The Reaction of IV with Phosphorus Pentachloride.—Varying amounts of a white solid melting at 180–182° after purification were obtained from all runs involving heating IV with an excess of phosphorus pentachloride, either with or without the presence of phosphorus oxychloride as a solvent. The run giving the largest amount of this solid is described here. A sample of 17.7 g. (0.049 mole) of IV was heated under reflux with 20 ml. of phosphorus oxychloride and 10.2 g. (0.049 mole) of phosphorus pentachloride for one hour. Then, at hourly intervals, 10.2 g. of the pentachloride was added and refluxing continued for 4 hours. After standing overnight, the mixture was poured into ice and ether. The solid was filtered from the two-phase mixture and rinsed with water and cold ether. After drying it amounted to 9 g.; m.p. 173–180°. Recrystallization from benzene raised the m.p. to 180–182°.

Anal. Calcd. for $C_{23}H_{20}O_4Cl_2$: C, 64.05; H, 4.67; Cl, 16.44. Found: C, 64.0; H, 4.30; Cl, 16.1.

The Reduction and Dehydration of IV.—A solution of 23.5 g. (0.065 mole) of IV in 100 ml. of anhydrous ether was added dropwise to a stirred suspension of 2.8 g. (0.073 mole) of lithium aluminum hydride in 100 ml. of ether. The mixture was heated under reflux with stirring for 24 hours. After standing an additional 38 hours, it was hydrolyzed in the usual manner with 6 *N*, sulfuric acid. Filtration of the two-phase mixture yielded 19.7 g. of gray solid; m.p. 80–106°. An additional 3 g. of solid melting at 90–99° was obtained by removal of the solvent from the organic phase. This material was combined and heated at 100° with 45 ml. of 85% phosphoric acid for 5 hours. After cooling, the acid was decanted and the viscous, glue-like organic phase was washed with water, dried, and recrystallized from acetone–methanol. It yielded 19.1 g. (85%) of solid melting at 100–102° (literature[7] for tris-(*p*-methoxyphenyl)-ethylene (VI), m.p. 100–101°).

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[CONTRIBUTION FROM THE WM. H. NICHOLS CHEMICAL LABORATORY, NEW YORK UNIVERSITY]

The Synthesis and Stereochemistry of Chaulmoogric Acid

BY KURT MISLOW AND I. V. STEINBERG

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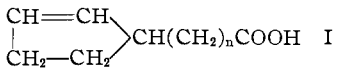
Electrolysis of a mixture of (+)-2-cyclopentene-1-acetic acid and ethyl hydrogen brassylate has yielded, after saponification of the product mixture, chaulmoogric acid identical with the natural product. Oxidation of (+)-2-cyclopentene-1-acetic acid to (−)-3-carboxyadipic acid, whose configuration is known, and, separately, reduction of (−)-2-cyclopentene-1-acetic acid to (−)-3-ethylcyclopentene, followed by oxidation to (+)-α-ethylglutaric acid, whose configuration is also known, establishes the configuration of the chaulmoogra oil acids by two independent paths.

The chaulmoogra oil acids, with the single exception of gorlic acid, are dextrorotatory members of a homologous series I. Interest in their



chemistry derives as much from their ancient renown in the chemotherapy of leprosy[1] as from the uniqueness of their structure: among seed fat acids, they are alone in having the cyclopentene system; further, together with sterculic acid,[2] they share the distinction of possessing a cycloalkene system, and at that a dissymmetric one.

The structure proof of I was initiated with extensive degradative work.[3] These investigations eventually led to a synthesis of dihydrochaulmoogric acid,[4] a synthesis[5] of chaulmoogric acid (I, $n = 12$) from hydnocarpic acid (I, $n = 10$), and the total synthesis of *dl*-chaulmoogric acid[6] and of *dl*-hydnocarpic acid.[7] Chaulmoogric acid, in turn, has been racemized to *dl*-chaulmoogric acid.[8]

The present investigation had as its first objective the realization of a total synthesis of naturally occurring, optically active chaulmoogric acid. In order to make our synthetic scheme adaptable to a feasible elucidation of the stereochemistry of the chaulmoogra oil acids, as well as to avoid laborious syntheses[6,7] followed by attempts at resolution of doubtful promise and of unavoidable tediousness, we resorted to anodic Kolbe coupling of a mixture of (+)-2-cyclopentene-1-acetic acid (II) and of ethyl hydrogen brassylate. In the design of this scheme, it had to be borne in mind that II is a β-substituted, γ,δ-unsaturated carboxylic acid with a center of asymmetry at the β-position, and that consequently[9] normal coupling could be expected, unattended by racemization.

Approximately eight recrystallizations from acetone–water of the brucine salt of 2-cyclopentene-1-acetic acid gave a pure diastereomer, from which optically pure (+)-II could be isolated. Electrolysis of a 3:1 mole ratio mixture of ethyl hydrogen brassylate and of freshly distilled (+)-II[10] gave a 30% yield of crude ethyl chaulmoograte, which was saponified to crude chaulmoogric acid. Recrystallization of the acid from ethanol yielded material substantially identical in melting point, rotation and infrared spectrum with the natural product. The total synthesis of chaulmoogric acid also represents a total synthesis of hydnocarpic acid and of alepric acid, the last two having been previously prepared[11] by degradation of chaulmoogric acid.

The remaining problem concerned the choice

(1) L. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," The Macmillan Co., New York, N. Y., 1941, p. 943.

(2) J. R. Nunn, *J. Chem. Soc.*, 313 (1952).

(3) (a) F. B. Power and F. H. Gornall, *ibid.*, 838 (1904); (b) F. B. Power and F. H. Gornall, *ibid.*, 851 (1904); (c) F. B. Power and M. Barrowcliff, *ibid.*, 884 (1905); (d) F. B. Power and M. Barrowcliff, *ibid.*, 557 (1907); (e) R. L. Shriner and R. Adams, THIS JOURNAL, **47**, 2727 (1925); (f) G. Stefanovic and I. Pejkovic, *Compt. rend.*, **238**, 697 (1954).

(4) C. R. Noller and R. Adams, THIS JOURNAL, **48**, 1080 (1926).

(5) W. M. Stanley and R. Adams, *ibid.*, **51**, 1515 (1929).

(6) G. A. Perkins and A. O. Cruz, *ibid.*, **49**, 1070 (1927).

(7) K. V. Bokil and K. S. Nargund, *Proc. Indian Acad. Sci.*, **13A**, 233 (1941); D. G. M. Diaper and J. C. Smith, *Biochem. J.*, **42**, 581 (1948).

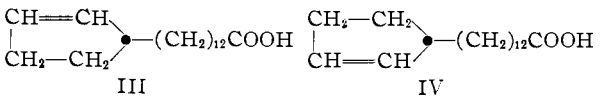
(8) W. S. Hinegardner, THIS JOURNAL, **55**, 2831 (1933).

(9) B. C. L. Weedon, *Quart. Revs.*, **6**, 380 (1952).

(10) In common with chaulmoogric acid (P. Baranger and R. Maréchal, *Compt. rend.*, **231**, 661 (1950)), 2-cyclopentene-1-acetic acid undergoes slow air oxidation; undeteriorated acid may be recovered from the oxidation mixture by distillation.

(11) N. P. Buu-Hoï, *Ann. chim.*, **19**, 446 (1944).

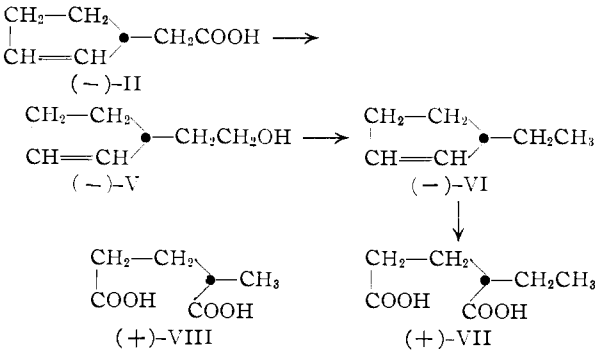
between two configurations, III and IV, conceivable for chaulmoogric acid.[12]



III IV

The problem was solved by two independent methods, one hinging on the configuration of derived α-ethylglutaric acid, the other on the stereochemistry of derived 3-carboxyadipic acid.

In accordance with the first method, (−)-II was reduced to (−)-2-(2-cyclopenten-1-yl)ethanol (V) with lithium aluminum hydride. The con-



(−)-II (−)-V (−)-VI (+)-VIII (+)-VII

version of V to the *p*-toluenesulfonate ester, followed by reduction of the ester with lithium aluminum hydride, yielded (−)-3-ethylcyclopentene (VI). Oxidation of VI with ozone, followed by hydrogen peroxide, gave (+)-α-ethylglutaric acid (VII). VII and (+)-α-methylglutaric acid (VIII) are seen to have the same configuration, if the Displacement Principle (*Verschiebungssatz*)[13] is applied to certain derivatives of VII and VIII, as recorded[14] in Table I. The configuration of

TABLE I

[M]D OF α-ALKYLGLUTARIC ACID DERIVATIVES

α-Alkyl group	Methyl ester	Free acid	1° Ion (0.5*M*, water)	2° Ion	Anhydride
Methyl	+42.6°	+32.3°	+19.6°	+2.6°	−56.8°
Ethyl	+27.5	+26.4	+10.7	−0.9	−32.9

VIII has been related to that of glyceraldehyde,[15] and its absolute configuration, as well as that of its precursors, is therefore[16] established.

(12) According to the conventional configurational representation here adopted, a hydrogen atom projecting above the plane of the paper is indicated by a heavy dot.

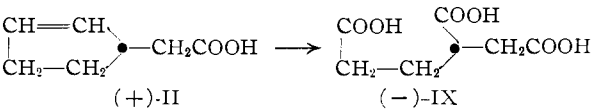
(13) K. Freudenberg in K. Freudenberg, "Stereochemie," F. Deuticke, Leipzig and Vienna, 1932, p. 693 ff.

(14) Data from E. Berner and R. Leonardsen, *Ann.*, **538**, 1 (1939).

(15) Pertinent correlations are: (−)-α-methylglutaric acid and (−)-α,α'-dimethylglutaric acid (A. Fredga, *Arkiv Kemi, Mineral. Geol.*, **24A**, no. 32 (1947)); (+)-α,α'-dimethylglutaric acid and (+)-dilactic acid (A. Fredga, *ibid.*, **14B**, no. 12 (1940)); (−)-dilactic acid from (+)-lactic acid (P. Vièles, *Ann. chim.*, [11], **3**, 143 (1935)); (+)-lactic acid and (−)-glyceraldehyde (M. L. Wolfrom, R. U. Lemieux, S. M. Olin and D. I. Weisblat, THIS JOURNAL, **71**, 4057 (1949)). See also V. H. T. James, *Chemistry & Industry*, 1388 (1953); *Ann. Reports*, **50**, 219 (1953); *J. Chem. Soc.*, 637 (1955).

(16) (+)-Glyceraldehyde has been directly related to (−)-tartaric acid (A. Wohl and F. Momber, *Ber.*, **50**, 455 (1917)). The absolute configuration of (+)-tartaric acid has been established (J. M. Bijvoet, A. F. Peerdeman and A. J. van Bommel, *Nature*, **168**, 271 (1951)); *cf.* also W. W. Wood, W. Fickett and J. G. Kirkwood, *J. Chem. Phys.*, **20**, 561 (1952)); the result is in agreement with the Fischer–Rosanoff convention.

A correlation between II and glyceraldehyde was also effected by a method independent of that elaborated in the preceding section. Oxidation of (+)-II with ozone, followed by hydrogen peroxide, afforded (−)-3-carboxyadipic acid (IX).



(+)-II (−)-IX

The configuration of IX may be deduced from two independent stereochemical link-chains. On the one hand, (+)-3-carboxyadipic acid is obtained from the oxidation of dihydroshikimic acid,[17] whose configuration relative to shikimic acid is established.[18] Shikimic acid itself has been related to 2-desoxygluconic acid[19] and therefore to D-glucose[20] and glyceraldehyde.[21] By another path, (+)-3-carboxyadipic acid has been related to (+)-3-methylhexane,[22] whose configuration relative to (+)-α-methylbutyric acid[23] and therefore to glyceraldehyde[24] is known.[25]

It follows therefore that the projections of (+)-II and (−)-II, as depicted above, are the correct stereochemical representations of the configurations of these enantiomers, and, further, that the configuration of chaulmoogric acid, which was obtained from (+)-II by methods not affecting the asymmetric center, is correctly represented by III, rather than by IV. It seems reasonable to suppose that the configurations of gorlic acid,[26] and of the lower homologs of I,[27] are also the same.[28]

Experimental[29]

2-Cyclopentene-1-acetic Acid.—Cyclopentadiene, prepared[30] from tech. 80% dicyclopentadiene, was treated[31] with hydrogen chloride to give 3-chlorocyclopentene in 62% yields. Ethyl 2-cyclopentene-1-malonate was obtained[31] in 75% yields (average of seven runs) from 3-chlorocyclopentene and sodiomalonic ester; the product boiled at 109–111° (2.7 mm.) and had n^{20}D 1.4533, n^{25}D 1.4515 (lit.[31] b.p. 120° (6 mm.), n^{20}D 1.4536). Alkaline hydrolysis of the diester, followed by decarboxylation at 155–190° of the air-dried, crude 2-cyclopentene-1-malonic acid[31] afforded 88% yields (average of six runs) of 2-cyclopentene-1-acetic acid, b.p. 109–114° (16 mm.), n^{20}D 1.4688, n^{25}D 1.4673 (lit.[31] b.p. 95–100° (4 mm.), n^{20}D 1.4682).

(17) K. Freudenberg and J. Geiger, *Ann.*, **575**, 145 (1952).

(18) H. O. L. Fischer and G. Dangschat, *Helv. Chim. Acta*, **18**, 1206 (1935).

(19) H. O. L. Fischer and G. Dangschat, *ibid.*, **20**, 705 (1937).

(20) M. Bergmann, H. Schotte and W. Leschinsky, *Ber.*, **56**, 1052 (1923).

(21) Reference 13, pp. 673–674.

(22) K. Freudenberg and W. Hohmann, *Ann.*, **584**, 54 (1954).

(23) W. Marckwald, *Ber.*, **37**, 1038 (1904).

(24) Pertinent correlations are: (−)-α-methylbutyric acid from (+)-2-butanol, with inversion (J. Kenyon, H. Phillips and V. P. Pittman, *J. Chem. Soc.*, 1072 (1935)); (+)-2-butanol and (+)-lactic acid (P. A. Levene, A. Walti and H. L. Haller, *J. Biol. Chem.*, **71**, 465 (1926); *cf.* also K. W. Wiberg, THIS JOURNAL, **74**, 3891 (1952)); (+)-lactic acid and (−)-glyceraldehyde (M. L. Wolfrom, R. U. Lemieux, S. M. Olin and D. I. Weisblat, THIS JOURNAL, **71**, 4057 (1949)).

(25) K. Freudenberg has recently summarized (*Monatsh.*, **85**, 537 (1954)) some of the relationship cited in this section.

(26) H. I. Cole and H. T. Cardoso, THIS JOURNAL, **60**, 612 (1938).

(27) H. I. Cole and H. T. Cardoso, *ibid.*, **61**, 2349 (1939).

(28) These acids are all structurally very similar, dextrorotatory, and isolated from the same plant family (*Flacourtiaceae*).

(29) Microanalyses by W. Manser, Zürich, and Schwarzkopf Laboratory, Woodside, N. Y.

(30) G. B. Kistiakowsky, *et al.*, THIS JOURNAL, **58**, 146 (1936).

(31) C. R. Noller and R. Adams, *ibid.*, **48**, 2444 (1926).

Resolution of 2-Cyclopentene-1-acetic Acid.—Brucine, of a number of alkaloids tested,[32] proved the most practicable resolving agent. In a typical resolution, brucine, 55.0 g., was added to a hot solution of 14.9 g. of 2-cyclopentene-1-acetic acid in 100 ml. of acetone to which had been added 3.5 ml. of water.[33] From the head fraction of 36.2 g., $[\alpha]^{28}D$ −18.84° (*c* 5.4, water), after eight recrystallizations from acetone–water, there was obtained 2.0 g. of product, $[\alpha]^{28}D$ +0.99° (*c* 5.0, water), whose rotation remained substantially unchanged on further recrystallization. The resolutions were reproducible; the pure diastereomeric salt always had $[\alpha]^{28}D$ + 1.2 ± 0.3° (water). One sample had $[\alpha]^{28}D$ +1.54° (*c* 7.1, water), m.p. 147.5–148.5°.

Anal. Calcd. for $C_{30}H_{36}N_2O_6$: C, 69.2; H, 6.97; N, 5.38. Found: C, 69.0; H, 7.26; N, 5.44.

The diastereomeric salt was dissolved in warm water, and the solution was made basic with concentrated aqueous ammonia. The precipitated brucine was filtered and the filtrate was acidified with dilute hydrochloric acid and extracted with ether. The ether extracts were washed with saturated sodium chloride solution, dried (sodium sulfate) and distilled. The desired acid, b.p. 105° (8 mm.), had $n^{25}D$ 1.4673, $[\alpha]^{30}D$ +109.2° (*c* 5.9, chloroform).

Anal. Calcd. for $C_7H_{10}O_2$: C, 66.6; H, 7.99. Found: C, 66.7; H, 7.76.

Oxidative Deterioration of (+)-2-Cyclopentene-1-acetic Acid.—A sample of the acid, $n^{25}D$ 1.4673, $[\alpha]^{28}D$ +106.9° (*c* 5.4, chloroform), on standing for eight months at room temperature, became yellow and viscous, $n^{25}D$ 1.4808, $[\alpha]^{30}D$ +66.0° (*c* 5.7, chloroform). Distillation gave a 55% recovery of acid, b.p. 122–123° (30 mm.), $n^{25}D$ 1.4678, $[\alpha]^{30}D$ +107.8° (*c* 5.7, chloroform), and a red, glassy residue.

Apparatus for Electrosynthesis.—The apparatus consisted of a cell, a source of d.c. current, an ammeter, a variable resistor of about 50 ohms, all connected in a circuit in series as described, and a voltmeter in parallel with the cell. The cell was a flat-bottom cylindrical glass vessel, 4 cm. in diameter and 11 cm. high. The cathode was a perforated platinum foil cylinder, 1.3 cm. in diameter and 5 cm. high, which was mounted vertically on a stout platinum wire, 0.1 cm. in diameter and 13 cm. long. The anode was a platinum wire, 0.038 cm. in diameter, wound in a loose coil of three turns, 1.7 cm. in diameter. The cathode was placed inside this coil and was prevented from coming into contact with it by three glass rods, 0.2 cm. in diameter, acting as spacers. The platinum leads from these electrodes passed through two short pieces of glass tubing mounted in a rubber stopper which fitted into the cell. Through this rubber stopper also was placed a water-cooled condenser.

The cell was provided with a magnetic stirrer, and an external cooling system in the form of a large crystallizing dish through which water was circulated during the electrolysis and which was mounted on the magnet casing.

Chaulmoogric Acid ((+)13-(2-Cyclopenten-1-yl)-tridecanoic Acid).—Ethyl hydrogen brassylate was prepared as follows. Technical azelaic acid was converted into the ester[34] (92.4% yield), which was reduced to 1,9-nonanediol, in 96.5% yield, by lithium aluminum hydride. In this step it was noted that the precipitate initially formed is a rubbery material which tends to arrest the stirring motion when there is little clearance between stirrer and flask. 1,9-Dibromononane was prepared[35] from the diol in 89.7% yield and converted,[34] *via* a malonic ester synthesis, to brassylic acid (80% yield), m.p. 103–107° after two recrystallizations from benzene (lit.[34] m.p. 113°). Ethyl brassylate, prepared[34] from the acid in 76.6% yield, boiled at 162–163° (1.3 mm.), $n^{25}D$ 1.4408. The ester (50.4 g., 0.168 mole) was dissolved in 250 ml. of methanol containing 0.084 mole of barium hydroxide (by direct titration), and the mixture was allowed to stand at room temperature for 17 hours. The crude barium ethyl brassylate was filtered, washed with alcohol, suspended in 300 ml. of water and treated with 25 ml. of concentrated hydrochloric acid. This mixture was shaken until the white solid had disappeared giving place to an oil, which was extracted with ether. The ether extracts, after washing and drying, yielded, on distillation, 36.6 g. (86%) of ethyl hydrogen brassylate, b.p. 187–191° (2.3 mm.), m.p. 44–52° (lit.[36] b.p. 191–193° (2 mm.), 56–57°); neut. equiv., calcd. 272; found, 255. Judging by these results the half ester was about 95% pure, assuming brassylic acid to be the contaminant.

A mixture of 38.5 g. of ethyl hydrogen brassylate and 5.14 g. of freshly distilled 2-cyclopentene-1-acetate acid, $[\alpha]^{30}D$ +107.8° (*c* 5.68, chloroform), 99% optically pure, was dissolved in a sodium methylate solution (from 0.39 g. of sodium and 50 ml. of methanol) to which had been added 5.5 ml. of distilled water. The solution was electrolyzed for 264 minutes in the apparatus described in the preceding section. The average current used was 1.27 amp., the average voltage was 114 v., the average current density based on an estimated anodic surface area of 2.26 cm.^{2} was 0.56 amp./cm.^{2} The *p*H at the end of the reaction was slightly above 7.

The solution was acidified with 2 ml. of acetic acid, the methanol stripped, and the residual oil dissolved in ether. The ether layer was successively washed with 5% sodium carbonate solution, water, dried (sodium sulfate) and evaporated. The residue (28 g.), on distillation, yielded 3.2 g. of a forerun, b.p. 75–110° (8 mm.), and 5 g. of impure ethyl chaulmoograte, b.p. 157–159° (1 mm.) (lit.[27] b.p. 222° (10 mm.)); the remainder solidified on cooling and consisted presumably of ethyl tetracosanedioate. The desired ester, on redistillation through a Podbielniak spinning band Mini-Cal column, gave 2.1 g. of a product, $n^{25}D$ 1.4590, $[\alpha]^{28}D$ +40.3° (chloroform) (lit.[27] $n^{25}D$ 1.4592, $[\alpha]^{25}D$ 55.4°), which was impure to judge by an analysis (4% low on carbon) and the rotation. This fraction was boiled for 24 hours in a solution of 2.0 g. of sodium hydroxide in 10 ml. of water and 5 ml. of ethanol. The ethanol was removed by distillation and the residual solution diluted with water and acidified. The flocculent white precipitate was filtered, dried and twice recrystallized from ethanol to give pure chaulmoogric acid as flat platelets, m.p. 67.7–68.5°, $[\alpha]^{26}D$ +61.7° (*c* 4.82, chloroform). Values reported in the literature are: melting point: 67–68°,[3c] 68°,[3a,3c,37b,5] 68.5°[27] and 69°[37a]; $[\alpha]D$ (chloroform): +56.0°,[3a] +58.6°[3c] +59.5°,[3c] +60.0°,[37a] +60.3°,[27] +61.9°[5] and +62.9°.[37b] Its infrared spectrum is indistinguishable from that of the natural product.[38]

Anal. Calcd. for $C_{18}H_{32}O_2$: C, 77.1; H, 11.50. Found: C, 76.4; H, 11.72.

(+)- and (−)-2-(2-Cyclopentene-1-yl)-ethanol.—A solution of 4.0 g. of (+)-2-cyclopentene-1-acetic acid, $[\alpha]^{30}D$ + 109.2° (*c* 5.9, chloroform), in 20 ml. of anhydrous ether was added dropwise to a solution of 1.6 g. of lithium aluminum hydride in 20 ml. of anhydrous ether, with cooling and stirring, over a period of 20 minutes. The reaction mixture, worked up in the usual way, yielded 3.0 g. (85%) of colorless oil, b.p. 97–98° (26 mm.), $n^{20}D$ 1.4730, $n^{25}D$ 1.4711, $[\alpha]^{26}D$ +127.4° (*c* 6.6, chloroform); lit.[31] (for racemic alcohol) b.p. 86–87° (16 mm.), $n^{20}D$ 1.4721; lit.[39] (for racemic alcohol) b.p. 82–83° (15 mm.), $n^{25}D$ 1.4695.

Anal. Calcd. for $C_7H_{12}O$: C, 75.0; H, 10.79. Found: C, 75.0; H, 10.70.

Following the same procedure, 20.6 g. of (−)-2-cyclopentene-1-acetic acid, $[\alpha]^{29}D$ −64.2° (*c* 4.6, chloroform), which had been obtained *via* the cinchonidine salt,[32] afforded 16.2 g. (89%) of levorotatory alcohol, b.p. 101–102° (24 mm.), $n^{25}D$ 1.4713, $[\alpha]^{32}D$ −72.3° (*c* 4.7, chloroform).

(−)-3-Ethylcyclopentane.—Anhydrous pyridine (24.8 g.) was added dropwise to a solution of 37.4 g. of *p*-toluene-

(32) The use of morphine, quinine, cinchonine, quinidine and strychnine proved less successful in our hands. Cinchonidine precipitated the (−)-acid, but recrystallization from acetone, ethanol or solvent mixtures (*e.g.*, acetone–water) did not yield a pure diastereomer.

(33) Preliminary experiments showed that the small increment of water reduces by about three-fourths the volume of solvent acetone needed, without affecting the efficiency of the resolution.

(34) P. Chuit, *Helv. Chim. Acta*, **9**, 264 (1926).

(35) W. L. McEwen, *Org. Syntheses*, **20**, 24 (1940).

(36) R. G. Jones, THIS JOURNAL, **69**, 2350 (1947).

(37) (a) E. Goulding and N. C. Akers, *Proc. Chem. Soc.*, **29**, 197 (1914); (b) T. Kariyone and Y. Hasegawa, *J. Pharm. Soc. Japan*, **54**, 141 (1934).

(38) Chaulmoogric acid, purchased from Bios Laboratories, N. Y., was recrystallized from ethanol. The resulting material melted at 66.8–67.0° and had $[\alpha]^{27}D$ +59.5° (*c* 2.1, chloroform). The infrared spectra were determined on 5% solutions in chloroform; the kind assistance of Dr. A. I. Kosak in this connection is gratefully acknowledged.

(39) J. v. Braun, E. Kamp and J. Kopp, *Ber.*, **70**, 1750 (1937).

sulfonyl chloride and 16.1 g. of (−)-2-(2-cyclopenten-1-yl)-ethanol, $[\alpha]^{32}D$ −72.3° (chf.), in 35 ml. of anhydrous ether; the mixture was stirred and kept at −15° throughout the addition. After one week in the refrigerator, the mixture was treated with cold dilute sulfuric acid, the ether layer separated, and the aqueous layer extracted twice with ether. The combined ether layers were washed with water, dried over sodium sulfate and stripped, yielding 39.1 g. of the desired (crude) tosyl ester as an oil $[\alpha]^{28.5}D$ −26.1° (*c* 5.1, chloroform). The ester was not purified further.

Anal. Calcd. for $C_{14}H_{18}O_3S$: S, 12.02. Found: S, 12.96.

A solution of 38.8 g. of the *p*-toluenesulfonate in 40 ml. of anhydrous ether was added dropwise to a solution of 5.8 g. of lithium aluminum hydride in 60 ml. of anhydrous ether. The addition required 45 minutes. The reaction mixture, worked up in the normal manner, yielded 2.1 g. (15%) of 3-ethylcyclopentene, b.p. 96–98° (760 mm.), $n^{25}D$ 1.4278, $[\alpha]^{24}D$ −69.9° (*c* 7.5, chloroform); lit.[40] (for racemic hydrocarbon) b.p. 96° (760 mm.), $n^{25}D$ 1.4300.

Anal. Calcd. for C_7H_{12}: C, 87.4; H, 12.58. Found: C, 86.9; H, 13.18.

Oxidation of (−)-3-Ethylcyclopentene.—Ozone was passed through a solution of 1.31 g. of (−)-3-ethylcyclopentene in 150 ml. of ethyl acetate, the mixture being immersed in a methanol–Dry Ice-bath throughout. After 30 minutes of passage at 5–6 bubbles per second, the reaction was complete, as evidenced by the oxidation of potassium iodide by the outflow of gases. The solution of ozonide was added, at the rate of three drops per second, to a well-stirred ice-cold mixture of 150 ml. of 5% sulfuric acid and 4 ml. of 30% hydrogen peroxide. The reaction mixture was concentrated on the steam-bath, made just alkaline with sodium carbonate, and evaporated to dryness. The dry salt mixture (39.8 g.) was treated with 50 ml. of water, acidified and extracted six times with ether. The combined ether solution was washed with 30% sodium chloride and dried. Distillation of the ether and acetic acid left 1.0 g. of a brown oil, which was treated with 10 ml. of water. Extraction with ether and evaporation of the extracts yielded 0.46 g. of **α-ethylglutaric acid** as a colorless viscous oil, $[\alpha]^{30}D$ +3.20° (*c* 6.25, ethanol), whose infrared spectrum was substantially identical with that of authentic α-ethylglutaric acid, resolved *via* the stychnine salt.[14] The spectra featured bands at 3.25 (shoulder), 3.40, 3.80 (shoulder), 5.85, 6.85, 7.05, 7.75–8.25, 8.50, 9.00, 9.30 (shoulder), 9.90 (shoulder), 10.75 and 11.70 (shoulder) μ. The acid was *ca.* 23% optically pure, based on $[\alpha]D$ (max.) 14.1° (ethanol).[14,41]

Oxidation of (+)-2-Cyclopentene-1-acetic Acid.—In a preliminary experiment racemic 2-cyclopentene-1-acetic acid (10 g.) in 150 ml. of anhydrous ethyl acetate was ozonized at −78°, and the solution of the ozonide added dropwise, over a period of 25 minutes, to an ice-cold well-stirred mixture of 20 ml. of 30% hydrogen peroxide and 150 ml. of 5% sulfuric acid. The solution was concentrated to about one-quarter the original volume and treated with 7.3 g. of calcium oxide. The filtrate from the resulting calcium sulfate was evaporated to 20 ml.; on standing in the refrigerator overnight, the solution deposited 2.0 g. of crystals. The crystals were filtered, treated with 8 ml. of acetone and the resulting suspension filtered from remaining calcium sulfate. The acetone filtrate, on concentration to 3 ml. and cooling, deposited 0.48 g. of needle rosettes, m.p. 117–118° (lit.[42] m.p. 116–118° for 3-carboxyadipic acid).

In precisely the same manner, 2.5 g. of 2-cyclopentene-1-acetic acid, $[\alpha]^{28}D$ +106.9° (*c* 5.4, chloroform), obtained *via* the brucine salt, was oxidized to give 0.6 g. of 3-carboxyadipic acid, m.p. 92–104°, $[\alpha]^{31}D$ −12.75° (*c* 5.2, acetone) (lit.[17] m.p. 102–103°, $[\alpha]^{20}D$ +27.2° (acetone)[43]).

(40) H. Adkins and A. K. Roebuck, THIS JOURNAL, **70**, 4041 (1948).

(41) Since the starting acid was 59% optically pure, and since racemization could not have taken place in any but the last step, the oxidation therefore entailed about 60% racemization.

(42) F. W. Kay and W. H. Perkin, Jr., *J. Chem. Soc.*, 1640 (1906).

(43) The starting acid, 98% optically pure, therefore yielded 3-carboxyadipic acid of only 47% optical purity, a fact reflected in the melting point range of the sample. The oxidation consequently entailed 52% racemization; *cf.* also ref. 41. It is interesting that the optical instability of 3-carboxyadipic acid and/or its esters has been noted in a similar connection (K. Freudenberg, H. Meisenheimer, J. T. Lane and E. Plankenhorn, *Ann.*, **543**, 162 (1940); ref. 17).

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The Utilization of Alkyl 2-Cyclohexylethyl Ketones in the Pfitzinger Reaction[1]

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The study of the behavior in the Pfitzinger reaction of mixed ketones, containing two methylene groups adjacent to the carbonyl function, has been extended to a series of cyclohexane alkanones, $C_6H_{11}CH_2CH_2CO$–R. Except for the first member of the series, only the α-methylene group of the unsubstituted alkyl of these ketones was found to participate in this reaction.

The condensation of an alkali metal salt of isatic acid with ketones, possessing at least one α-methylene group, to form substituted cinchoninic acids is termed the Pfitzinger reaction.[2] The original techniques have been extended by many workers, and reviews are available which contain critical discussions of the practical and theoretical implications.[3]

Buu-Hoï and Cagniant[4] in their attempts to prepare a series of substituted cinchoninic acids from the alkyl phenyl ketones, $C_6H_5CO(CH_2)_nCH_3$, observed that of the latter only those for which *n* is equal to or less than 2 condense in the usual fashion with isatin. Subsequently, however, valerophenone[5] and caprophenone[6] have been found to give the expected substituted cinchoninic acid on prolonged heating.

In order to study the possibility of steric hindrance in this condensation, a new series of ketones, alkyl 2-cyclohexylethyl ketones, was prepared and studied utilizing the "normal" Pfitzinger conditions. The ketones prepared are summarized in Table I. Since we were able to isolate solid semi-

(1) From the Ph.D. thesis of Charles G. Skinner, June, 1953.

(2) W. Pfitzinger, *J. prakt. Chem.*, [2] **33**, 100 (1888); **38**, 583 (1888); **56**, 283 (1897); **66**, 263 (1902).

(3) (a) W. C. Sumpter, *Chem. Revs.*, **34**, 393 (1949); (b) R. C. Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1952, pp. 222–229; (c) Vol. IV, pp. 47–56, pp. 215–225.

(4) Ng. Buu-Hoï and P. Cagniant, *Bull. soc. chim.*, 123 (1946).

(5) L. K. Yourtee, Ph.D. dissertation, University of Texas, June, 1948.

(6) (a) Unpublished results (1949) by H. R. Henze and R. E. Leslie, University of Texas; (b) G. P. Mueller and R. E. Stobaugh, THIS JOURNAL, **72**, 1598 (1950).