sulfate. Evaporation left 3.65 g. of crude *exo*-acid IVa. After an unsuccessful attempt to purify this material by chromatography on silica gel, purification was effected by re-partitioning between ether and bicarbonate, followed by repeated distillation, whereupon there was obtained IVa of m.p. 42–43°, Beilstein test negative, infrared spectrum free of absorption at 5.6 μ and identical with that of pure racemic IVa, $[\alpha]^{25}\mathrm{D}$ $-6.58°$ (*c* 2.2, *l* 4).

Anal. Calcd. for $C_8H_{10}O_2$: C, 69.55; H, 7.29. Found: C, 69.56; H, 7.38.

The methyl ester IVb, prepared from the above acid and diazomethane, was a liquid of $[\alpha]^{25}\mathrm{D}$ $-10.2°$ (*c* 1.8, *l* 1).

The *endo*-unsaturated acid IIIa, regenerated from the above iodolactone in the usual manner, had $[\alpha]^{25}\mathrm{D}$ $-52.3°$ (*c* 2.6, *l* 1) (compare the starting IIIa which had $[\alpha]\mathrm{D}$ $-55.4°$). No attempt was made to purify further the recovered IIIa.

C. IVa → IIa.—Hydrogenation of 0.50 g. of IVa, $[\alpha]^{25}\mathrm{D}$ $-6.58°$, in ethyl acetate over 10% palladium-on-charcoal, with subsequent distillation of the product gave 0.50 g. of IIa, m.p. 55–57°, inert to aqueous permanganate, infrared spectrum identical with that of the racemate, $[\alpha]^{25}\mathrm{D}$ $-10.7°$ (*c* 2.4, *l* 1).

Anal. Calcd. for $C_8H_{12}O_2$: C, 68.56; H, 8.62. Found: C, 68.58; H, 8.66.

The methyl ester IIb, prepared with diazomethane from a sample of IIa which had been obtained by direct resolution[2] and which had $[\alpha]^{25}\mathrm{D}$ $-8.06°$ (*c* 2.57, *l* 4), was obtained as a colorless liquid $[\alpha]^{25}\mathrm{D}$ $-9.91°$ (*c* 2.8, *l* 1). The infrared spectrum was identical with that of racemic IIb; $n^{25}\mathrm{D}$ 1.4618 (compare the racemate[12] $n^{25}\mathrm{D}$ 1.4618); Bode reported[15] $n^{20}\mathrm{D}$ 1.4643 for racemate prepared from what was presumably epimerically impure racemic IIa of m.p. 48°.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.04; H, 9.30.

Synthesis of *endo*-Norbornanecarboxylic Acid-2,3-^{14}C (Ia).—A sample of methyl acrylate-2,3-^{14}C (supplied by Volk Radiochemical Co. on authorization from the Atomic Energy Commission) of total activity 0.5 mc. in 0.7 ml. of toluene as solvent was diluted with 14.1 g. of freshly distilled (b.p. 79.5–80°) unlabeled methyl acrylate, treated with 0.2 g. of hydroquinone, chilled to 0–5° and treated with freshly distilled (b.p. 40–42°) cyclopentadiene in 25 ml. of dry ether during 25 minutes. After an additional 8.5 hours, the mixture was allowed to stand overnight at room temperature. The ether was removed by distillation and the crude ester mixture was saponified directly by boiling for 4 hours with a solution of 20 g. of sodium hydroxide in 115 ml. of water. The mixture was acidified with 5 *N* sulfuric acid and extracted with three portions of ether. The extract was washed with water, dried over magnesium sulfate, evaporated and distilled to give 8.8 g. of crude mixed acids. Three grams of unlabeled IIIa was added, and the mixture was subjected to iodolactone separation in the usual manner. The resulting iodolactone (19.1 g.) was reconverted to the unsaturated *endo*-acid IIIa with zinc in acetic acid. The crude IIIa was diluted with three more grams of unlabeled IIIa and re-partitioned between ether and bicarbonate to remove a trace of iodolactone. The resulting IIIa (9.2 g.) was chemically pure as evidenced by infrared spectrum and a negative Beilstein test. Hydrogenation in the usual manner gave 7.2 g. of pure Ia, m.p. 62–65°, infrared spectrum identical with that of an authentic sample, apparent activity 2965 ± 12 c./min. Recrystallization did not change the m.p. or activity.

Isotope Dilution Analysis of (+)-*endo*-Norbornanecarboxylic Acid.—The optically active acid used had m.p. 48–51°, infrared spectrum identical with that of an authentic sample of the racemate, $[\alpha]^{25}\mathrm{D}$ $+16.7°$ (*c* 2.5, *l* 4). A mixture of 3.7325 g. of this material and 3.8104 g. of the above radioactive sample was twice recrystallized from acetonitrile to give the racemate, m.p. 63–65°, optically inactive. This material showed an apparent activity of 1615 ± 12 c./min. The m.p. and activity were unchanged by further recrystallization.

Radioactivity measurements were carried out with the "infinitely thick" layer technique previously described.[16] Counts of individual mountings were readily reproducible to about 0.5% average deviation, but independent mountings could not be reproduced to better than 1%. This was due apparently to some property of films of crystalline Ia. Attempts to improve mounting reproducibility were made by counting the amide of Ia. These samples were even worse in this respect; independent mountings showed a scatter of about 5%. In the calculation of statistical error, therefore, the error of an individual activity of Ia was taken as 1%. The statistical error was calculated by standard methods,[17] assuming weighing errors to be negligible. Equation 3 was put in the form

$$E = [(x + B)^2 - (C_0/C_\pm)(x^2 + Bx)]^{1/2}$$

and differentiated with respect to $(C_0/C_\pm)$; Q, the error in E is then given by[17]

$$Q^2 = \left(\frac{\partial E}{\partial(C_0/C_\pm)}\right)^2 r^2 = \frac{(x^2 + Bx)^2 r^2}{4[(x + B)^2 - (x^2 + Bx)C_0/C_\pm]}$$

where r is the error of $C_0/C_\pm$. The uncertainty in the absolute value of % E was 2.6%; *i.e.*, the starting acid was 51.8–54.4% optically pure. This gives the values $[\alpha]\mathrm{D}$ 30.6–32.1° for optically pure acid.

Coincidence loss, as determined by the single paired-source method,[18] was much smaller than the reproducibility of counting and therefore no correction was applied.

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