A solution of 1.3 g. (0.010 mole) of crude 2-cycloheptene-1,4-diol in 30 ml. of acetone was cooled to −10° in an ice-salt-bath. A solution of 1.40 g. (0.0140 mole) of chromic anhydride in 6 ml. of distilled water and 2.5 ml. of concentrated sulfuric acid was added dropwise during the course of 0.5 hour with vigorous stirring. The reaction mixture was allowed to stir at room temperature for 3 hr., diluted with 100 ml. of distilled water and extracted with three portions of ether. The yellow ether extract was washed with 5% sodium bicarbonate solution and with water and dried over sodium sulfate. The ether was removed under reduced pressure giving 0.44 g. (35% of the theoretical) of a pale-yellow paste. The infrared absorption spectrum of the crude material showed maxima at 5.98 and 6.22 μ in chloroform. The ultraviolet absorption spectrum showed $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 229 mμ (10,900).

The bis-2,4-dinitrophenylhydrazone was prepared in the usual manner and was recrystallized twice from nitrobenzene–ethanol giving scarlet cubes, m.p. 294–295°. The ultraviolet absorption spectrum showed maxima at $\lambda_{\max}^{\mathrm{CHCl_3}}$ 271 (51,900) and 397 mμ (72,400).

Anal. Calcd. for $C_{19}H_{16}N_8O_8$: C, 47.11; H, 3.33. Found: C, 47.40; H, 3.52.

Pyrolysis of V.—Photo-γ-tropolone methyl ether (V, 50 mg.) was dropped into a neutral Pyrex-helices packed, vertical column[52] 6 inches in length preheated to 360°. A stream of nitrogen was passed through the column to sweep the product through (contact time approximately 10 sec.). The column was cooled to room temperature and washed with chloroform. This chloroform wash was combined with a chloroform solution of the collected product. The infrared absorption spectrum of this chloroform solution was identical in every respect with that of authentic γ-tropolone methyl ether. The residue obtained by removal of the chloroform *in vacuo* showed $\lambda_{\max}^{95\%\ \mathrm{EtOH}}$ 223 and 325 mμ (authentic γ-tropolone methyl ether 223 and 325 mμ). There was no visible charring or decomposition during the pyrolysis.

Pyrolysis of VIII.—Pyrolysis of 20 mg. of VIII under conditions identical with those described above gave, after washing the column with chloroform, a product which had infrared absorption identical to pure tetrahydrophoto-γ-tropolone methyl ether.

Conversion of V to Tropone.—An excess of sodium borohydride was added to a solution of 100 mg. of V in 10 ml. of methanol. The solution was then heated at reflux for 0.5 hr., and the excess hydride was decomposed with 1.0 *N* hydrochloric acid. The resulting solution was extracted with ether, and the ether extract was dried over sodium sulfate. The ether was removed under reduced pressure. The residue was then triturated with ethyl acetate, filtered and the ethyl acetate removed under reduced pressure giving 65 mg. of a colorless liquid. The infrared absorption spectrum of this liquid showed hydroxyl absorption (2.96 μ) but no carbonyl absorption. The ultraviolet absorption spectrum showed only low intensity end absorption.

A solution of 24.7 mg. of the crude alcohol in 5.0 ml. of 1.0 *N* hydrochloric acid was heated at reflux. Aliquots were removed periodically for determination of the ultraviolet spectrum. The typical tropone ultraviolet absorption spectrum[59] with maxima at 225, 228, 231.5, 239, 304 and 312 mμ developed to maximum intensity (28% conversion to tropone) in 11 hr.

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[59] H. J. Dauben, Jr., and H. J. Ringold, THIS JOURNAL, **73**, 876 (1951), and W. von E. Doering and F. L. Detert, *ibid.*, **73**, 877 (1951).

AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Terpenoids. XLIII.[1] On the Absolute Configuration on Guaiol. Correlation with Nepetalinic Acid[2]

BY E. J. EISENBRAUN, THOMAS GEORGE,[3] B. RINIKER[4] AND CARL DJERASSI

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The sesquiterpene guaiol (I) has been related *via* (+)-dihydroguaiol (IIa) with bis-homonepetalinic acid (IVa), which has been prepared from a nepetalinic acid (VI) of known stereochemistry. This interconversion establishes the absolute configuration of C-4, while a tentative assignment of the absolute configuration of C-10 has been made by optical rotatory dispersion studies on a relevant transformation product (Va) of guaiol (I).

Information on the absolute configuration of sesquiterpenes of the perhydroazulene type is rather meager and is largely based on optical rotatory dispersion studies among guaianolides[5a] and related sesquiterpenes.[5b] Guaiol (I) does not lend itself directly to such an approach and it was of interest to gain some stereochemical insight into this molecule by classical chemical interconversions. For this purpose, we selected as reference compounds the nepetalinic acids[6] (*e.g.*, VI) since several isomers with known absolute configuration[7] are available. It should be noted that a successful interrelation would settle the absolute configuration of guaiol (I) at C-4 and possibly at C-10 (*vide infra*), but that no conclusions could be reached with respect to the third center of asymmetry (C-7).

The initial steps involved a repetition and extension of transformations, which were first performed by Plattner and collaborators[8] in the guaiol (I) series. The catalytic hydrogenation of the double bond of guaiol is difficult[8] and if too drastic conditions are used, hydrogenolytic removal of the tertiary hydroxyl group is also encountered, leading to products which are of no utility for our purpose. According to Plattner,[8a] high pressure hydrogenation of I with Raney nickel catalyst led to a mixture from which a pure, *crystalline, levorotatory* dihydroguaiol could be separated. For reasons outlined below, we are assigning structure IIb to Plattner's

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[1] Paper XLII, E. J. Eisenbraun, F. Burian, J. Osiecki and C. Djerassi, THIS JOURNAL, **82**, 3476 (1960).

[2] The major portion of the experimental work was carried out in the Department of Chemistry of Wayne State University. We are indebted to the National Institutes of Health of the U. S. Public Health Service for financial support (grants No. RG-3863 and CY-2919 at Wayne State University and grants No. RG-6840 and CY-4818 at Stanford University).

[3] Predoctorate fellow (1959–1960) of the Danforth Foundation.

[4] Postdoctorate research fellow (1955–1956).

[5] (a) C. Djerassi, J. Osiecki and W. Herz, *J. Org. Chem.*, **22**, 1361 (1957); L. Dolejs, M. Soucek, M. Horak, V. Herout and F. Sorm, *Coll. Czech. Chem. Commun.*, **23**, 2195 (1958); D. H. R. Barton and J. E. D. Levisalles, *J. Chem. Soc.*, 4518 (1958); D. H. R. Barton and P. T. Gilham, *Proc. Chem. Soc.*, 391 (1959). (b) G. Büchi, S. W. Chow, T. Matsuura, T. L. Popper, H. H. Rennhard and M. S. Wittenau, *Tetrahedron Letters*, *No. 6*, 14 (1959).

[6] S. M. McElvain and E. J. Eisenbraun, THIS JOURNAL, **77**, 1599 (1955).

[7] R. B. Bates, E. J. Eisenbraun and S. M. McElvain, *ibid.*, **80**, 3420 (1958).

[8] (a) P. A. Plattner and L. Lemay, *Helv. Chim. Acta*, **23**, 897 (1940); (b) P. A. Plattner and G. Magyar, *ibid.*, **25**, 581 (1942).

dihydroguaiol (m.p. 78–79°). From the mother liquors, there was separated an *oily, dextrorotatory* isomer, which may not have been pure and which in the present study is shown to possess structure IIa. While our subsequent degradations have been carried out separately with both dihydroguaiols, a successful tie-up with the nepetalinic acids (VI) was only possible with the dextrorotatory series (IIa).

Our initial hydrogenations were carried out with Raney nickel catalyst essentially according to the literature directions[8a] and furnished the two isomeric dihydroguaiols, the crystalline, levorotatory isomer IIb predominating. Subsequently, it was noted that hydrogenation with a ruthenium dioxide catalyst provided larger amounts of the desired dextrorotatory dihydroguaiol (IIa) and this proved to be the method of choice. Plattner and Magyar[8b] have reported that chromium trioxide oxidation of crystalline, levorotatory dihydroguaiol (IIb) led to levorotatory 2,8-dimethylbicyclo[0,3,5]decanone-5 (IIIb) and its ring scission product, the crystalline dibasic acid IVb. These authors noted that the dibasic acid might also be represented by structure XI, but they favored IVb since the acid was also produced by ozonization of the monobenzylidene derivative of the ketone IIIb.

After repeating and fully confirming these oxidation results of the Swiss workers[8b] we turned to a similar sequence in the dextrorotatory dihydroguaiol series (IIa) and isolated a dextrorotatory ketone, for which the stereoformula IIIa was proved rigorously. As is shown in Fig. 1, the rotatory dispersion curves of the ketones proved to be particularly useful criteria, since they possessed Cotton effect curves of opposite sign.

In contrast to the levorotatory ketone IIIb, which formed[8b] a nicely crystalline monobenzylidene derivative, similar condensation of IIIa with benzaldehyde led to an oily isomer. Ozonolysis of this oily derivative provided the dibasic acid IVa (also produced directly in the chromium trioxide oxidation of IIIa), which initially resisted attempts at crystallization, in contrast to the high melting (m.p. 187–188°) isomeric dibasic acid IVb. However, the oily dibasic acid IVa could be converted into a crystalline bis-amide X and saponification of the latter now gave a crystalline acid (m.p. 85–86°).

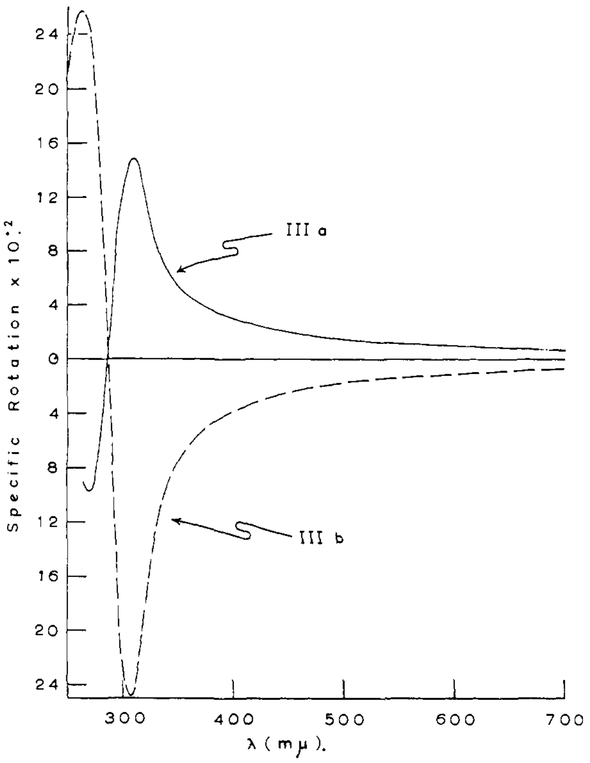

Fig. 1.—Optical rotatory dispersion curves (methanol solution) of (+)-(IIIa)- and (−)-(IIIb)-2,8-dimethylbicyclo[0,3,5]decanone-5.

It was recognized, of course, that the dibasic acid IVa might actually possess structure XI, but this was excluded as follows. Originally, we attempted to degrade the acid IVa by a double Barbier–Wieland degradation to a nepetalinic acid (VI), but in view of experimental complications we turned to the alternative, namely bis-homologation of a nepetalinic acid. For this purpose there was selected the most readily available isomer (m.p. 85–86°, $[\alpha]_D$ +31°), which was carefully purified[6] through its barium salt and which is known[7] to possess the absolute configuration implicit in stereoformula VI. Lithium aluminum hydride reduction of this nepetalinic acid (VI) provided a crystalline diol VII, whose di-tosylate VIII was heated with ethanolic potassium cyanide.[9] Treatment of the resulting bis-nitrile IX with alkaline hydrogen peroxide[10] gave the amide X of bis-homonepetalinic acid and further hydrolysis yielded the free acid. This acid, as well as its amide, proved to be identical with the dibasic acid IVa and amide derived from dextrorotatory dihydroguaiol (IIa), thus establishing the latter's absolute configuration at carbon atoms 1, 4 and 5. The above interconversion also demonstrates unequivocally the site of condensation with benzaldehyde and of ring scission of the ketone IIIa. It is interesting to note that during the preparation of the present manuscript, there appeared an article[5b] where rotatory dispersion evidence was used which led to the same absolute configuration of the C-4 methyl group in aromadendrene and its congeners, all of which are closely related biogenetically to guaiol.

If the assumption can be made that hydrogenation of the double bond of guaiol does not involve initial migration and that it proceeds, therefore, by *cis*-addition of hydrogen—as has been proved for the dextrorotatory isomer IIa—then it follows that the crystalline, levorotatory dihydroguaiol possesses structure IIb.

The absolute configuration of C-10 of guaiol cannot be approached through the nepetalinic acid (VI), because its stereochemistry is not known at that center. An attempt has been made, therefore, to gain some insight through rotatory dispersion studies.[11] For this purpose, the dibasic acid

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[9] See M. E. Ali and L. N. Owen, *J. Chem. Soc.*, 2111 (1958).

[10] C. R. Noller, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 586.

[11] C. Djerassi, "Optical Rotatory Dispersion: Applications to Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1960.

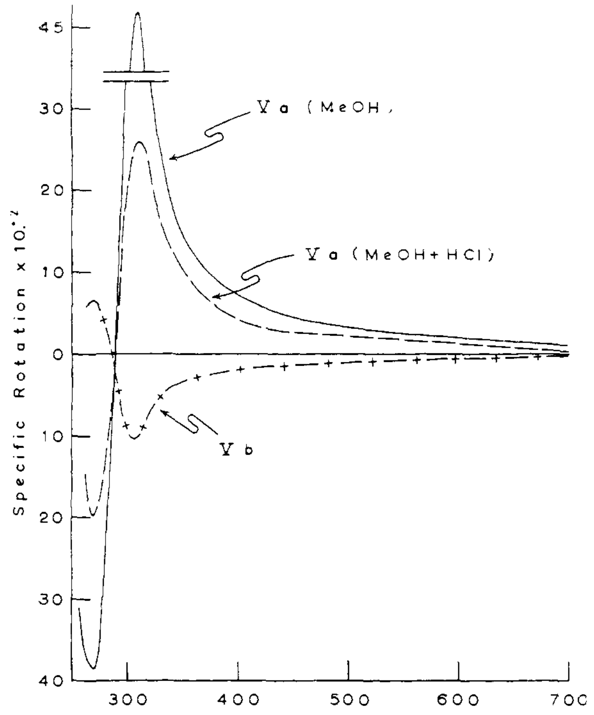
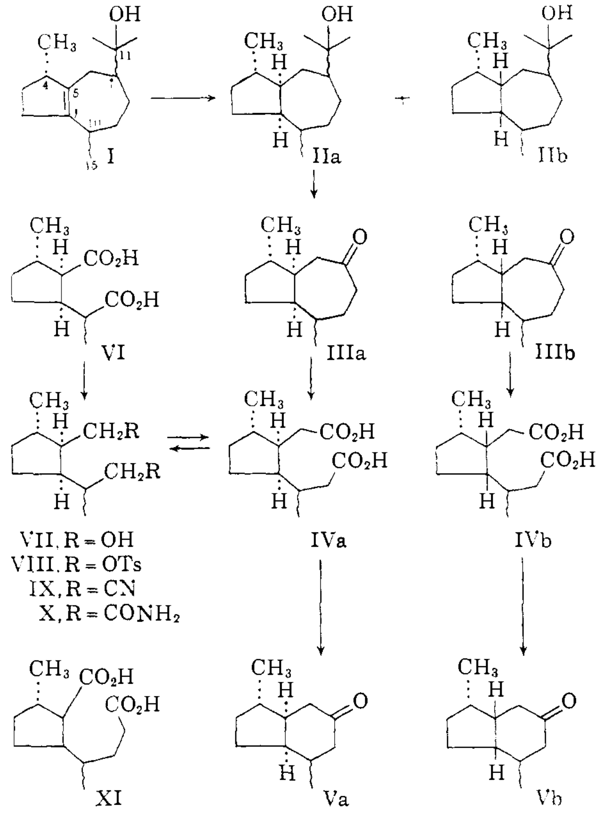


Fig. 2.—Optical rotatory dispersion curves of (+)-*cis*-3,7-dimethylhydrindan-5-one (Va) (methanol solution with and without addition of hydrochloric acid) and (−)-*cis*-3,7-dimethylhydrindan-5(or 4?)-one (Vb) (methanol solution).

IVa of established structure was cyclized by thermal decomposition of its barium salt to give (+)-*cis*-3,7-dimethylhydrindan-5-one (Va). Just as its higher homolog, the bicyclodecanone IIIa (see Fig. 1), the corresponding hydrindanone Va also exhibited (Fig. 2) a positive Cotton effect curve. Of particular pertinence is the observation (Fig. 2) that the addition of hydrochloric acid caused a marked reduction in the rotatory dispersion amplitude, demonstrating the formation of an appreciable amount of the corresponding ketal.[12] As shown in a large number of cases,[12] such ketal formation represents virtual proof of the unhindered environment of the carbonyl group. In particular, this rotatory dispersion evidence does not permit that the methyl group (C-15 in guaiol) in the six-membered ring acquire an axial orientation. If the ketone Va were of rigid conformation, then this information would be sufficient to establish the absolute configuration of this center. Unfortunately, this is not the case in a *cis*-fused hydrindanone and for each orientation of the methyl group, two interchangeable conformations can be written with the cyclohexanone ring in the chair form.

One pair is represented by conformations A $\rightleftarrows$ C and the other by B $\rightleftarrows$ D. Of these, conformations B, C and D all possess at least one axial methyl or methylene group β to the ketone and such a stereochemical feature has been found[12] in molecules of rigid conformation to be sufficient to inhibit ketal formation. Thus, only conformation A remains



and using this rotatory dispersion criterion, the clear-cut answer can be given that the 15-methyl group of guaiol should have the β-orientation using the steroid notation in conjunction with stereoformula I.

A second approach to this problem can be made through the octant rule,[13] which can often be used to predict the sign and approximate magnitude of a Cotton effect curve of a cyclohexanone. Application of the octant rule leads to the following tentative predictions: A, weakly positive; B, weakly negative; C, negative; D, negative. It will be noted from Fig. 2 that the ketone Va actually exhibits a strongly positive Cotton effect and while this again is qualitatively compatible only with conformation A, the quantitative difference beween the prediction and the experimental Cotton effect amplitude is sufficiently large to raise the question of whether the ketone Va does not exist partially or completely in a non-chair form conformation or indeed a boat form (as far as the cyclohexanone ring is concerned). If this should actually be the case, then the above ketal-formation evidence cannot be applied at present and it is with this reservation in mind that we are proposing only tentatively the β-configuration for the 15-methyl group of guaiol (I).[13a]

Figure 2 also includes the rotatory dispersion curve in methanol solution of the levorotatory hy-

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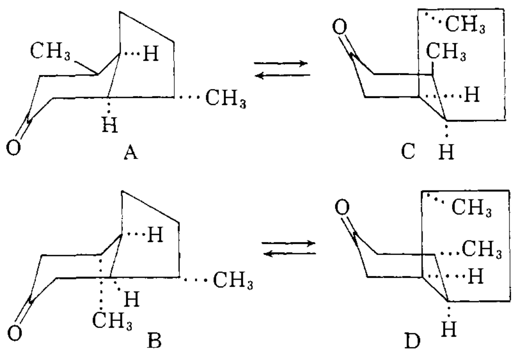
(12) C. Djerassi, L. A. Mitscher and B. J. Mitscher, THIS JOURNAL, **81**, 947 (1959).

(13) See Chapter 13 in ref. 11 and W. Moffitt, A. Moscowitz, R. B. Woodward, W. Klyne and C. Djerassi, manuscript in preparation.

(13a) NOTE ADDED IN PROOF.—While there is no chemical evidence available which bears on the absolute configuration of C-7, L. Dolejs and F. Sorm (*Tetrahedron Letters*, No. *17*, 1 (1959)) have pointed out that all perhydroazulenic sesquiterpenes bearing an actual or modified isopropyl substituent at C-7 exhibit the same absolute configuration. If this argument is applied to guaiol, then in terms of stereoformula I, the C-7 substituent is α-oriented.



drindanone Vb. Here again, a reduction in amplitude was observed upon the addition of hydrochloric acid, indicating the unhindered nature of its carbonyl group. This would tend to suggest that the ketone has structure Vb, derived from the dibasic acid formulation IVb, rather than the alternate expression with the ketone group adjacent to the ring juncture which might be expected from cyclization of a dibasic acid such as XI. However, the conformational picture is sufficiently complicated so as not to warrant at this time further speculation on this point.

Experimental[14]

Hydrogenation of Guaiol (I). (a) With Raney Nickel Catalyst.—A solution of 14.0 g. of guaiol (I)[15] in 80 cc. of ethanol and 7 g. of W-2 Raney nickel catalyst was shaken for 15 hr. at 140° under a hydrogen pressure of 50 atm. Filtration of the catalyst, evaporation of the solvent and distillation yielded a colorless oil (13.5 g.), b.p. 138–142° (11 mm.), which was chromatographed on acid-washed alumina. Elution with hexane furnished 8.0 g. of a hydrocarbon fraction, which was not examined further, while mixtures of hexane-benzene removed 4 g. of a mixture of dihydroguaiols. Crystallization from pentane at −14° led to 2.1 g. of (−)-dihydroguaiol (IIb),[8a] m.p. 74–78°, $[\alpha]_D$ −47°. Except for an additional 0.2 g. of IIb, which crystallized on longer standing at −14°, the remainder of the alcohol fraction remained as an oil and represented largely (+)-dihydroguaiol (IIa), $[\alpha]_D$ +14.5°.

(b) With Ruthenium Dioxide Catalyst.[16]—A typical hydrogenation with 12.5 g. of guaiol (I) and 1.25 g. of ruthenium dioxide catalyst in ethanol solution at room temperature and 1500 p.s.i. required 5 hr. for completion. When the dihydroguaiol fraction (4.2 g.) was separated as above, it remained non-crystalline and judging from its rotation ($[\alpha]_D$ +21.6° in MeOH), it was represented largely by isomer IIa. This material was used for the subsequent oxidations.

Chromium Trioxide Oxidation[8b] of (−)-Dihydroguaiol (IIb).—A solution of 2.1 g. of (−)-dihydroguaiol (IIb) (m.p. 74–78°) in 10.5 cc. of acetic acid was added with stirring at 70° over a period of 1 hr. to a solution of 1.84 g. of chromium trioxide in 10.5 cc. of water and 22.5 cc. of acetic acid. After stirring for an additional 2 hr. at 70–80°, 200 cc. of water was added, the product was extracted with ether and separated into a neutral and an acidic fraction.

The neutral (1.45 g.) material was chromatographed on 45 g. of acid-washed alumina, elution with pentane–benzene and benzene affording 0.74 g. of **(−)-2,8-dimethylbicyclo-(0,3,5)decanone-5 (IIIb)**.[8] For rotatory dispersion measurements, a sample was transformed into its semicarbazone[8] and after two recrystallizations (m.p. 200–210°), this was decomposed with oxalic acid and the resulting ketone rechromatographed. Finally, the ketone IIIb was distilled at a bath temperature of 130–135° (11 mm.), $\lambda_{\max}^{\text{capill.}}$ 5.82 μ; R.D. (Fig. 1) in methanol (*c* 0.144): $[\alpha]_{700}$ −76°, $[\alpha]_{589}$ −107°, $[\alpha]_{308}$ −2500°, $[\alpha]_{263}$ +2570°, $[\alpha]_{250}$ +2120°.

The acidic portion (0.32 g.) crystallized spontaneously and after one recrystallization from methylene chloride–pentane exhibited m.p. 175–185°. Further recrystallization from acetone–heptane raised the m.p. of the acid[8] (IIIb or XI) to m.p. 187–188°.

(−)-*cis*-3,7-Dimethylhydrindan-5-one (Vb).[17]—A finely pulverized mixture of 100 mg. of the above recrystallized acid (m.p. 183–187°) and 7.0 mg. of hydrated barium hydroxide was placed in a 3 - bulb microdistillation apparatus and inserted into a metal bath at 200°. The temperature was raised rapidly over a period of 8 min. to 330° and the resulting distillate was chromatographed on 2 g. of alumina, eluted with 1:1 pentane–benzene and redistilled at a bath temperature of 120° (11 mm.), yield 50 mg., $\lambda_{\max}^{\text{capill.}}$ 5.80 μ; R.D. (Fig. 2) in methanol (*c* 0.062): $[\alpha]_{700}$ −46°, $[\alpha]_{589}$ −73°, $[\alpha]_{308}$ −1050°, $[\alpha]_{268}$ +656°, $[\alpha]_{263}$ +568°. The addition of one drop of hydrochloric acid changed the rotation of the trough to −350°.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.08; H, 10.75.

The yellowish-orange **2,4-dinitrophenylhydrazone** exhibited m.p. 110–112° after three recrystallizations from methanol–methylene chloride.

Anal. Calcd. for $C_{17}H_{22}N_4O_4$: C, 58.94; H, 6.40; N, 16.18. Found: C, 59.06; H, 6.57; N, 16.41.

Chromium Trioxide Oxidation of (+)-Dihydroguaiol (IIa).—The oxidation of 1.30 g. of the liquid (+)-dihydroguaiol (IIa) was performed as described above for the solid isomer IIb using 1.37 g. of chromium trioxide. Chromatography of the neutral fraction (850 mg.) yielded 600 mg. of **(+)-2,8-dimethylbicyclo(0,3,5)decanone-5** (IIIa). A central fraction (288 mg.) of the chromatogram was transformed into the semicarbazone and a small amount of crystalline semicarbazone (due to contamination of the starting dihydroguaiol (IIa) with a small amount of IIb) was filtered. The remaining non-crystalline semicarbazone (corresponding to IIIa) was cleaved by heating under reflux for 1.5 hr. with 10% oxalic acid solution and the resulting ketone was again chromatographed and then distilled at a bath temperature of 145° and 11 mm., $\lambda_{\max}^{\text{capill.}}$ 5.80 μ; R.D. (Fig. 1) in methanol (*c* 0.105): $[\alpha]_{700}$ +68°, $[\alpha]_{589}$ +100°, $[\alpha]_{310}$ +1490°, $[\alpha]_{270}$ −976°, $[\alpha]_{265}$ −895°.

Anal. Calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18; O, 8.88. Found: C, 79.51; H, 11.20; O, 8.71.

The yellow **2,4-dinitrophenylhydrazone** of **IIIa** was recrystallized from methylene chloride and exhibited m.p. 116–120°.

Anal. Calcd. for $C_{18}H_{24}N_4O_4$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.90; H, 6.52; N, 15.23.

For the preparation of the **monobenzylidene** derivative, 5.0 g. of the ketone IIIa (still contaminated with some IIIb derived from IIb present in the starting material IIa used for this oxidation experiment), was diluted with 3 cc. of ethanol and was mixed with 0.25 g. of sodium hydroxide dissolved in 0.5 cc. of water and 2 cc. of ethanol. Freshly distilled benzaldehyde (3 g.) was added followed by sufficient ethanol to give a homogeneous solution. After stirring for 4 hr., 0.9 g. of solid monobenzylidene derivative[8b] corresponding to the contaminant IIIb was filtered off. The ethanol was removed by distillation, the residue was extracted with ether, washed with water, dried and evaporated. Chromatography of the residual oily benzylidene derivative (4.3 g.) on 150 g. of Merck acid-washed alumina and elution with 1:1 hexane-benzene afforded 2.78 g. of the oily monobenzylidene derivative of IIIa,

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[14] Melting points and boiling points are uncorrected. We are indebted to Miss B. Bach for the infrared and ultraviolet absorption spectra and to Dr. A. Bernhardt, Mülheim, Germany, for the microanalyses. Unless noted otherwise, rotations were measured in chloroform solution. The optical rotatory dispersion curves were measured by Mrs. R. Riniker and Mrs. T. Nakano.

[15] The first experiments were conducted with guaiol kindly donated by Prof. George Buchi (M.I.T.). Subsequent specimens were purchased from Fritzsche Bros., Inc., New York.

[16] We are indebted to Prof. W. S. Johnson and Dr. Carolyn B. Abrahams (University of Wisconsin) as well as to Drs. R. T. Rapala and William B. Scanlon (Eli Lilly and Co.) for carrying out several of these hydrogenations.

[17] As pointed out in the discussion section, since the dibasic acid could be represented by either IIIb or XI, it is possible that this ketone is actually (−)-*cis*-3,7-dimethylhydrindan-4-one.

λ_{max}^{EtOH} 279 mμ (log ε 4.26).[18] The analytical specimen was distilled at 130-135° (0.005 mm).

Anal. Calcd. for $C_{19}H_{24}O$: C, 85.02; H, 9.01. Found: C, 84.57; H, 8.72.

Bis-homonepetalinic Acid (IVa). (a) From Nepetalinic Acid (VI).—Reduction of 2.13 g. of nepetalinic acid (VI)[6,19] in ether solution with 3 g. of lithium aluminum hydride was carried out by heating under reflux for 4 hr. and the **nepetalinic acid diol (VII)** was isolated by ether extraction, after initial decomposition with sulfuric acid; yield 1.41 g., m.p. 69-74°. One recrystallization from hexane-chloroform raised the m.p. to 75-77°, $[\alpha]_D$ −7.4°; the analytical specimen (m.p. 80-81.5°) was sublimed at 80° (0.2 mm.).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.60; H, 11.67.

The above described diol VII (1.1 g.), dissolved in 4.5 cc. of pyridine was added dropwise at 0° to a vigorously stirred solution of 2.51 g. of *p*-toluenesulfonyl chloride in 4.0 cc. of pyridine. After keeping for 2 hr. at 0° and an additional 2 hr. at 20°, the mixture was poured into ice-water and the **ditosylate VIII** was extracted with ether, washed free of pyridine with dilute hydrochloric acid and then dried and evaporated.

A 1.07-g. sample of the crude ditosylate was heated under reflux for 24 hr. with 0.428 g. of potassium cyanide, 6 cc. of ethanol and 1 cc. of water. The precipitated potassium *p*-toluenesulfonate was collected and the filtrate was concentrated *in vacuo*. The **bis-nitrile IX** was isolated with ether and was distilled at 130° (0.5 mm.), yield 210 mg., $\lambda_{max}^{CHCl_3}$ 4.45μ, $[\alpha]_D$ −30.8°.

Anal. Calcd. for $C_{12}H_{18}N_2$: C, 75.75; H, 9.54; N, 14.71. Found: C, 75.18; H, 9.34; N, 15.11.

A mixture of 200 mg. of the nitrile IX, 0.05 cc. of 6 *N* sodium hydroxide, 1.25 cc. of 30% hydrogen peroxide and 0.75 cc. of ethanol was stirred vigorously for 4 hr. at 50-55°. **Bis-homonepetalinic amide (X)** precipitated directly (176 mg., m.p. 201-203°) and after recrystallization from chloroform, it exhibited m.p. 207-208°, $[\alpha]_D$ −21.8° (*c* 0.87 in methanol); λ_{max}^{KBr} 2.95, 5.99 and 7.04 μ; R.D. in methanol (*c* 0.349): $[\alpha]_{589}$ −21°, $[\alpha]_{500}$ −30°, $[\alpha]_{400}$ −56°, $[\alpha]_{325}$ −98°.

Anal. Calcd. for $C_{12}H_{22}N_2O_2$: C, 63.68; H, 9.80; N, 12.38; O, 14.14. Found: C, 63.31; H, 9.30; N, 12.72; O, 14.79.

Saponification to **bis-homonepetalinic acid (IVa)** was accomplished by heating 196 mg. of the amide X under reflux for 4 hr. with 2 cc. of 15% sodium hydroxide solution. The cooled solution was extracted with ether and the aqueous portion was acidified with hydrochloric acid and again extracted with ether. After washing with water, drying and evaporating the ether, there was obtained 110 mg. of the acid IVa, m.p. 82-84°. Recrystallization from chloroform-hexane afforded the analytical specimen with m.p. 85-86°, $[\alpha]_D$ +9.5°.

Anal. Calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83; O, 28.04. Found: C, 63.14; H, 9.15; O, 27.79.

(b) **From Guaiol.**—Ozone was passed at 0° through a solution of 4.0 g. of the monobenzylidene derivative of (+)-2,8-dimethylbicyclo(0,3,5)decanone-5 (IIIa) in 25 cc. of methylene chloride until the issuing gas gave a positive test with starch-iodide paper. The solution was then added dropwise with stirring to a mixture of 150 cc. of 10% sodium hydroxide solution and 30 cc. of 30% hydrogen peroxide, stirred at room temperature for 2 hr. and then heated on the steam-bath for an equal length of time. After acidification with hydrochloric acid, steam was passed through the solution to remove the bulk of the benzoic acid, the remainder being eliminated by sublimation from the steam-nonvolatile portion (heating at 78° (1 mm.)). The residual oily acid (substantially IVa) weighed 1.97 g. and resisted attempts at crystallization.[20]

Consequently, for further purification, 0.42 g. of the oily dibasic acid from the ozonization was heated under gentle reflux for 45 min. with 2.1 cc. of freshly distilled thionyl chloride, the solution was cooled and poured into 15 cc. of ammonium hydroxide. The precipitated solid was filtered and dried; yield 104 mg., m.p. 201-203°. After three crystallizations from chloroform, the amide exhibited m.p. 207-208°, $[\alpha]_D$ −21° (*c* 0.875 in methanol); R.D. in methanol (*c* 0.349): $[\alpha]_{589}$ −20°, $[\alpha]_{500}$ −29°, $[\alpha]_{400}$ −53°, $[\alpha]_{325}$ −101°. Identity with the amide X derived from nepetalinic acid (VI) by sequence (a) was established by mixture melting point determination and infrared spectral comparison. Furthermore, saponification of 97 mg. of the amide by the above-described procedure yielded 54 mg. of acid (m.p. 79-81°) whose melting point rose to 85-86° upon recrystallization from chloroform-hexane. $[\alpha]_D$ +9°. No depression in melting point was observed upon admixture with authentic bis-homonepetalinic acid (IVa) and the infrared spectra were identical.

(+)-*cis*-3,7-Dimethylhydrindan-5-one (Va).—The pyrolysis of 150 mg. of bis-homonepetalinic acid (IVa) with 15 mg. of barium hydroxide octahydrate was carried out exactly as described above for the cyclization of the isomeric acid IVb (or XI). The ketone Va was distilled at a bath temperature of 100-105° (1.5 mm.) and showed $\lambda_{max}^{CHCl_3}$ 5.85μ, $[\alpha]_D$ +219° (*c* 0.545 in methanol). R.D. (Fig. 2) in methanol (*c* 0.09 to 300 mμ, *c* 0.018 below 295 mμ): $[\alpha]_{600}$ +176°, $[\alpha]_{589}$ +220°, $[\alpha]_{310}$ +4660°, $[\alpha]_{270}$ −3870°, $[\alpha]_{257.5}$ −3100°. As shown in Fig. 2, the addition of one drop of hydrochloric acid changed the rotation of the peak at 310 mμ to +2590°.

Anal. Calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.92; O, 9.63. Found: C, 79.35; H, 10.80; O, 10.07.

The **2,4-dinitrophenylhydrazone** crystallized from methylene chloride-methanol in yellowish-orange needles, m.p. 97-100°.

Anal. Calcd. for $C_{17}H_{22}N_4O_4$: C, 58.94; H, 6.40; N, 16.18. Found: C, 58.67; H, 6.28; N, 16.19.

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(18) For comparison, the crystalline monobenzylidene derivative[8b] of IIIb was found to exhibit λ_{max}^{EtOH} 277 mμ (log ε 4.27).

(19) This specimen was purified through its barium salt and showed m.p. 85-86°, $[\alpha]_D$ +31.3°.

(20) This applied also to the 250 mg. of acid fraction isolated in the above-described chromium trioxide oxidation of 1.30 g. of (+)-dihydroguaiol (IIa). Crystallization failed even after chromatography on silica gel and elution with chloroform-methanol (100:1).