Synthesis of Chaminic Acid

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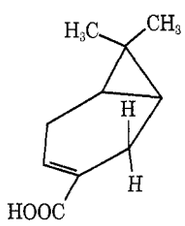
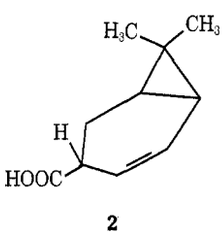
Chaminic acid, a bicyclic terpene from *Chamaecyparis nootkatensis*, has been synthesized. 5-Hydroxy-1,3-cyclohexanedicarboxylate, obtained by hydrogenating the benzenoid compound, is dehydrated with acetyl chloride to give in part the corresponding lactone and in part the acetate of the cyclic acid anhydride. Excess methylmagnesium chloride with either compound furnishes the same adduct, 5-hydroxy-1-(α-hydroxyisopropyl)cyclohexanecarboxylic acid. Chlorination to the α-chloroisopropyl derivative, esterification, and oxidation give rise to methyl 5-oxo-3-(α-chloroisopropyl)cyclohexanecarboxylate, which cyclizes with base to methyl 2-oxo-7,7-dimethylnorcarane-4-carboxylate. A double bond β,γ to the carboxyl group is then introduced by brominating the oxo compound, reducing the bromo ketone to bromohydrin, and eliminating the elements of hypobromous acid with zinc. The final step, yielding the desired *dl*-chaminic acid, consists in isomerizing the double bond to the α,β position with alkali. Arguments are presented allowing assignment of stereochemistry to the several intermediates.

Chaminic acid and chamic acid, terpenes isolated from the heartwood of the tree *Chamaecyparis nootkatensis*,[1] have been assigned the structures and absolute configurations as formulated in **1** and **2**.[2,3] The in-



1
chaminic acid



2
chamic acid

sect-repellent properties and the decay resistance of this heartwood may be attributed to one or possibly both of these compounds. We now wish to describe a synthesis of *dl*-chaminic acid[4] proceeding through cis or trans *dl*-chamic acid.[9]

The starting point was 5-hydroxyisophthalic acid (**3** diacid), readily accessible by alkali fusion of commercially available 5-sulfoisophthalic acid.[10] Catalytic hydrogenation (rhodium–alumina) of the dimethyl ester **3** saturated the ring to give dimethyl 5-hydroxy-1,3-cyclohexanedicarboxylate (**4**, 70%). Refluxing the corresponding diacid with acetyl chloride led to 5-acetoxy-1,3-cyclohexanedicarboxylic acid anhydride (**5**, 65%) plus the mixed anhydride of 5-hydroxy-1,3-cyclohexanedicarboxylic acid lactone (**6**, 10%). Excess methylmagnesium chloride either with anhydride **5** or with the acid lactone **7** from **6** furnished the same adduct **8** in good yield. Cold concentrated hydrochloric acid reacted selectively with the tertiary hydroxy group in **8** to form the tertiary chloride **9** (98%). After esterification of the carboxylic acid group in **9**, oxidation of the ring hydroxyl furnished cyclohexanone **10** (84%). This cyclized in the presence of potassium *tert*-butoxide to the desired bicyclic intermediate **11** (70%), with the cis form of **11** predominating.

The final stages of the synthesis called for removing the keto group of **11** and inserting an ethylenic link, as in **14**. Attempts to generate a double bond by elimination procedures using the cyclohexanol corresponding to cyclohexanone **11** failed. Thus low-temperature sulfonylation, expected to furnish the tosylate or the mesylate, gave products evidently with the three-membered ring opened. Neither the methyl xanthate nor the ethyl carbonate ester was obtained despite many trials under different conditions.[11] The tosylhydrazone derivative of ketone **11** could be obtained, but heating the lithium salt in aprotic solvent, instead of the desired olefin,[12] gave an actylenic material, probably methyl 7-methyl-6-octen-1-yne-4-carboxylate, as the major product.[13]

The sequence that succeeded in converting ketone **11** to chaminic acid (**1**) started with the bromination of **11** with phenyltrimethylammonium perbromide[14] to give α-bromo ketone **12**. Sodium borohydride reduced the bromo ketone to the bromohydrin **13**, which with

(1) B. Carlsson, H. Erdtman, A. Frank, and W. E. Harvey, *Acta Chem. Scand.*, **6**, 690 (1952).

(2) H. Erdtman, W. E. Harvey, and J. G. Topliss, *ibid.*, **10**, 1381 (1956).

(3) T. Norin, *Ark. Kemi*, **22**, 123 (1964).

(4) During the course of the work, a report appeared on the two-step conversion of 3-hydroxy-4-methylene-7,7-dimethylbicyclo[4.1.0]heptane to chaminic acid.[5] Since the bicyclo starting material had been derived before in several steps from Δ^3-carene,[6,7] whose preparation in turn can be traced back through many steps to simple starting materials,[8] a formal synthesis has already been achieved, although by a circuitous route.

(5) K. Gollnick and G. Schade, *Tetrahedron*, **22**, 133 (1966). Also see L. Borowiecki and W. Zacharewicz, *Rocz. Chem.*, **37**, 1143 (1963) [*Chem. Abstr.*, **60**, 4185 (1964)].

(6) S. P. Acharya and H. C. Brown, *J. Amer. Chem. Soc.*, **89**, 1925 (1967).

(7) P. J. Kropp, *ibid.*, **88**, 4926 (1966); K. Gollnick, S. Schroeter, G. Ohloff, G. Schade, and G. O. Schenck, *Justus Liebigs Ann. Chem.*, **687**, 14 (1965).

(8) O. Wallach, H. Kruse, and Fr. Kerkhoff, *ibid.*, **275**, 111 (1893); O. Wallach and H. Schrader, *ibid.*, **279**, 377 (1894); A. Baeyer, *Chem. Ber.*, **27**, 1915, 3485 (1894); K. N. Menon and J. L. Simonsen, *J. Indian Inst. Sci.*, **10A**, 1 (1927) [*Chem. Abstr.*, **21**, 3192 (1927)]; J. A. Simonsen, "The Terpenes," Vol. I, Cambridge University Press, New York, N. Y., 1957, pp 148, 150.

(9) Initial attempts by Cynthia L. Deyrup and Arthur P. Iodice at elaborating chaminic acid from *cis*-caronic acid, which already contains a three-membered ring, as well as attempts at forming both rings at once by application of an intramolecular diazo ketone cyclization directed specifically to ketone **11**, proved unsuccessful.

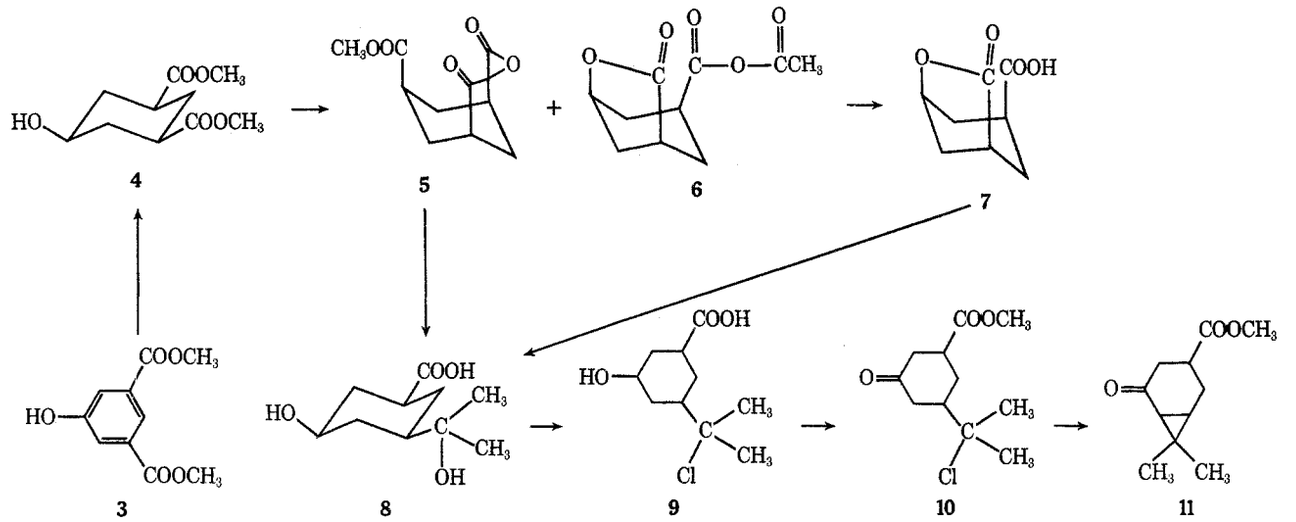
(10) *Cf.* K. Heine, *Chem. Ber.*, **13**, 491 (1880); H. Lonnies, *ibid.*, **13**, 203 (1880).

(11) Examples of the Chugaev elimination in related compounds may be found in U. T. Bhalerao, J. Plattner, and H. Rapoport, *J. Amer. Chem. Soc.*, **92**, 3429 (1970); W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc. C*, 485 (1967); also see C. H. Depuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

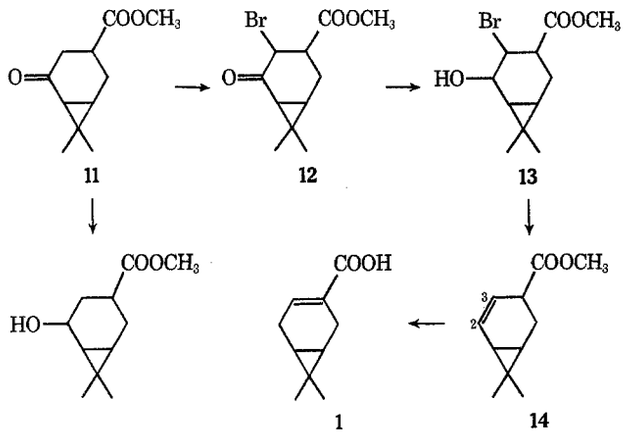
(12) Many examples are known: R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967); W. G. Dauben, *et al.*, *ibid.*, **90**, 4762 (1968); F. Y. Edamura and A. Nickon, *J. Org. Chem.*, **35**, 1509 (1970).

(13) Analogous processes have been observed: *e.g.*, *cf.* J. W. Wheeler, R. H. Chung, Y. N. Vaishnov, and C. C. Shroff, *J. Org. Chem.*, **34**, 545 (1969); R. M. Coates and R. M. Freidinger, *Chem. Commun.*, 871 (1969); G. Ohloff and W. Pickenhagen, *Helv. Chim. Acta*, **54**, 1789 (1971).

(14) W. S. Johnson, J. D. Bass, and K. L. Williams, *Tetrahedron*, **19**, 861 (1963); D. Vorländer and E. Siebert, *Chem. Ber.*, **52**, 283 (1919); *cf.* C. Berger, M. Franck-Neumann, and G. Ourisson, *Tetrahedron Lett.*, 3451 (1968).



zinc in methanol eliminated the elements of HOBr to give either *cis*-chamic ester (**14**) or methyl chamate

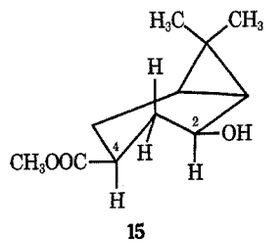


itself (**2**).[15] Instead of trying to purify this compound, it was isomerized with alkali[2] to give the desired *dl*-chaminic acid (**1**). The synthetic material corresponded well in its infrared, ultraviolet, and nuclear magnetic resonance spectra as well as in in melting point with the data[2,3] for the optically active forms.[16] The overall yield in the four-step **11** to **1** process came to 25% when manipulation at each stage was held to a minimum.

Stereochemistry.—Formation of lactone **7** establishes the fact that the hydroxyl group and one of the carboxy groups are on the same side of the cyclohexane ring; formation of acid anhydride **5** shows that both carboxy groups must be on the same side of the ring. These features, as well as the fact that anhydride **5** and lactone **7** both furnish the same Grignard adduct **8**, fix the all-cis configuration in hydrogenation product **4**. The reactions leading to intermediates **8**, **9**, and **10** involve no harsh conditions, so that we have assumed that the cis geometry is carried over to the chloro ketone **10**.

The base-catalyzed cyclization of **10** to **11** afforded two isomers **11** in a combined yield of 70%. That these were stereoisomers **16** and **19** rather than structural isomers was proved by their interconversion on contact with base.

Sodium borohydride reduces the cis keto ester **11** to the all-cis hydroxy ester **15** (60%) with both substituent groups equatorial. This assignment relied on published nuclear magnetic resonance data for the four geometric forms of 2-hydroxy-3,7,7-trimethylbicyclo[4.1.0]heptane.[6] In this set, when the hydroxyl is cis to the cyclopropane ring, the *gem*-dimethyl groups show chemical shifts differing by 7.5 and 13.5 Hz. In contrast, in both of the forms with hydroxyl trans to the cyclopropane ring, the chemical shift difference is 4.5 Hz. In our compound **15**, the chemical-shift difference is 8 Hz, a value that fits better with the cis assignment for the 2-hydroxyl group than the trans. Another indicator is the observed $W_{1/2}$ = 25 Hz for the C–H signal at position 2 in **15**, a value that fits the axial 2-H better than the equatorial.[17]



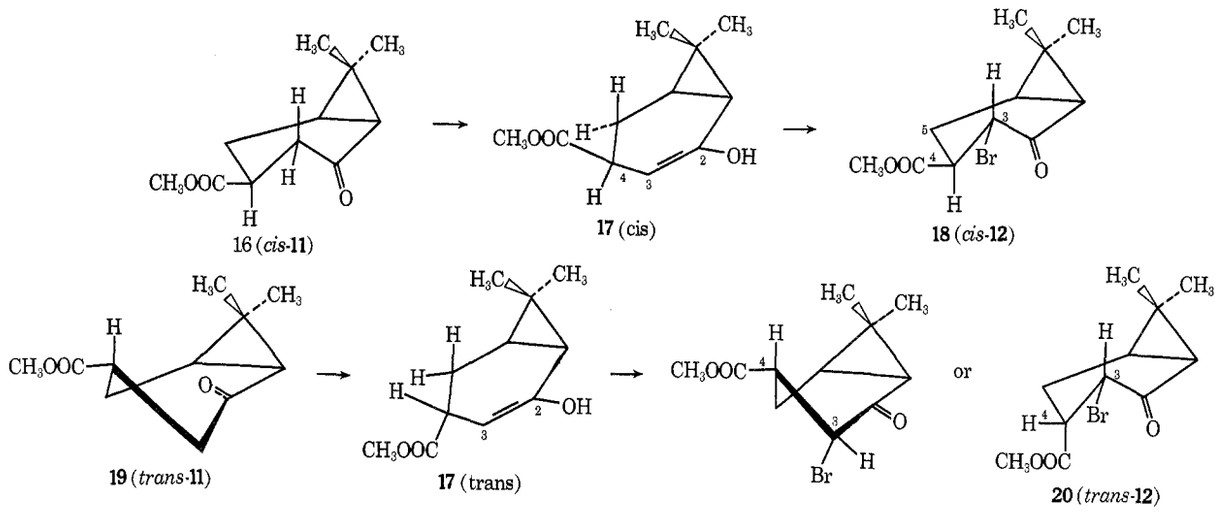
The stereochemical analysis for bromo compound **12** (**18**) leads to the conclusion that the 3-bromo and the adjacent 4-carbomethoxy group are both equatorial, and that the 4-carbomethoxy group is cis to the three-membered ring. The infrared ketone absorption peak for bromo compound **18** appears at a frequency 20 cm^{-1} higher than that for its precursor, **16**, a shift corresponding closely to those observed in equatorial α-bromocyclohexanones (as in **18**) but not to the shift for axial α-bromocyclohexanones (about 5 cm^{-1} to *lower* frequency).[18] So far as the geometric relation of the 3-bromo and 4-carbomethoxy groups in **18** is concerned, the coupling constant (12.5 Hz) of the 3-H with the 4-H corresponds far better to an axial–axial dihedral angle than to the angle for any equatorial–

(15) Related sequences have been reported. Thus *cf.* E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 6267 (1956); M. Akhtar and S. Marsh, *Biochim. J.*, **102**, 462 (1967) [*Chem. Abstr.*, **66**, 52355b (1967)].

(16) Partial resolution (*ca.* 33%) of *dl*-chaminic acid into chaminic acid (dextro) and isochamic acid (levo) was achieved by fractionally recrystallizing the quinine salts. The optical rotatory dispersion curves of the partially resolved materials were close to being mirror images of each other.

(17) R. M. Silverstein and G. C. Bassler, "Spectroscopic Identification of Organic Compounds," Wiley, New York, N. Y., 1967.

(18) E. J. Corey, T. H. Topie, and W. A. Wozniak, *J. Amer. Chem. Soc.*, **77**, 5415 (1955).



axial or equatorial–equatorial arrangement.[19] Accordingly the Br and $COOCH_3$ groups are taken as trans (equatorial–equatorial) as in **18**.

The assignments of cis and trans geometry to the two forms of keto ester **11** (see **16** and **19**) are made by considering the detailed steps in the subsequent bromination process. The intermediates in the bromination will be the enol *cis*-**17** derived from cis compound **16** and the enol *trans*-**17** derived from trans compound **19**. Dreiding models suggest that the enol forms have very little flexibility, and that both enols **17** will have their 4-C bent somewhat away from the *gem*-dimethyl groups. The alternate arrangement with the 4-C bent toward the *gem*-dimethyl grouping leads to appreciable steric interactions between the endo methyl group and the resulting upward-pointing axial group at position 4, no matter whether the axial group is carbomethoxy or hydrogen. Neither model *cis*-**17** nor *trans*-**17** offers much open space for approach of the bulky brominating agent from the side of the *gem*-dimethyl group, while both show more room on the opposite less hindered side. Accordingly in both enols, deposition of the bromo group at position 3 would be favored from the side opposite the *gem*-dimethyl groups, and therefore bromo ketone product **18** will be formed from cis precursor **16**, and product **20** from trans precursor **19**. Since only in conformation **18** are the bromo and ester groups disposed equatorially, both the starting material **16** and its bromo product **18** will have the ester group cis to the three-membered ring. The other cyclization product **19** (the isomer obtained in smaller amounts) accordingly has its ester group trans to the three-membered ring.

Experimental Section

General.—Melting points and boiling points are uncorrected. Thin layer chromatograms were obtained with commercially available supported layers of silica gel impregnated with a fluorescent material. Nuclear magnetic resonance spectra were recorded on a 60-MHz spectrometer. The analyses for elements were performed by Chemalytics, Inc., Tempe, Ariz., Galbraith Laboratories, Inc., Knoxville, Tenn., Scandinavian Microanalytical Laboratories, Herlev, Denmark, and Werby Laboratories, Inc., Boston, Mass.

Preparation and Alkali Fusion of 5-Sulfoisophthalic Acid.[10]—A mixture of isophthalic acid (85 g, 0.51 mol) and 20–23% fuming sulfuric acid (150 ml) was stirred and heated at 200–240° for 5 hr, or until quenching a few drops of the reaction mixture in cold water no longer gave a precipitate. The cooled mixture was poured over crushed ice, and the resulting solution was stirred until no more solid dissolved and filtered. Cooling the filtrate to −10° produced a slurry, which was filtered. The crystals of 5-sulfoisophthalic acid were dissolved in water, and the solution (*ca.* 300 ml) was treated with concentrated sulfuric acid (125 ml) and cooled again to −10°. The resulting crystals of 5-sulfoisophthalic acid were collected and sucked as dry as possible before dissolving them in absolute ethanol (550 ml). A solution of 112 g (2 mol) of potassium hydroxide in 500 ml of absolute alcohol was slowly introduced to precipitate the tripotassium salt, which was collected and dried in a vacuum oven overnight (251 g).

The tripotassium salt was added gradually to a melt of potassium hydroxide pellets (600 g) at 280°. Gas evolution was noted. The temperature was then held at 325° for 5 hr. The solid cooled melt was mixed with 1.4 l. of water, the alkaline mixture was filtered, and to the filtrate was added 840 ml of concentrated hydrochloric acid to pH 2. Filtration of the mixture at room temperature afforded crude 5-hydroxyisophthalic acid as a white solid. Several crystallizations from water produced 59 g of 5-hydroxyisophthalic acid, mp 305–306.5° (lit.[10] mp 284–285° for the dihydrate). The sample for analysis showed mp 296–299°.

Anal. Calcd for $C_8H_6O_5 \cdot {}^1/_2H_2O$: C, 50.01; H, 3.67. Found: C, 49.90; H, 3.46.

When a commercial source of 5-sulfoisophalic acid monosodium salt was located, the commercial material was used in the alkali fusion instead of the tripotassium salt, with essentially the same results.

Dimethyl 5-Hydroxyisophthalate (3).—A solution of the above hemihydrate of 5-hydroxyisophthalic acid (40 g, 0.21 mol) in 500 ml of anhydrous methanol containing 5 ml of concentrated sulfuric acid was refluxed for 2 days. After filtration, the clear solution was stripped of solvent. The residue was taken up in ethyl acetate (400 ml) and the solution was washed free of acids with aqueous sodium bicarbonate. The dried ($MgSO_4$) ethyl acetate solution was stripped of solvent, and then kept warm in an open flat dish until the resulting white, fluffy crystals of dimethyl 5-hydroxyisophthalate (**3**), mp 162–163.5° (lit.[10] mp 159–160°), reached constant weight (37 g, 85%): ir (mineral oil) 3360 (OH), 1710 and 1730 ($COOCH_3$), 1625, and 1610 cm^{-1}; ir ($CHCl_3$) 1710 (sh) and 1720 cm^{-1} (peak, $COOCH_3$); nmr (CD_3COCD_3) δ 8.12 (q, 1, J = 2 Hz, H-2), 7.71 (d, 2, J = 2 Hz, H-4 and H-6), 3.94 (s, 6, 2 $COOCH_3$), and 2.09–3.70 ppm (solvent impurity plus OH).

Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80. Found: C, 57.14; H, 4.83.

Dimethyl 5-Hydroxy-1,3-cyclohexanedicarboxylate (4) by Hydrogenation of Dimethyl 5-Hydroxyisophthalate (3).—Suspensions of 5% rhodium-on-alumina catalyst (Englehardt Industries, Inc.) in methanol containing the isophthalate ester plus a small amount of acetic acid were shaken under hydrogen (55 psi) until either the correct amount of hydrogen had been absorbed or hydrogen uptake had stopped. Batches of ester ranging from 5 to 23 g were successfully converted, in each case with the weight of catalyst equal to $^1/_5$ the weight of ester, and with the

(19) *Cf.* F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 135.

volume of 1% acetic acid in methanol corresponding to 10–20 times the weight of ester. To avoid fire, it was necessary to have the methanol cooled to 0° before allowing it to come in contact with the catalyst. Hydrogenation required about 12 hr for the larger amounts.

Catalyst and solvent were removed from the hydrogenation mixtures. The combined residues from several preparations were dissolved in chloroform and were washed first with 10% aqueous potassium hydroxide and then with saturated salt solution. Solvent was distilled from the dried chloroform solution, and the remaining oily product was pumped at 0.1 mm for several hours. The combined yield (70.1 g) corresponded to a quantitative conversion. This material retained no sign of the 1625- or 1610-cm^{-1} absorptions attributable to the aromatic ring.

The hydrogenation product was divided into equal parts and each half was chromatographed through about ten times its weight of silica gel. The developing solvent was chloroform, followed by chloroform–ether mixtures with increasing proportions of ether, and finally ether. Fractions were monitored and were combined on the basis of thin layer chromatographic results (ether solvent). In this way was obtained a total of 13.9 g (22%) of dimethyl 1,3-cyclohexanedicarboxylate, R_f 0.89, and 48.6 g (70%) of dimethyl 5-hydroxy-1,3-cyclohexanedicarboxylate (**4**), R_f 0.43.

The structure of the lesser product, the hydrogenolysis product, bp 64–66° (0.05 mm), was assigned on the basis of its infrared absorption spectrum, ir ($CHCl_3$) 1740 cm^{-1} ($COOCH_3$), no absorption in the OH region.

The desired all-cis hydroxy diester **4** showed bp 116–128° (0.05) mm); ir ($CHCl_3$) 3500–3450 (OH) and 1735 cm^{-1} ($CO-OCH_3$); nmr (CCl_4) δ 1.0–2.6 (m, 8, ring protons at positions 1, 2, 3, 4, 6) and 3.54–3.65 ppm (m, 8, remaining protons dominated by CH_3O singlet at 3.65 ppm).

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.89; H, 7.48.

Dichromate oxidation of dimethyl 5-hydroxy-1,3-cyclohexanedicarboxylate (**4**) afforded the corresponding keto diester (57%; mp 110–113° before recrystallization from ethyl acetate): mp 118.5–122°; ir ($CHCl_3$) 1730 cm^{-1}; nmr ($CDCl_3$) δ 1.0–2.61 (m, 8, ring, protons), 3.73 ppm (s, 6, 2 $COOCH_3$).

Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.08; H, 6.66.

Saponification of the hydroxy diester was accomplished by refluxing a mixture of 14.1 g (0.065 mol) of diester **4** and 5.5 g of sodium hydroxide with 40 ml of water for 1 day. After appropriate treatment of the reaction mixture, crystallization of the crude product from tetrahydrofuran–benzene gave 10.2 g (83%) of 5-hydroxy-1,3-cyclohexanedicarboxylic acid, mp 198–199°, ir (KBr pellet) 3600–2400 (OH and COOH) and 1715 cm^{-1} (shoulder at 1688 cm^{-1}).

Anal. Calcd for $C_8H_{12}O_5$: C, 51.06; H, 6.42. Found: C, 50.84; H, 6.36.

Acetyl Chloride Treatment of 5-Hydroxy-1,3-cyclohexanedicarboxylic Acid.—When a mixture of acetyl chloride (60 ml) and hydroxy diacid (12.7 g, 0.067 mol) was refluxed for 7 hr, the insoluble crystalline starting material gradually dissolved. Volatile material was removed, and the residue was pumped at 0.1 mm for several hours. The crystalline residue was fractionally recrystallized from acetone to give a total of 9.3 g (65%) of pure, less soluble 5-acetoxy-1,3-cyclohexanedicarboxylic acid anhydride (**5**), mp 190–193°, showing a single spot at R_f 0.72 (ethyl acetate), and approximately 1.0 g (10%) of less pure mixed anhydride **6** between acetic acid and 5-hydroxy-1,3-cyclohexanedicarboxylic lactone. The acetoxy anhydride **6** in chloroform showed infrared absorption peaks at 1810 and 1765 (cyclic anhydride) and 1740 cm^{-1} (acetate C=O); nmr (deuterated acetone) δ 5.03 (m, 1, H α to acetate), 3.03 (m, 2, H's α to anhydride carbonyls), 2.70 (broad s, 1, equatorial H at position 2), 2.12 (m, ring H's, 1.85 ppm (s, $OOCCH_3$).

Anal. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70. Found: C, 56.68; H, 5.88.

Lactone 7 of 5-Hydroxycyclohexane-1,3-dicarboxylic Acid from the Mixed Acetic Anhydride 6.—The unpurified crystalline mixed anhydride as a solution in chloroform showed maxima at 1810 and 1765 (anhydride), 1780 (γ-lactone), and a shoulder at 1745 cm^{-1} (some of the acetoxy anhydride). Since this material lost acetic acid readily, it was not purified but instead was hydrolyzed directly to the lactone **7**.

Refluxing a mixture of 3.3 g of the mixed anhydride–lactone with 10 ml of water for 45 min gradually dissolved the solid. Allowing the cooled solution to stand for 2.5 hr deposited 2.3 g of the desired lactone **7** of 5-hydroxy-1,3-cyclohexanedicarboxylic acid as crystals, mp 190–192°, ir (KBr pellet) 3500–2500 (COOH) and 1770 and 1685 cm^{-1} (γ-lactone and carboxyl carbonyls).

Anal. Calcd for $C_8H_{10}O_4$: C, 56.47; H, 5.92. Found: C, 56.59; H, 6.04.

5-Hydroxy-3-(α-hydroxyisopropyl)cyclohexanecarboxylic Acid (8) from Methylmagnesium Chloride and 5-Acetoxy-1,3-cyclohexanedicarboxylic Anhydride (5).—A solution of the acetoxy anhydride (5.0 g, 0.024 mol) in 300 ml of absolute tetrahydrofuran was added at 0° over 1.5 hr to methylmagnesium chloride (0.17 mol) in solution (58 ml) with the same solvent. The reaction mixture was stirred during addition and for 1 hr thereafter. Then saturated ammonium chloride solution (*ca.* 35 ml) was added dropwise to the mixture still at 0° until no further precipitate formed. The supernatant liquid was decanted from the heavy semisolid lower phase, which was then rinsed by decantation with two 20-ml portions of ether. Adding more ammonium chloride solution (*ca.* 150 ml) changed the clumped mass to discrete particles. This was followed with concentrated hydrochloric acid (to pH 2) and finally with enough water to dissolve all the solid. The acidic aqueous phase (*ca.* 400 ml) was ether extracted continuously for 1 week, with the solvent replaced every 2 days. Removal of ether from the combined extracts left crude product, which on recrystallization from concentrated water solution afforded pure, chunky, white crystals (85%) of 5-hydroxy-3-(α-hydroxyisopropyl)cyclohexanecarboxylic acid (**8**): mp 166.5–168°; ir (KBr pellet) 3600–2400, with sharper maxima at 3530 and 3375, 1705 cm^{-1}.

Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.55; H, 9.03.

5-Hydroxy-3-(α-hydroxyisopropyl)cyclohexanecarboxylic Acid (8) from Methylmagnesium Chloride and the Lactone 7 of 5-Hydroxycyclohexane-1,3-dicarboxylic Acid.—A solution of lactone **7** (0.50 g, 0.003 mol) in 65 ml of absolute tetrahydrofuran was added dropwise to a stirred tetrahydrofuran solution of methylmagnesium chloride (5.4 ml of 2.8 *M*, 0.016 mol) at 0° over a period of 15 min. After the mixture had been stirred further for 21 hr, product was isolated essentially as described before. Recrystallizations from water gave 5-hydroxy-3-(α-hydroxyisopropyl)cyclohexanecarboxylic acid (0.36 g, 60%), mp 166–167.5°. When this product was mixed with the same material prepared from the anhydride, the melting point was 167.5–168.5°. The infrared absorption curves were indistinguishable.

5-Hydroxy-3-(α-chloroisopropyl)cyclohexanecarboxylic Acid (9).—After 3.8 g of 5-hydroxy-3-(α-hydroxyisopropyl)cyclohexanecarboxylic acid (**8**) was dissolved in 60 ml of concentrated hydrochloric acid at 0° by stirring, the solution was stored cold for 16 hr. Filtration afforded the desired chloro compound **9**, which was dried overnight under reduced pressure to give 3.7 g (98%) of crystalline product, mp 165.5–166.5°. Although this was suitable for use in the next step, a sample (mp 168.5–169°) for analysis was prepared by recrystallizations from acetone–hexane.

Anal. Calcd for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.76; Cl, 16.06. Found: C, 54.23; H, 7.87; Cl, 16.21.

This material **9**, pelleted with potassium bromide, showed infrared absorptions at 3500 and 2500 (broad), 3420, and 1705 cm^{-1}.

The ketone corresponding to hydroxy acid **9** was prepared by introducing 14 drops of chromium(VI) solution to a solution (0°) of chlorohydroxy acid **9** (107 mg) in 10 ml of acetone. The oxidant was made up by adding 2.3 ml of concentrated sulfuric acid to 2.88 g of chromium(VI) trioxide dissolved in 4 ml of water and then diluting with water to 10 ml. After 0.5 hr at 0°, the reaction mixture was filtered, and volatiles were removed from the filtrate. Water (4 ml) was added to the residue, which was then extracted thoroughly with chloroform. The dried extract was treated with a little isopropyl alcohol, the resulting blue mixture was filtered, and the filtrate was stripped of solvent. Crystallizations from benzene–hexane gave white crystals (76 mg, 71%) of 5-oxo-3-(α-chloroisopropyl)cyclohexanecarboxylic acid (acid corresponding to **10**): ir (KBr) 3700–2500, 1725, 1685 cm^{-1}; ir ($CHCl_3$) 1750 and 1710 cm^{-1}. Material melting at 129.5–130° was analyzed.

Anal. Calcd for $C_{10}H_{15}ClO_3$: C, 54.92; H, 6.91; Cl, 16.21. Found: C, 54.89; H, 6.65; Cl, 16.17.

Methyl 5-Oxo-3-(α-chloroisopropyl)cyclohexanecarboxylate (10) by Oxidation of the 5-Hydroxyl Ester.—The starting ester,

methyl 5-hydroxy-3-(α-chloroisopropyl)cyclohexanecarboxylate, prepared from acid 9 with diazomethane in ether–methanol, showed ($CHCl_3$) absorptions at 3600 (sharp) and 1730 cm^{-1}; nmr signals ($CDCl_3$) were seen at δ 3.66 (s, $COOCH_3$), *ca.* 3.55 (m, HCOH), 3.51 (s, OH), 1.56 [s, $C(CH_3)_2$], 2.5–1.0 ppm (m, ring H's).

With the temperature at 5–8°, acid chromium trioxide solution (12 ml, see above) was added over 45 min to a stirred solution of this ester (9.4 g, 0.037 mol) in 200 ml of acetone. After another 15 min at 0°, the mixture was filtered, the crushed solids were rinsed with acetone, and the combined filtrates were evaporated. Water (20 ml) was added to the residue, which was thoroughly extracted with chloroform. The extracts were washed twice with small portions of 5% bicarbonate and twice with saturated aqueous sodium chloride, and then treated with solid sodium sulfate, some sodium bicarbonate, and a few milliliters of isopropyl alcohol. Removal of solvent from the dry solution left a crystalline residue, which when rinsed with hexane and air dried weighed 8.2 g and showed mp 67.5–68° (softening at 65°). Chromatography through a 2 × 50 cm column of silica gel with chloroform as solvent was monitored by thin layer chromatography. Removal of solvent, etc., furnished 7.3 g (84%) of one-spot methyl 5-oxo-3-(α-chloroisopropyl)cyclohexanecarboxylate (**10**): mp 69–71.5°; ir ($CHCl_3$) 1735 and 1715 cm^{-1}; nmr ($CDCl_3$) δ 3.69 (s, 3, $COOCH_3$), 2.56 (m, H's next to keto group), 2.7–1.0 (m, H's at positions 1, 2, 3), 1.58 ppm [d, J = 3 Hz, $ClC(CH_3)_2$]. Integration of the signals from 2.56 to 1.0 ppm showed 14 protons as demanded.

Methyl 2-Oxo-7,7-dimethylnorcarane-4-carboxylate (11) by Cyclization of Methyl 5-Oxo-3-(α-chloroisopropyl)cyclohexanecarboxylate (10).—Approximately 1.2 g (0.03 g-atom) of clean pieces of potassium was dissolved in 40 ml of boiling *tert*-butyl alcohol that had been distilled from calcium hydride. A solution of methyl 5-oxo-3-(α-chloroisopropyl)cyclohexanecarboxylate (**10**, 3.7 g, 0.016 mol) in 30 ml of benzene was added dropwise over a period of 25 min to the *tert*-butoxide solution kept cool with a bath of cold water. The milky amber reaction mixture was stirred at room temperature for 45 min. Some ice was added and the mixture was evaporated to a volume of *ca.* 5 ml, diluted with an equal volume of water, and extracted twice with ether. The aqueous layer at 0° was brought to pH 2 with 6 *N* hydrochloric acid, and the acid mixture was extracted with ether to remove the carboxylic acid product. The extract, after rinsing with saturated aqueous salt solution and drying, was stripped of volatiles to yield *ca.* 3.0 g of yellow viscous 2-oxo-7,7-dimethylnorcarane-4-carboxylic acid (acid corresponding to **11**): ir ($CHCl_3$) 1710 (COOH), 1680 (cyclopropyl ketone), and 900 cm^{-1} (cyclopropane ring).

Esterification with diazomethane afforded the methyl ester in near-quantitative yield. This was chromatographed over 100 g of silica gel, with ether–hexane (15:85) as solvent, and with fractions combined with the help of thin layer chromatographic monitoring.

Methyl *cis*-2-oxo-7,7-dimethylnorcarane-4-carboxylate (**11**), R_f 0.72 (hexane–ether–methanol, 20:10:1), was isolated in 42% yield (1.3 g): ir ($CHCl_3$) 1730, 1680, and 900 cm^{-1}; uv (95% ethanol at 1 × 10^{-4} *M*) λ_{max} 208 nm (log ε 3.72); nmr (CCl_4) δ 3.62 (s, 3, $COOCH_3$), 1.16 (s, *gem*-dimethyl), and 1.0–3.0 ppm (m, cyclohexane protons). The signals from 1.16 to 3.0 ppm integrated to 13 protons. A sample of **11** for analysis was prepared by a bulb-to-bulb distillation.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.25; H, 8.19.

Methyl *trans*-2-oxo-7,7-dimethylnorcarane-4-carboxylate (**11**), R_f 0.53, was obtained in 0.63-g yield. Together with a second fraction (0.24 g) showing the presence of a trace of extraneous material at R_f 0.62, the yield of the trans isomer was 28%: ir ($CHCl_3$) 1725 and 1675 cm^{-1}, with the fingerprint region substantially different from that of the cis isomer; uv (95% ethanol, 8 × 10^{-5} *M*) λ_{max} 208 nm (log ε 3.67); nmr (CCl_4 with bulb-to-bulb distilled material) δ 3.64 (s, 3, $COOCH_3$), 1.0–3.0 (m, cyclohexane ring protons), 1.16 (s, exo CH_3), 1.08 ppm (s, endo CH_3). The signals from 3.0 to 1.08 ppm integrated to 13 protons as required.

Interconversion of Cis and Trans Isomers of Methyl 2-Oxo-7,7-dimethylnorcarane-4-carboxylate (11). A. Trans to Cis.—The trans isomer **19** (0.63 g, 0.0033 mol) in 10 ml of *tert*-butyl alcohol was added slowly to a solution of potassium (0.4 g, 0.01 g-atom) in 15 ml of *tert*-butyl alcohol. The dark brown solution was stirred at room temperature under nitrogen for 40 min. After part of the solvent was removed, the concentrated solution was added dropwise to 7 ml of cold 6 *N* hydrochloric acid. Adding an excess of solid sodium bicarbonate neutralized the mixture, which was then distilled until all the *tert*-butyl alcohol had been removed. Addition of a few drops of aqueous sodium hydroxide raised the pH from 8 to 9. The basic solution was rinsed twice with ether and acidified with cooling to pH 2, and the acid products were extracted thoroughly with ether. The combined extracts were dried, and the viscous yellow residue (0.55 g) dissolved in methanol was esterified with ethereal diazomethane. After several hours, the filtered solution was evaporated to give 0.51 g of methyl esters. Column chromatography though silica gel in a 1.2 × 50 cm column using 700 ml of ether–hexane (15:85) followed by 950 ml of ether–hexane (20:80) gave several fractions, one of which consisted of homogeneous methyl *cis*-2-oxo-7,7-dimethylnorcarane-4-carboxylate (**16**, 0.10 g, 19%) with R_f 0.78, and another of the trans isomer **19** (0.15 g, 27%) with R_f 0.48. The identity of the cis and trans isomers was established by R_f comparisons and by infrared absorption curves, which were identical, respectively, with those of the previously isolated compounds.

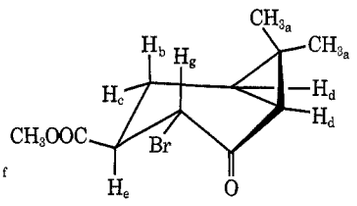
B. Cis to Trans.—The cis isomer **16** (26 mg) in 2 ml of dry *tert*-butyl alcohol was stirred with 5 ml of a 0.77 solution of potassium *tert*-butoxide for 1 hr. Processing similar to that described above gave 25 mg of reesterified crude methyl esters. Thin layer chromatography (two developments) showed four spots; the R_f values of two of the darkest corresponded to those of authentic cis and trans esters spotted on the same plate.

Methyl 2-Hydroxy-7,7-dimethylnorcarane-4-carboxylate by Reduction of the Corresponding Oxo Compound 11.—A cold solution of sodium borohydride (46 mg, 1.2 mmol) in 4 ml of methanol was added to 98 mg (0.5 mmol) of methyl *cis*-oxo-7,7-dimethylnorcarane-4-carboxylate (**11**) dissolved in cold methanol (5 ml). The mixture was allowed to come to room temperature and was stirred further for 3 hr. Solvent was removed, 4 ml of water was added to the residue, and the mixture, held at 0°, was brought to pH 2–3 with hydrochloric acid. The aqueous phase was extracted with ether, which after rinsing with 5% aqueous bicarbonate and then water was dried ($MgSO_4$). Removal of all solvent left 78 mg of product which showed no ketone absorption at 1675 cm^{-1}. Column chromatography through 1.2 g of silica gel using first benzene and then 1:1 benzene–chloroform as developing solvents gave fractions containing a total of 58 mg of one-spot, solvent-free hydroxy ester (60%): ir ($CHCl_3$) 3600 and 3450 (OH) and 1730 cm^{-1} ($COOCH_3$): nmr ($CDCl_3$) δ 4.32 (m, $W_{1/2}$ = 25 Hz), 3.66 (s, $COOCH_3$), 1.66 (s, OH), 0.9–2.5 (m, cyclohexane ring protons at 1, 3, 4, 5, 6), 1.2 (s, exo CH_3), 1.09 ppm (s, endo CH_3). The first two signals corresponded to 4 protons, all the others to 14. A sample for analysis was prepared by bulb-to-bulb distillation.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.59; H, 9.23.

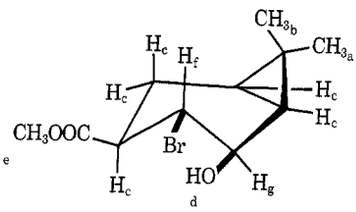
Methyl 3-Bromo-2-oxo-7,7-dimethylnorcarane-4-carboxylate (12).—A 0° solution of methyl *cis*-2-oxo-7,7-dimethylnorcarane-4-carboxylate (**11**, 0.45 g, 2.3 mmol) in 20 ml of freshly distilled tetrahydrofuran was treated with portions of phenyltrimethylammonium perbromide[14] (total weight 0.90 g, 2.4 mmol; mp 114–115.5°). After 50 min of stirring, another 20 mg of perbromide was added and the mixture was stirred further for 5 min.

The mixture, containing a white precipitate, was poured into an ice-cold water solution of 5% sodium bicarbonate (15 ml) plus 0.1 *N* sodium thiosulfate (16 ml). The separated bromination product **12** was taken up in ether, and the ether solution was washed, dried, and stripped of solvent. The viscous residue deposited crystals after standing at 0°, and, after trituration with a small amount of cold methanol, furnished 0.19 g (30%) of crystalline methyl 3-bromo-2-oxo-7,7-dimethylnorcarane-4-carboxylate (**12**), mp 112.5–113.5°. Other preparations gave the same product with mp 115–115.5°. Assay with the help of infrared absorption showed that the mother liquor contained appreciable additional amounts of the desired product; the estimated total yield was *ca.* 50%. The crystalline material showed ir ($CHCl_3$) 1730 ($COOCH_3$) and 1695 cm^{-1} (α-bromo ketone); uv (95% alcohol, 8 × 10^{-5} *M*) λ_{max} 212 nm (log ε 3.575); nmr ($CDCl_3$) δ 4.53 (d, J_{eg} = 12.5 Hz, 1, H_g), 3.75 (s, 3, H_f), 3.21 (sextet, J_{eg} = J_{eb} = 12.5 Hz; J_{ec} = 5 Hz, 1, H_e), 1.7 (m, H_d), 1.5–2.5 (m, H_b and H_c), 1.21 ppm (s, H_a). The signals on the high-field side of δ 2.5 ppm integrated to 10 protons, as required.



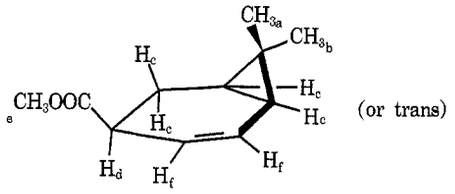
Anal. Calcd for $C_{11}H_{15}BrO_3$: C, 48.01; H, 5.49; Br, 29.02. Found: C, 47.97; H, 5.54; Br, 29.12.

Methyl 2-Hydroxy-3-bromo-7,7-dimethylnorcarane-4-carboxylate (13) from Oxo Compound 12.—Solid sodium borohydride (24 mg, 0.63 mmol) was added to an ice-cold solution of methyl 3-bromo-2-oxo-7,7-dimethylnorcarane-4-carboxylate (62 mg, 0.24 mmol) in methanol (7 ml). After 35 min, methanol was stripped, water was added to the residue, and the mixture was extracted thoroughly with ether. The oil obtained after removing ether from the dried extract weighed 63 mg (100%) and was taken as product **13**: ir ($CHCl_3$) 3670 and 3450 (OH) and 1730 cm^{-1} ($COOCH_3$), with the ketone peak at 1695 cm^{-1} missing; nmr ($CDCl_3$) δ 3.8–4.6 (m, 2, H_f and H_g), 3.68 (s, 3, H_e), 2.5 (m, H_d), 1.0–3.0 (m, H_c), 1.18 (s, H_b), 1.06 ppm (s, H_a). The signals other than those for H_e, H_f, and H_g integrated to 12 protons.



Bromohydrin **13** decomposes on standing; the infrared and nuclear magnetic resonance absorption curves of the decomposition product are consistent with those expected for methyl 3-isopropylbenzoate.

***dl*-Chaminic Acid (1).**—A solution of 63 mg of unpurified bromohydrin **13** in 10 ml of methanol was refluxed for 22 hr with 0.64 g of "activated" granular zinc.[20] After standing overnight, solvent was removed and the residue was extracted with chloroform. The liquid (58 mg) left after stripping solvent from the filtered extract was taken as the Δ^2-unsaturated product **14**: ir ($CHCl_3$) 3500 (broad, weak band corresponding to a low concentration of OH), 1725 ($COOCH_3$), and 1640 and 1600 cm^{-1} (weak). The nuclear magnetic resonance absorption curve closely resembled that published[3] for natural chamic acid when the acid–ester differences are taken into account. Preparative layer chromatography over silica gel using 200:15:1.5 hexane–ether–methanol afforded material with ir ($CHCl_3$) peaks at 1725 ($COOCH_3$) and 1640 and 1655 cm^{-1} (isolated and conjugated double bonds); nmr ($CDCl_3$) δ 5.84 (m, *ca.* 2, H_f), 3.68 (s, 3,



(or trans)

H_e), 3.15 (m, H_d), 2.5–0.8 (m, H_c), 1.08 (s, H_b), 0.92 ppm (s, H_a). The integration ratio for the H_e and H_f protons to all the rest was *ca.* 5:11 as required by methyl 7,7-dimethylnorcar-2-ene-4-carboxylate (**14**). A very small peak at δ 0.73 ppm confirmed the infrared evidence in suggesting the presence of a small proportion (less than 5%) of methyl chaminate in this material.

Instead of isolating the Δ^2 isomer **14**, the mixture was converted to the conjugated chaminic acid (**1**) as follows. A mixture of crude Δ^2 isomer (49 mg) with 25% aqueous sodium hydroxide was refluxed for 2 hr. The cooled homogeneous system was rinsed with ether (discarded), and after acidification (pH 2) was extracted thoroughly with ether. Removal of all solvent from the dried ether extract left a tacky residue (26 mg, 55%) which showed a nuclear magnetic resonance spectrum almost identical with that obtained subsequently for pure *dl*-chaminic acid (**1**). Purification of this material was accomplished by thick layer chromatography (50:60:1 hexane–ether–acetic acid) followed by rinsing the crystals so obtained with a few drops of hexane. The resulting *dl*-chaminic acid (**1**) showed mp 101–103°.

Preparative Directions for *dl*-Chaminic Acid (1) from Methyl 2-Oxo-7,7-dimethylnorcarane-4-carboxylate (11).—Bromination of the oxo compound **11** (0.69 g) essentially as described before gave 0.25 g of crystalline bromo ketone **12**, mp 112.5–113.5°, as well as an oily impure fraction (see below). The crystalline bromo ketone was reduced with excess sodium borohydride to give 0.26 g of semicrystalline bromohydrin **13**. This was treated with zinc in methanol for 42 hr; the filtered (Celite) solution was then refluxed for 2.5 hr in the presence of 0.75 g of sodium hydroxide with 2 ml of water. Methanol was removed under reduced pressure, water was added, and the alkaline solution was processed as before to give 0.13 g of semicrystalline *dl*-chaminic acid (**1**). Two crystallizations from benzene afforded crystalline product (0.06 g), mp 102–104°, in 40% overall yield from the crystalline bromo ketone.

When the above oily impure bromo ketone was put through the same steps crude *dl*-chaminic acid (**1**) was obtained, which was then chromatographed through a small column of silica gel (1:5 ether–hexane), with the less pure fractions being rechromatographed. *dl*-Chaminic acid (**1**) was obtained, mp 97.5–100.5° (0.11 g). A finel recrystallization of the combined crystalline products from methanol gave 0.14 g (25% from methyl *cis*-2-oxo-7,7-dimethylnorcarane-4-carboxylate, **11**), mp 104.5–105.5°. The value reported for the optically active forms is 105–106°.[2,3] The synthetic material showed uv (1.1×10^{-4} *M* in 95% alcohol) λ_{max} 218 nm (log ϵ 3.871) [lit.[2] λ_{max} 218 nm (log ϵ 3.860)]; ir ($CHCl_3$) 3500–2400 (broad), 1680, 1647, 1655 cm^{-1} (sh) (the spectrum was the same as that described for natural chaminic acid[2]); nmr ($CDCl_3$) δ 10.7 (broad s, COOH), 7.05 (broad s, 1, vinyl H), 2.33 (m, 4, 2 ring CH_2's), 1.1–0.5 (m, cyclopropane H's), 1.07 (s, exo CH_3), 0.73 ppm (s, endo CH_3). The signals for the two methyl groups plus the two cyclopropane H's integrated to eight protons.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.27; H, 8.49. Found: C, 72.03; H, 8.76.

Formation of the quinine salt of racemic chaminic acid followed by fractional crystallization from benzene–hexane appeared to offer a practical resolution method for the levorotatory enantiomer (isochamic acid). Fractional precipitation of the less soluble isochamic salt by adding hexane to a benzene solution of racemic material containing a deficiency of quinine left the uncombined chaminic acid in solution. Appropriate processing, including crystallizations from methanol, afforded the partially resolved materials in good recovery. With rotations determined using methanol as solvent, the partially resolved chaminic acid, mp 104.5–105°, showed $[\alpha]_{590}$ *ca.* +2.1° (lit.[2] +6°); the partially resolved isochamic acid, mp 102.5–103°, showed $[\alpha]_{590}$ *ca.* −2.3 (lit.[2] −6°). Thus the extent of resolution was 30–40%. Resolution to optical purity was not pursued.

Registry No.—**1**, 38859-06-2; **2** methyl ester, 38859-07-3; **3**, 13036-02-7; **3** free acid, 618-83-7; **4**, 38859-08-4; **4** corresponding keto derivative, 38859-09-5; **4** free acid, 38859-10-8; **5**, 38859-11-9; **6**, 38859-12-0; **7**, 38859-13-1; **8**, 38859-14-2; **9**, 38859-15-3; **9** methyl ester, 38859-17-5; **10**, 38859-18-6; **10** free acid, 38859-16-4; *cis*-**11**, 38859-19-7; *trans*-**11**, 38859-20-0; **11** corresponding hydroxy derivative, 38858-06-9; *cis*-**12**, 38859-21-1; **13**, 38859-22-2; **14**, 38859-23-3.

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(20) L. F. Fieser and W. S. Johnson, *J. Amer. Chem. Soc.*, **62**, 575 (1940).