isoprenoid quinones that can be converted to chromanols or chromenols, such as members of the coenzyme Q group and variously substituted analogs.[3,12]

Registry No.—I·Acetonitrile-d_3 complex, 13169-30-7; I·pyridine-d_5 complex, 13127-55-4; 8-methyltocol·acetonitrile-d_3 complex, 13136-70-4; 8-methyltocol·pyridine-d_5 complex, 13136-71-5; 5-methyltocol·acetonitrile-d_3 complex, 13136-72-6; 5-methyltocol·pyridine-d_5 complex, 13136-73-7; 5,8-dimethyltocotrienol·acetonitrile-d_3 complex, 13136-74-8; 5,8-dimethyltocotrienol·pyridine-d_5 complex, 13136-75-9; 7-methyltocol·acetonitrile-d_3 complex, 13136-76-0; 7-methyltocol·pyridine-d_5 complex, 13136-77-1; 5,7,8-trimethyltocol, 59-02-9; 5,7,8-trimethyltocol·pyridine-d_5, 13136-78-2; 5,7,8-trimethyltocol·benzene-d_6, 13136-79-3; 5,7,8-trimethyltocol·chlorobenzene, 13136-80-6; 5,7,8-trimethyltocol·furan, 13136-81-7; 5,7,8-trimethyltocol·acetonitrile-d_3, 13136-82-8; 5,8-dimethyltocol, 148-03-8; 5,8-dimethyltocol·pyridine-d_5, 13136-84-0; 5,8-dimethyltocol·benzene-d_6, 13136-85-1; 5,8-dimethyltocol·chlorobenzene, 13136-86-2; 5,8-dimethyltocol·furan, 13136-87-3; 5,8-dimethyltocol·acetonitrile-d_3, 13136-88-4; 7,8-dimethyltocol, 119-11-9; 7,8-dimethyltocol·pyridine-d_5, 13136-90-8; 7,8-dimethyltocol·benzene-d_6, 13233-10-8; 7,8-dimethyltocol·chlorobenzene, 13136-91-9; 7,8-dimethyltocol·furan, 13136-92-0; 7,8-dimethyltocol·acetonitrile-d_3, 13136-93-1; 5,7-dimethyltocol, 493-35-6; 5,7-dimethyltocol·pyridine-d_5, 13136-95-3; 5,7-dimethyltocol·benzene-d_6, 13136-96-4; 5,7-dimethyltocol·chlorobenzene, 13136-97-5; 5,7-dimethyltocol·furan, 13136-98-6; 5,7-dimethyltocol·acetonitrile-d_3, 13136-99-7.

(12) Commercial designations have been included in the text of this article for the purpose of adequately describing experimental procedure; they are not be be construed as an endorsement by the Department of Agriculture of one particular product over that of competitive products.

Senecio Alkaloids. V. The Synthesis of Trichodesmic Acid[1]

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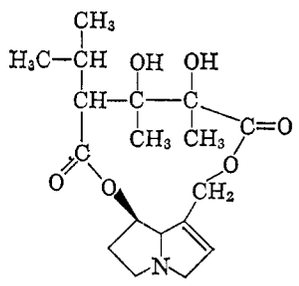
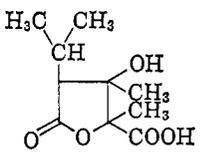
Received March 9, 1967

Trichodesmic acid, the necic acid derived from the alkaloid trichodesmine, has been synthesized from 2,3-dimethyl-4-isopropyl-2-cyclopentenone. The stereospecific hydroxylation step in the synthesis eliminates all but one racemic structure for this acid.

The alkaloid trichodesmine, $C_{18}H_{27}NO_6$, has been obtained from *Trichodesma incanum*,[3] *Crotalaria juncea*,[4] *Heliotropium arguzioides*,[5] and *Crotalaria rubiginosa*.[6] The original degradation studies were inconclusive[3,7] and later work[4,8,9] formulated trichodesmine as I.

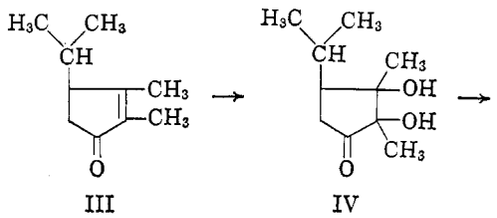


I

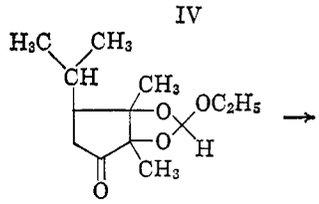


II

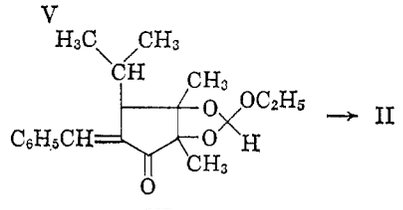
After catalytic reduction of I, acidic hydrolysis gave trichodesmic acid, $C_{10}H_{16}O_5$, for which the structure 2,3-dihydroxy-3,5-dimethylhexane-2,4-dicarboxylic acid 2(γ)-lactone (II) was proposed. Four racemic modifications are possible for II.



III IV



V



VI

Trichodesmic acid has been synthesized from (±)-2,3-dimethyl-4-isopropyl-2-cyclopentenone (III).[10] This compound, on *cis* hydroxylation with osmium tetroxide, gave in 75–80% yield a crystalline glycol racemate (IV). To our knowledge, this is the simplest

(1) This is the fifth paper in this series and the first to be numbered. The previous articles in sequence are J. D. Edwards, Jr., T. Hase, and N. Ichikawa, *Chem. Commun.*, 364 (1965); J. D. Edwards, Jr., T. Hase, C. Hignite, and T. Matsumoto, *J. Org. Chem.*, **31**, 2282 (1966); J. D. Edwards, Jr., T. Matsumoto, and T. Hase, *ibid*, **32**, 244 (1967); J. D. Edwards, Jr., and T. Matsumoto, *ibid*, **32**, 1837 (1967).

(2) (a) To whom inquiries should be directed: Department of Chemistry, University of Southwestern Louisiana, Lafayette, La. 70501. (b) Robert A. Welch Foundation Postdoctoral Fellow.

(3) G. P. Menshikov and M. Rubinstein, *Ber.*, **68**, 2039 (1935).

(4) R. Adams and M. Gianturco, *J. Am. Chem. Soc.*, **78**, 1922 (1956).

(5) S. T. Akramov, F. Kiyamitdinova, and S. Yu. Yunusov, *Dokl. Akad. Nauk Uz. SSR*, **4**, 30 (1961); *Chem. Abstr.*, **60**, 16209 (1964).

(6) C. K. Atal, R. K. Sharma, C. C. J. Culvenor, and L. W. Smith, *Australian J. Chem.*, **19**, 2189 (1966).

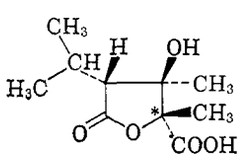
(7) N. J. Leonard in "The Alkaloids," Vol. I, R. H. F. Manske and H. L. Holmes, Ed., Academic Press Inc., New York, N. Y., 1950, pp 118, 160; Vol. VI, R. H. F. Manske, Ed., 1960, p 100.

(8) S. Yu. Yunusov and N. V. Plekhanova, *J. Gen. Chem. USSR*, **29**, 670 (1959).

(9) Structures proposed in these studies[4,8] differ only in the configuration assigned to the glycol grouping, *erythro* and *threo*.

(10) R. H. Eastman and A. V. Winn, *J. Am. Chem. Soc.*, **82**, 5908 (1960).

apparent example of a stereospecific attack by osmium tetroxide from the least hindered side to give one of the two possible diastereomeric *cis* glycols.[11] This glycol, after protection as the orthoformate ester (V), was converted to the benzylidene derivative (VI) which, on ozonolysis, gave, after decomposition with alkaline peroxide, (±)-trichodesmic acid (II). This acid lactone racemate was resolved by means of cinchonidine and one of the diastereomeric salts, mp 247–248°, gave on decomposition the (+) enantiomer, mp 209–211°, $[\alpha]_D$ +2.96°, which was shown to be identical with trichodesmic acid. Decomposition of the other cinchonidine salt, mp 226–227°, gave the enantiomer of trichodesmic acid. This method of synthesis indicates the structure of trichodesmic acid to be VII (2*R*,3*R*,4*R*) or the mirror image (2*S*,3*S*,4*S*) and since a number of necic acids—senecic, integerrinecic, hygrophyllinecic, jaconecic, and that in retusamine—all have the same absolute configuration on the carbon starred in VII, it is suggested that this is the structure of trichodesmic acid. The synthetic enantiomeric acid lactones were converted to the corresponding methyl esters by reaction with diazomethane.



VII

Experimental Section[12]

(±)-2,3-Dimethyl-4-isopropyl-2-cyclopentenone (III).—The acid-catalyzed isomerization of *d*-isothujone gives in 60% yield[10] a mixture of carvenone (40%), 2,3-dimethyl-4-isopropyl-2-cyclopentenone (40%), and 4,5-dimethyl-3-isopropyl-2-cyclopentenone (20%). We could not resolve this mixture by preparative gas chromatography. However, with a 15 ft × 3/8 in. DEGS (30%) column, the separation of 4,5-dimethyl-3-isopropyl-2-cyclopentenone (retention time 28 min) from the other two components (retention time 37 min, column temperature 190°, injector 300°, helium flow 215 cc/min, injection volume 0.25 cc) was possible. The 4,5-dimethyl-3-isopropyl-2-cyclopentenone was identified by infrared spectroscopy and the semicarbazone derivative.[10] After refluxing this ketone for 72 hr with aqueous potassium carbonate, complete rearrangement to (±)-III took place as shown by infrared spectroscopy.[10,13]

Using the semicarbazone prepared[10] from this ketone for seeding purposes, a simpler procedure for the isolation of (±)-III was possible. The acid-catalyzed isomerization mixture was stirred under reflux for 72 hr with aqueous potassium carbonate.[10] The infrared spectrum showed no band at 1605 cm^{-1} where 4,5-dimethyl-3-isopropyl-2-cyclopentenone has strong absorption. Extraction and distillation (72–73° at 2.3 mm) gave a mixture of carvenone and (±)-III. The semicarbazone mixture prepared from this distillate was separated easily by fractional crystallization from methanol. The less soluble semicarbazone of (±)-III was recrystallized two times and the melting point (205–220°) was above that of the semicarbazone of carvenone. Hydrolysis and steam distillation[10] gave (±)-III.

2,3-Dihydroxy-2,3-dimethyl-4-isopropyl-2-cyclopentanone (IV).—To a solution of 7.62 g of osmium tetroxide (0.03 mole) in 30 ml of anhydrous ether there was added a solution of 4.56 g (0.03 mole) of (±)-III in 20 ml of anhydrous ether. With stirring and cooling, 5 ml of anhydrous pyridine was added dropwise at 10–15°. After standing at room temperature for 3 days, the solvent was decanted from the crystals, after which they were washed with ether. The crystals were dissolved in 110 ml of methylene chloride and hydrogen sulfide was passed through the solution. The osmium metal was filtered, washed with methylene chloride and ether, and the filtrate was evaporated to dryness under vacuum. The crystalline residue (4.47 g) was recrystallized from petroleum ether (bp 30–60°) to give 4.23 g of colorless crystals, mp 55–57°. Repeated recrystallizations did not change this melting point. No studies were made to determine if any of the *cis* diastereomer was formed. The infrared spectrum (3% $CHCl_3$) showed the presence of hydroxyl (3300–3550, 1110 cm^{-1}) and carbonyl (1750 cm^{-1}) and the absence of the carbon–carbon double bond.

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.61; H, 10.03.

2,3-Diacetoxy-2,3-dimethyl-4-isopropylcyclopentanone.—To 90 mg of IV in 15 ml of anhydrous toluene, there were added 3.0 ml of isopropenyl acetate and a few crystals of *p*-toluenesulfonic acid. After refluxing for 4 hr, the mixture was slowly distilled until about 5 ml remained. A small amount of solid sodium bicarbonate was added and, after stirring for a few minutes, the mixture was filtered and the residue washed with ether. The filtrate was evaporated to dryness under vacuum and the residue was chromatographed on silica gel (30 g, E. Merck AG, 0.08 mm) and eluted with purified chloroform containing 3% anhydrous ether. Fractions 1–3 (170 ml) gave 28 mg and were discarded. Fraction 4 (25 ml) gave 34 mg of crystals, mp 79–80°, which were recrystallized from petroleum ether to give colorless crystals, mp 80–81°.

Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.18; H, 8.25.

Ortho Ester (V).—A solution of 510 mg of IV and 2.0 ml of triethyl orthoformate in 10 ml of anhydrous toluene containing a few crystals of *p*-toluenesulfonic acid was refluxed for 5 hr and then slowly distilled during 2 hr to give 7 ml of distillate. After standing overnight, some solid sodium bicarbonate was added to the reaction vessel and this was stirred for a few minutes, filtered, and the residue washed with ether. The filtrate was evaporated to dryness under vacuum and the residual oil chromatographed on 30 g of silica gel and eluted with purified chloroform. Fraction 1 (105 ml) gave 19 mg which was discarded. Fractions 2–5 (275 ml) gave 633 mg of a colorless oil (V). The infrared spectrum (3% $CHCl_3$) showed the presence of carbonyl (1750 cm^{-1}) and the absence of hydroxyl groups.

Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.49; H, 9.04.

Fraction 6 (200 ml) gave 20 mg which, from the infrared spectrum, appeared to be a mixture of the ortho ester and a dehydrated product. A solution of 22 mg of V in 1.0 ml of methanol and 5 drops of 5% sulfuric acid was allowed to stand at room temperature for 1.5 hr. The reaction mixture was extracted with ether, washed with water, dried, and after evaporation of the ether under vacuum gave a residue of 14 mg. The infrared spectrum of this product was identical with that of IV.

Benzylidene Derivative (VI).—A mixture of 370 mg of V, 370 mg of benzaldehyde, 5 ml of methanol, and 2 ml of 10% aqueous potassium hydroxide was allowed to stand at room temperature for 24 hr. After addition of water, the mixture was extracted with ether, washed with water, dried, and the ether was removed under vacuum. The residue was chromatographed on 30 g of silica gel and eluted with purified chloroform containing 3% anhydrous ether. Fraction 1 (95 ml) gave 4 mg and was discarded. Fractions 2–4 (75 ml) gave 500 mg of VI (oil). The infrared spectrum in chloroform showed the presence of carbonyl (1715 cm^{-1}).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.51; H, 7.74.

(±)-Trichodesmic Acid.—The oxygen gas stream from a Welsbach laboratory ozonator was passed through 30 ml of purified chloroform containing 2.86 g of VI at −30° until a positive (iodometric) ozone test was given. The solution was evaporated to dryness under vacuum at room temperature and to the residue there was added 54 ml of 10% hydrogen peroxide and 9 ml of 40% aqueous potassium hydroxide. After stirring at room temperature for 1 hr, the alkaline solution was washed with ether and acidified with 8 ml of 40% sulfuric acid. After

(11) E. I. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, p 358.

(12) All elemental analyses were by Huffman Laboratories, Inc., Wheatridge, Colo. Melting points are uncorrected and were determined on a Fisher-Johns apparatus. Rotations of the acid lactones were made with a Perkin-Elmer Model 141 polarimeter. The authors are indebted to Professor Tom J. Mabry, University of Texas, for these determinations. The authors also gratefully acknowledge the assistance of Robert W. Preston, undergraduate research participant, in the preparation of VII.

(13) The authors are indebted to Professor R. H. Eastman, Stanford University, for a copy of this infrared spectrum.

standing for 1.5 hr, this was saturated with sodium chloride and extracted five times with ether. Evaporation of the ether gave a colorless solid which was refluxed with 40 ml of carbon tetrachloride to dissolve the benzoic acid. Not all of the solid went into solution. After cooling, the solid was collected, washed with carbon tetrachloride, and recrystallized from ether–petroleum ether to give 720 mg of colorless crystals, mp 194–195°.

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.52; H, 7.52.

Resolution of (±)-Trichodesmic Acid.—A mixture of 21.6 mg of (±)-trichodesmic acid and 29.5 mg of cinchonidine was dissolved in 1.0 ml of methanol by heating. After standing in the refrigerator overnight, the colorless crystals were collected, washed with methanol, and recrystallized from methanol: yield 14 mg, mp 247–248° dec, $[\alpha]_D$ −95.5° (*c* 0.20, ethanol).

Anal. Calcd for $C_{29}H_{38}O_6N_2$: C, 68.21; H, 7.50; N, 5.49. Found: C, 68.36; H, 7.44; N, 5.46.

The filtrate from the above was evaporated under vacuum and the residue was recrystallized from methanol–ethyl acetate to give 16 mg of colorless crystals, mp 226–227° dec, $[\alpha]_D$ −72.5° (*c* 0.40, ethanol).

Anal. Calcd for $C_{29}H_{38}O_6N_2$: C, 68.21; H, 7.50; N, 5.49. Found: C, 68.09; H, 7.61; N, 5.29.

(+)-Trichodesmic Acid.—The cinchonidine salt, mp 247–248° (84 mg), was dissolved in 5 ml of 5% sulfuric acid and extracted five times with ether. The combine extracts were washed with water, dried, and evaporated to dryness under vacuum to give a residue of 32 mg. This was recrystallized from ether–petroleum ethr to give colorless crystals, mp 209–211° dec, $[\alpha]_D$ +2.96° (*c* 1.25, ethanol). A mixture melting point with trichodesmic acid,[14] mp 209–211°, was undepressed. The infrared (KBr) was identical with that published.[4]

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.37; H, 7.42.

(−)-Trichodesmic Acid.—Decomposition of 141 mg of the cinchonidine salt, mp 226–227°, as above, gave a residue of 50 mg. Recrystallization from ether–petroleum ether gave 43 mg of colorless crystals, mp 201–203° dec, $[\alpha]_D$ −2.5° (*c* 0.4, ethanol). A mixture melting point with trichodesmic acid (mp 202–204°) was 193–197°. The infrared (KBr) spectrum had the same bands as (+)-trichodesmic acid but of less intensity.

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.78; H, 7.49.

The cinchonidine salt, mp 226–227°, apparently contained a small amount of the diastereomer which would explain the lower melting point and specific rotation of (−)-trichodesmic acid. Because of insufficient material, it was not possible to repeat the resolution.

Trichodemic Acid Methyl Esters. A. (±)-Trichodesmic Acid.—A solution of 20 mg of (±)-trichodesmic acid in 3 ml of ether was treated with a slight excess of an etheral diazomethane solution. After 10 min the solution was evaporated to dryness under vacuum and the residue recrystallized from ether–petroleum ether to give 18 mg of colorless crystals, mp 116–119°.

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.56; H, 7.84.

B. (+)-Trichodesmic Acid.—In the same way, 25 mg of (+)-trichodesmic acid gave 23 mg of colorless crystals, mp 69–70°, $[\alpha]_D$ −6.83° (*c* 0.41, ethanol).

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.53; H, 7.80.

C. (−)-Trichodesmic Acid.—From 20 mg of (−)-trichodesmic acid after crystallization there was obtained 11 mg of ester, mp 69–70°. The infrared spectrum ($CHCl_3$) was identical with that above.

Anal. Calcd for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.11; H, 7.86.

Registry No.—IV, 13136-61-3; V, 13136-62-4; VI, 13136-63-5; (+)-VII, 13136-64-6; (+)-VII cinchonidine salt, 13127-54-3; (+)-VII methyl ester, 13136-65-7; (−)-VII, 13136-66-8; (−)-VII cinchonidine salt, 13136-67-9; (−)-VII methyl ester, 13136-68-0; 2,3-diacetoxy-2,3-dimethyl-4-isopropylcyclopentanone, 13136-69-1.

Acknowledgment.—This work was supported by a grant from the Robert A. Welch Foundation. The authors gratefully acknowledge this support.

(14) This sample was supplied by Professor Yunusov. A sample of trichodesmic acid (insufficient for recrystallization) obtained from Professor Roger Adams in 1959 and stored at room temperature had a melting point of 202–204° which was not depressed on admixture with the synthetic acid. The authors are indebted to Professors Yunusov and Adams for these samples.

Monocyclic Terpene Alcohols. IV. Birch Reduction of *p*-Isopropylbenzoic Acid (Cumic Acid)[1,2]

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Selective reductions of the title compound with lithium and ethanol were achieved by careful control of the reaction conditions to promote either kinetically or thermodynamically controlled protonations of intermediate anions. Dihydro derivatives (*cis*- and *trans*-*p*-mentha-2,5-dien-7-oic acid and *p*-mentha-1,5-dien-7-oic acid) and tetrahydro derivatives (*cis*- and *trans*-*p*-menth-2-en-7-oic acid and *p*-menth-1-en-7-oic acid) could be prepared in high yields. On the light of the present findings, conflicting results described in the bibliography of the Birch reduction of *p*-alkylated aromatic acids are rationalized.

As a possible route to valuable intermediates in the synthesis of *p*-menthen-7-ols and *p*-menthadien-7-ols, we investigated the Birch reduction[3] of *p*-isopropylbenzoic acid (cumic acid I).

It is known[3a] that the influence of a carboxyl group in the reduction of a benzene ring outweighs that of other groups present and the formation of a 1,4-dihydro derivative is strongly favored. Thus, in a study of the reduction of aromatic acids and amides by sodium and alcohol in liquid ammonia, Kuehne and Lambert[4] reported that benzoic and *o*-toluic acids afforded the corresponding 1,4-dihydrobenzoic and 1,4-dihydro-*o*-toluic acids; however, under the same conditions, *p*-toluic acid gave mainly unconjugated tetrahydro acids. To account for the last result,

(1) Part III of this series: F. Camps, J. Castells, and J. Pascual, *J. Org. Chem.*, **31**, 3510 (1966).

(2) Supported by Grant FG-Sp-135 from the U. S. Department of Agriculture.

(3) (a) A. J. Birch, *Quart. Rev.* (London), **4**, 69 (1950); (b) A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958); (c) "Steroid Reactions," C. Djerassi, Ed., Holden-Day, Inc., San Francisco, Calif., 1963, pp 267–288; (d) H. Smith, "Organic Reactions in Liquid Ammonia. Chemistry in Non-Aqueous Ionising Solvents," Vol. 1, Part 2, John Wiley and Sons, Inc., New York, N. Y., 1963; (e) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Inc., New York, N. Y., 1965, p 50.

(4) M. E. Kuehne and B. F. Lambert, *J. Am. Chem. Soc.*, **81**, 4278 (1959).