[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Stereospecific Hydrogenation of α-Pinene Derivatives

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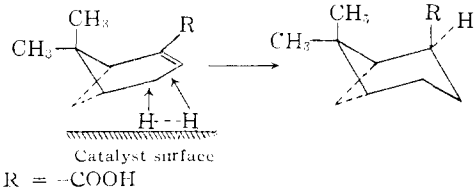
The low pressure catalytic hydrogenation of four α-pinene derivatives, dissolved in acetic acid or ethanol, with platinum at room temperature has been shown to be highly stereospecific. In each case, the stereospecificity appears to be due to steric factors which determine the preferential mode of adsorption of the substrate at the catalytic surface, and leads to a selective addition of hydrogen from the methylene bridge side of the molecule.

In a previous study,[3] it was established that α-pinene reacts thermally with dienophiles to form 1–1 adducts, and that this reaction is stereoselective. It was also found that some of these adducts when hydrogenated at low pressure over Adams platinum catalyst yielded only one of two possible diastereoisomers.

These observations prompted us to extend the hydrogenation studies to several other α-pinene derivatives, including myrtenic acid (Ia), myrtenol (Ib), nopol (Ic) and diethyl nopylmalonate (Id). In each case, the hydrogenation proceeded in a highly stereospecific manner to give a single identifiable product.

It has been recognized for some time[4] that steric factors may play a dominant role in bringing about preferential adsorption of a substrate on a catalytic surface, and thus determine the configuration of the product formed. The application of these concepts to situations involving many complex molecules has proved to be very valuable.[5]

In the present study it was assumed from the outset that effective adsorption (*i.e.*, one which could lead to facile hydrogenation) of an α-pinene nucleus at a catalytic surface is determined largely by the relative steric requirements of the methylene and isopropylidene bridges. As a result, reduction under the mild conditions employed here should lead to *cis* addition of hydrogen overwhelmingly from the methylene bridge side of the molecule as



Ia, R = –COOH
Ib, R = –CH_2OH
Ic, R = –CH_2CH_2OH
Id, R = –$CH_2CH_2CH(COOC_2H_5)_2$
IIa, R = –COOH
IIb, R = –CH_2OH
IIc, R = –CH_2CH_2OH
IId, R = –$CH_2CH_2CH(COOC_2H_5)_2$

Results from the present study are in full accord with this view.

Such a mode of addition of hydrogen, however, would lead to the formation of the thermodynamically less stable isomer, since there is developed in the primary product a considerable strain due to non-bonded repulsive forces between the axial group "R" and one of the methyl groups of the isopropylidene bridge. Our examples appear, therefore, to be extreme cases analogous to those already found in simpler 1,3-disubstituted cyclohexanes.[6]

We have observed that myrtenic acid (Ia) can be hydrogenated to yield a solid compound whose structure has been established as *cis*-dihydromyrtenic acid (IIa).

The methyl ester III of this acid can be readily isomerized with sodium methoxide to a new ester (IV) which, on hydrolysis, yields a liquid dihydromyrtenic acid (V) to which we have assigned the *trans* configuration. It is not surprising that this substance appears to be the same as that formed by the direct reduction of myrtenic acid with sodium and alcohol,[7] since the latter process would be expected to lead to the more stable isomer. That the liquid dihydromyrtenic acid is truly isomeric with IIa, and not merely an impure form of it, was demonstrated by the fact that when subjected to a Curtius degradation, the liquid acid produced a solid amine (VII), and the solid acid yielded a liquid amine (VI). Each of these amines was readily converted into isomeric, crystalline *p*-toluenesulfonamides.

The above-mentioned ester isomerization constitutes a powerful argument in support of the configurations assigned to the acids IIa and V, because it involves the rearrangement of the carbomethoxy group from an axial to an equatorial conformation with consequent diminution of intramolecular strain.

Other independent evidence follows from the rate data shown in Table I.

TABLE I

RATES OF SAPONIFICATION OF *cis*- AND *trans*-METHYL DIHYDROMYRTENATE IN METHANOL (85%)

t, °C.	$k_{cis} \times 10^5$	$k_{trans} \times 10^5$	k_{trans}/k_{cis}
40	3.20 ± 0.07	59.3[8]	18.5
50	9.25 ± 0.44	131[8]	14.2

As expected, the *trans*-ester IV having an equatorial—and thus less hindered—carbomethoxyl group saponifies more rapidly.

The stereospecific, catalytic hydrogenations of

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(4) R. L. Burwell, Jr., *Chem. Revs.*, **57**, 895 (1957).

(5) J. R. Lewis and C. W. Shoppee, *Chemistry & Industry*, 807 (1953).

(6) W. G. Dauben and K. S. Pitzer in "Steric Effects in Organic Chemistry," M. S. Newman, Editor, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 18.

(7) J. L. Simonsen in "The Terpenes," Cambridge University Press, 2nd edition, 1949, p. 226.

(8) Due to a slight drift in the second order rate constants for the *trans*-ester IV, the values reported are those extrapolated to zero time.

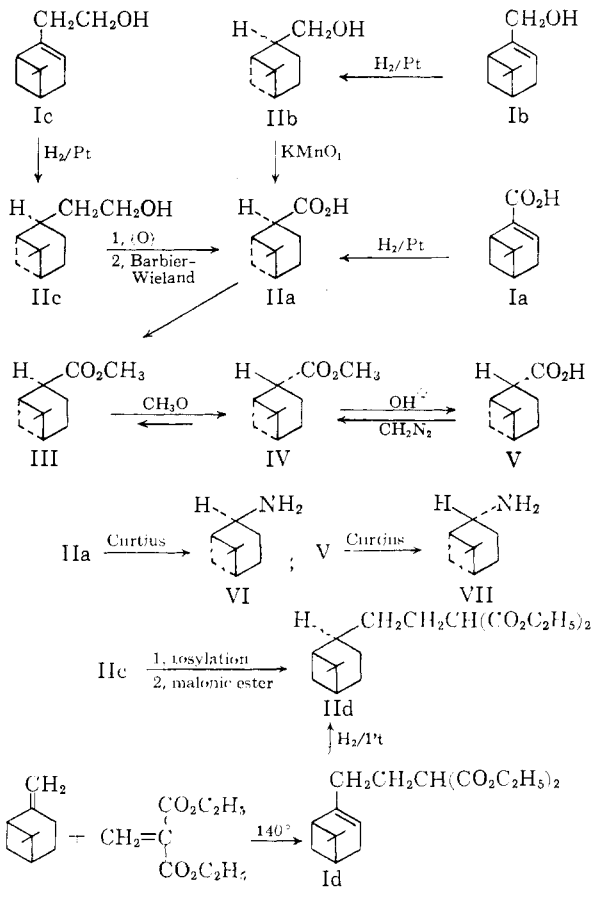
myrtenol (Ib)[9] and nopol (Ic)[10] have already been reported and structures have been assigned to the products on the basis of physical data. Although it was formerly concluded[10] that *trans*-dihydronopol is obtained from the catalytic hydrogenation of nopol, a re-examination of the Raman spectra has now led to the view[11] that this product is, in fact, the *cis* isomer. Our studies, based upon chemical transformations, are in complete agreement with this revised formulation.

It has now been shown that formulas IIb and IIc are correct for the products derived from the catalytic hydrogenation of myrtenol and nopol, respectively, since each of these substances gave only *cis*- dihydromyrtenic acid on oxidative degradation.

In addition, the 1–1 adduct Id, obtained from the thermal reaction of β-pinene with methylenemalonic ester,[3] gave a single isomer (IId) when hydrogenated, and this is identical with the compound formed by the alkylation of malonic ester with *cis*-dihydronopyl tosylate.

In conclusion, it is now quite clear that the low temperature, low pressure hydrogenation of α-pinene derivatives in acetic acid or ethanol solution over Adams platinum catalyst not only proceeds in a stereospecific manner but that the products all appear to possess the *cis* configuration.

A generalized reaction scheme is



(9) G. Dupont and W. Zacharewicz, *Bull. soc. chim. France*, **2**, 535 (1935).

(10) J. Allard and R. Berge, *ibid.*, 1787 (1956).

(11) J. Allard, C. Vignalon and M. Lacombe, *ibid.*, 196 (1958).

Experimental

cis-**Dihydronopol (IIc).**—Redistilled nopol ($n^{25}D$ 1.4918, $\alpha^{25}D$ −35.6° (10 cm.)) was reduced in portions (40 g.) in absolute ethanol (80 ml.) as solvent over Adams catalyst (0.5 g. of PtO_2) at room temperature and 50 p.s.i. in a Parr hydrogenation apparatus. After removal of the catalyst by filtration, the solution was fractionated to give a quantitative yield of *cis*-dihydronopol, b.p. 108–110° (2 mm.), $n^{25}D$ 1.4878, $\alpha^{25}D$ −28.6° (10 cm.); lit. values[10] b.p. 123–125° (10 mm.), $n^{25}D$ 1.488, $\alpha^{25}D$ −27.5°.

The acid phthalate of the above alcohol (41.5 g.) was prepared from phthalic anhydride (37 g.); yield 70.5 g.(89.4%), m.p. 124–125.5°, reported[10] m.p. 123–123.5°. The pure alcohol, regenerated from the acid phthalate, proved to be indistinguishable from the hydrogenation product above, and possessed the properties: $n^{25}D$ 1.4875, $\alpha^{25}D$ −28.6° (10 cm.). The hydrogenation of nopol was, therefore, highly stereospecific.

cis-**Dihydronopoic acid** was prepared earlier by Bain[12] from the oxidation of dihydronopol, but no attempt was made to determine its exact configuration. In our hands, *cis*-dihydronopol (16.8 g.) when oxidized with chromic oxide (15 g.) in acetic acid (60 ml.) at 50° gave *cis*-dihydronopoic acid; yield 40%, m.p. 51.5–53°, reported[12] m.p. 56–58°.

cis-**Methyl Dihydronopoate.**—Dihydronopoic acid (16.2 g.) was dissolved in thionyl chloride (36 ml.) and the solution was heated under reflux for 0.5 hour and allowed to stand overnight. The excess thionyl chloride was removed under vacuum and the residue (24 g.) boiled with methanol (100 ml.) for four hours. Evaporation of the excess methanol gave an oil which was washed with sodium bicarbonate solution and distilled; yield 13.2 g. (76%), b.p. 87–90.5° (1.5 mm.), $n^{25}D$ 1.4689, $\alpha^{25}D$ −17.63° (10 cm.).

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.61; H, 10.28.

Barbier–Wieland Degradation of *cis*-Methyl Dihydronopoate.—To a solution of phenylmagnesium bromide, prepared from bromobenzene (23.5 g.) and magnesium (3.5 g.) in dry ether (40 ml.), was added a solution of *cis*-methyl dihydronopoate (10.7 g.) in dry ether (100 ml.). The mixture was allowed to react at 30° for 4.5 hours, and dry benzene (150 ml.) was added. Ether was then distilled until the temperature of the reaction mixture reached 65°, and the solution was stirred at this temperature for an additional 1.5 hours. The Grignard complex was decomposed by pouring the cooled mixture into ice-cold ammonium chloride solution (acidified with about 4 ml. of hydrochloric acid). Extraction with benzene, followed by drying, evaporation of the benzene and distillation in a sausage flask gave diphenyl-(*cis*-10-pinyl)-carbinol (16.3 g., 93%), b.p. 190–192° (0.5 mm.). A solution of the alcohol (16.3 g.) in acetic anhydride (100 ml.) was heated on a steam-bath for 0.5 hour, then cooled slightly while a solution of chromic oxide (11 g.) in acetic acid (100 ml., 90%) was added over a period of 5 minutes, and the whole was heated for another 15 minutes on a steam-bath. After cooling to below 50°, methanol (10 ml.) was added to reduce the excess chromic oxide. The acetic acid and acetic anhydride were then removed under reduced pressure on a rotating evaporator, and the acid was isolated from the residue in the usual manner. Vacuum sublimation of the acidic fraction (at 0.5–0.6 mm.) gave *cis*-dihydromyrtenic acid (1.35 g., 16%), m.p. 103–105°. Recrystallization from dilute acetic acid gave an analytical sample, m.p. 111–113°.

Anal. Calcd. for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.47; H, 9.76.

Catalytic Hydrogenation of Myrtenic Acid (Ia).—A solution of myrtenic acid (2 g.) in glacial acetic acid (20 ml.) was hydrogenated in the presence of Adams catalyst (50 mg. of PtO_2). The hydrogenation was completed after two hours, and the catalyst was removed by filtration. The filtrate was warmed and diluted with water until it became slightly turbid. On cooling, *cis*-dihydromyrtenic acid separated; yield 1.8 g. (90%), m.p. 91–92°. Recrystallization from a large volume of water containing a wetting agent (Tide) gave flat needles, m.p. 111–112°.

cis-**Dihydromyrtenol.**—Myrtenol[13] (20 g.) was dissolved

(12) J. P. Bain, THIS JOURNAL, **68**, 638 (1946).

(13) We are indebted to Dr. J. P. Bain of The Glidden Co. for a generous sample of this alcohol.

in ethanol (100 ml., 95%) and hydrogenated at 50 p.s.i. pressure at room temperature using Adams catalyst (0.2 g. of PtO_2). This hydrogenation was noticeably faster than that for nopol. After removal of the catalyst by filtration, the solution was concentrated and the residue fractionated to give *cis*-dihydromyrtenol; yield 18.6 g. (90%), b.p. 101–103° (3.5 mm.), $n^{25}D$ 1.4880. The reported[9] values are b.p. 113–113.8° (14 mm.), $n^{22}D$ 1.4896.

The above alcohol (15 g.) was dispersed by means of a high-speed stainless steel stirrer in a solution containing sulfuric acid (50 ml.) and water (400 ml.) at 20°. Finely powdered potassium permanganate (21 g.) was added in small portions as fast as the purple color was discharged and manganese dioxide precipitated. The manganese dioxide was reduced by the addition of sodium metabisulfite, and the entire mixture was extracted thoroughly with benzene. Extraction of the benzene solution with sodium hydroxide, followed by acidification with hydrochloric acid, gave a white crystalline acid (5.8 g.), m.p. 109–110°. Further recrystallization from dilute acetic acid gave pure *cis*-hydromyrtenic acid, m.p. 111–112°.

Isomerization of Methyl *cis* Dihydromyrtenate (III).—A solution of *cis*-dihydromyrtenic acid (8.8 g.) in ether (100 ml.) was treated with ether (100 ml.) containing a slight excess of diazomethane. After 20 minutes the evolution of nitrogen ceased and the excess diazomethane was destroyed by the dropwise addition of acetic acid. The ethereal solution was washed with sodium bicarbonate solution, dried and distilled to give pure methyl *cis*-dihydromyrtenate; yield 6.7 g. (70%), b.p. 78–78.5° (2.6 mm.), $n^{25}D$ 1.4675.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.41; H, 10.17.

The above ester (11 g.) was added to a solution of sodium methoxide prepared from sodium (6 g.) and anhydrous methanol (120 ml.), and the mixture was heated at its boiling point for 4 hours. Water (50 ml.) was added, and the whole was distilled until the temperature at the still-head reached 95°. The remaining aqueous solution was cooled, acidified with hydrochloric acid, and extracted with benzene. Fractionation of the benzene solution gave crude *trans*-dihydromyrtenic acid; yield 7.4 g. (72%), b.p. 118–119° (1 mm.), $n^{25}D$ 1.4848. This product, obtained by equilibration of the methyl esters, undoubtedly contains a few per cent. of the *cis*-acid. The physical constants for pure *trans*-dihydromyrtenic acid, prepared by sodium–alcohol reduction of myrtenic acid,[7] are b.p. 142–144° (8 mm.), $n^{25}D$ 1.4858.

Methyl *trans*-dihydromyrtenate, used in the kinetic experiments, was prepared from the above acid (7 g.) by treatment with diazomethane; yield 5.5 g. (72%), b.p. 88–91° (7 mm.), $n^{25}D$ 1.4680.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96; sapn. equiv., 182.2. Found: C, 72.70; H, 10.01; sapn. equiv., 180.5.

Curtius Degradation of *cis*-Dihydromyrtenic Acid (IIa).—*cis*-Dihydromyrtenic acid (2 g.) was converted to its acid chloride with thionyl chloride. The acid chloride, thus obtained, was dissolved in acetone (20 ml.), cooled to 0°, and treated with a solution of sodium azide (3 g.) in water (10 ml.). After 5 minutes, the solution was poured into ice-cold sodium chloride solution and extracted with ether. The ethereal solution was washed with sodium bicarbonate solution and finally with water. Dilute acetic acid (50 ml., 70%) was then added, the ether removed under vacuum at room temperature and the remaining solution heated at 90° for two hours. Hydrochloric acid (30 ml.) was then added and the mixture held at a temperature of 70–90° overnight. All solvents were removed under vacuum, and the residue was dissolved in water, made alkaline, and extracted with ether. The liquid *cis*-6,6-dimethylnorpin-2-ylamine (VI) was distilled in a micromolecular still at a block temperature of 42–62° at 0.5 mm.; yield 1.16 g. (69%), $n^{25}D$ 1.4847.

The tosylate, prepared in the usual manner, melted at 106.5–107°.

Anal. Calcd. for $C_{16}H_{23}NSO_2$: C, 65.51; H, 7.90. Found: C, 65.20; H, 8.06.

Curtius Degradation of *trans*-Dihydromyrtenic Acid (V).—By the procedure outlined above, *trans*-dihydromyrtenic acid (1.35 g.), obtained by isomerization of the *cis* isomer, gave crude *trans*-6,6-dimethylnorpin-2-yl amine (VII) as a semi-solid mass (m.p. 69–79°) which was converted directly to its tosylate, m.p. 131.5–132°.

Anal. Calcd. for $C_{16}H_{23}NSO_2$: C, 65.51; H, 7.90. Found: C, 65.50; H, 7.82.

Ethyl *cis*-Dihydronopylmalonate (IId). (a) **By Alkylation.**—*p*-Toluenesulfonyl chloride (31.7 g.) was added in small portions to a cooled solution of *cis*-dihydronopol (25.5 g.) in dry pyridine (60 ml.) and ether (100 ml.). The mixture was allowed to stand at 0° for four days and then poured onto ice and hydrochloric acid. The hexane extract of this mixture was washed with cold, dilute hydrochloric acid and dried. Removal of the hexane left a residue of crude tosylate as light yellow oil; yield 45 g. (92%). This product (38 g.) was allowed to react with ethyl malonate (21 g.), in the usual manner, to give ethyl *cis*-dihydronopylmalonate; yield 20.6 g. (56%), b.p. 135–140° (0.01 mm.), $n^{25}D$ 1.4656, $\alpha^{25}D$ −18.12° (10 cm.).

(b) **By Hydrogenation.**—Ethyl nopylmalonate[3] (42 g.) was dissolved in absolute ethanol (100 ml.) and hydrogenated over Adams catalyst (0.5 g. of PtO_2) at room temperature and 50 p.s.i. Removal of the catalyst and solvent gave a residue which yielded ethyl *cis*-dihydronopylmalonate on fractionation; yield 35.8 g. (84%), b.p. 135–137° (0.01 mm.), $n^{25}D$ 1.4654, $\alpha^{25}D$ −17.11° (10 cm.).

Anal. Calcd. for $C_{18}H_{30}O_4$: C, 69.64; H, 9.74. Found: C, 69.56; H, 9.52.

The infrared spectra of the samples of ethyl *cis*-dihydronopylmalonate obtained by methods a and b above were indistinguishable. In addition, each sample reacted with urea to give identical derivatives, namely, 5-*cis*-dihydronopylbarbituric acid, m.p. 204.5–206°.

Anal. Calcd. for $C_{15}H_{22}O_3N_2$: C, 64.72; H, 7.97. Found: C, 64.51; H, 8.41.

Kinetic Measurements.—All solutions were kept CO_2 free. Commercial methanol (4 l.) was dried by distillation from magnesium turnings (50 g.) and iodine (1 g.). The first fractions of the distillate were discarded. Aqueous methanol (85%) for the kinetic measurements was prepared by mixing dry methanol (850 parts) with carbon dioxide-free distilled water (150 parts). All runs were carried out using the same stock solution. Sodium hydroxide in 85% methanol solution was prepared by dissolving cleaned sodium (approx. 7 g.) in 85% methanol (500 ml.) and adding an amount of distilled water exactly equivalent to the amount of sodium used. The resulting solution was about 0.65 *N* in sodium hydroxide.

A 25-ml. volumetric flask half-filled with 85% methanol was immersed in a water-bath maintained at ±0.1° of the desired temperature. Exactly 5 ml. of sodium hydroxide stock solution was then added and the volume was brought up to about 22 ml. with 85% methanol. The contents of the flask were allowed to reach the desired temperature and the ester (0.25–0.3 g.) was added from a small weighing pipet. The time of addition of the ester was taken as zero time. The volume of the solution was immediately brought up to 25 ml. with 85% methanol, and the flask was swirled in the water-bath for about one to two minutes and inverted several times to mix the contents thoroughly. At certain time intervals, corresponding to about 25, 40, 55 and 70% saponification, 5-ml. aliquots of the reaction mixture were withdrawn, added to 5 ml. of dilute hydrochloric acid (about 0.15 *N*) and titrated with sodium hydroxide solution, using phenolphthalein as indicator. The initial concentration of base was determined separately in a blank run.

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