[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, STANFORD UNIVERSITY]

The Configurations of the Methylnopinols[1]

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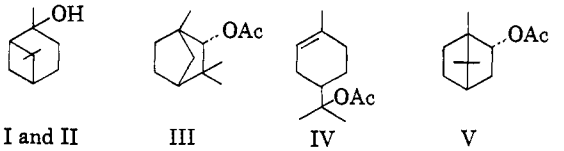
The configurations of two methylnopinols have been assigned on the basis of their conversions to derivatives of borneol or α-fenchol.

Discussion

Two stereoisomers of pinene hydrate or methylnopinol are well characterized, the lower melting isomer (I, m.p. 59°) having been prepared by Wallach by the reaction of methylmagnesium iodide with nopinone,[2] and the higher melting isomer (II, m.p. 79°) by Lipp by permanganate oxidation of *l*-pinane.[3] In connection with a study of the reactions of pinene hydrocarbons we have attempted to prepare some simple derivatives of the methylnopinols. Although we have not succeeded in isolating an unrearranged derivative, the major products of acetylation appear to establish unambiguously the relative configurations of the methylnopinols.

On prolonged heating with acetic anhydride, isomer I is converted in 40–50% yield to α-fenchyl acetate (III), identified by its infrared spectrum and by its subsequent conversion to α-fenchol. A small amount of terpinyl acetate (IV) is formed, and the remaining products are hydrocarbons. Similarly treated isomer II provides bornyl acetate (V) in 5% yield, terpinyl acetate and hydrocarbons. The yield of terpinyl acetate is somewhat dependent on the period of heating since this ester is converted to hydrocarbons in the presence of acetic acid. The addition of pyridine to the acetylation mixture sharply inhibits the disappearance of both of the methylnopinols, suggesting that the unrearranged acetate is not an intermediate in the conversion to fenchyl, bornyl or terpinyl acetates. The magnesium salt of isomer II reacts at room temperature with acetic anhydride to produce bornyl acetate in 40–50% yield. In no case was α-fenchyl acetate detected in the acetylation mixture of methylnopinol(II), or bornyl acetate in that of isomer I. In contrast, α- and β-pinene yield both fenchyl and bornyl derivatives when treated with organic acids.[4] Table I gives the product distribution for the acetylation reactions as determined by liquid–vapor partition chromatography.



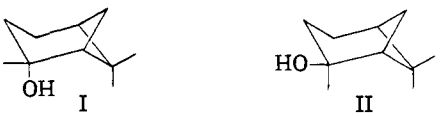
I and II III IV V

Assignment of configuration follows from consideration of the stereochemical course of the reaction. Migration of the bridge atom *trans* to the departing hydroxyl group accompanied by backside attack by acetate ion at the bridgehead atom produces the corresponding rearranged acetate in the *endo* configuration. Therefore the hydroxyl group of the bornyl acetyl yielding isomer II must be *trans* to the disubstituted bridge, whereas the hydroxyl group of the α-fenchyl acetate yielding isomer I will be *trans* to the unsubstituted bridge. That isomer I is formed in the Grignard reaction with nopinone supports this assignment.[5] The most probable conformations for the two isomers will place the hydroxyl group in the equatorial position for isomer II and in the axial position for isomer I, accounting for the markedly different proportion of rearranged products, and for the greater reactivity of II.

TABLE I

THE PRODUCTS OF ACETYLATION OF METHYLNOPINOL

Reactant	Duration, hr., of heating at 100°	Bornyl acetate, %	α-Fenchyl acetate, %	Terpinyl acetate, %	Hydrocarbons, %
Alcohol I	10–12	...	40–50	5–10	40–50
Alcohol II	5–6	5	...	40–60	30–50
Magnesium salt of alcohol II	...	40–50	...	...	40–50



I II

The reaction cannot have proceeded by way of the non-classical ion postulated by Roberts and co-workers for norbornyl systems[6]; otherwise both methylnopinols would have yielded the same products, in the *exo* configuration.

We suggest that the higher melting methyl nopinol (II) be designated as *cis* and the lower melting (I) as *trans* so that they may be represented as derivatives of *cis*- and *trans*-pinane.[3]

Experimental

Separations by Liquid–Vapor Partition Chromatography (L–v.p.c.).—The liquid-vapor partition apparatus employs a 9′ × 5/16″ column packed with Carbowax 4000 30% on Johns–Manville C-22 fire-brick crushed to 30–60 mesh. Detection is accomplished by a single element thermal conductivity gauge coupled with a General Electric model 8CE3CM1 recording microammeter. Retention times at a flow rate of 100 ml./min. of helium are given in Table II. The criteria for identity in this project have been superimposability of infrared spectra and correspondence of l–v.p.c. retention times.

(1) This work was supported by a grant from the Hercules Powder Co. Inquiries may be addressed to W. D. B. at P. O. Box 526, Saginaw, Mich.

(2) O. Wallach, *Ann.*, **356**, 227 (1907).

(3) A. Lipp, *Ber.*, **56**, 2098 (1923).

(4) M. Delepine, *Bull. soc. chim. France*, [4] **35**, D1478 (1924).

(5) D. J. Cram and F. A. A. Elhafez, THIS JOURNAL, **74**, 5828 (1952).

(6) J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *ibid.*, **76**, 4501 (1954).

TABLE II

RETENTION TIMES OF ORGANIC MATERIALS (IN MINUTES ±1 MINUTE)

Compound	152°	160°
Methylnopinol I	24	19
Methylnopinol II	28	22
Bornyl acetate	23	20
α-Fenchyl acetate	18	15
Terpinyl acetate	..	30
Borneol	40	30
α-Fenchol	..	20

Infrared analyses were obtained using a Perkin–Elmer model 21 recording spectrophotometer employing sodium chloride optics.

Methylnopinols.—Each isomer was recrystallized from absolute ether and its purity was established by partitioning a sample dissolved in cyclohexane.

Acetylation of Methylnopinol I.—Two grams of the alcohol dissolved in 5 cc. of acetic anhydride was heated at the steam-bath for 10 hours. The reaction mixture was decomposed with cold, saturated sodium bicarbonate solution and extracted with ether. A sample of the crude oil was partitioned by l–v.p.c. to determine the product distribution. The product was distilled to remove most of the hydrocarbons and some of the terpinyl acetate identified by its infrared spectrum. The acetate fraction of the center distillation cut was then removed by repetitive partitioning of 50-μl. portions. The material collected was twice repartitioned, yielding a colorless oil of $n^{22}D$ 1.4550 shown to be α-fenchyl acetate by comparison of its infrared spectrum with that of an authentic sample. The acetate (0.100 g.) was allowed to stand overnight in methanolic potassium hydroxide. The methyl alcohol was boiled off, and the residue was taken up in ether. The oil remaining after evaporation of the ether was partitioned, yielding a partially solid material shown to be α-fenchol by its infrared spectrum.

Acetylation of Methylnopinol II.—Three grams of methylnopinol dissolved in 5 cc. of acetic anhydride was heated for five hours at the steam-bath. The product was treated as described above for isomer I. Multiple partitioning of the minor acetate fraction provided a partially solid material indicated to be bornyl acetate by its infrared spectrum. To 0.10 g. of acetate dissolved in 2–3 cc. of absolute ether was added a small lump of lithium aluminum hydride. After several hours water was added to decompose the excess hydride, and the ether layer was removed and evaporated. The residue was dissolved in cyclohexane and partitioned, yielding a single crystalline solid melting at 200–203° and shown to be borneol by its infrared spectrum.

Acetylation of the Magnesium Salt of Methylnopinol II.—A solution of 1.0 g. of the methylnopinol in 10 cc. of ether was added dropwise to a solution of *n*-propylmagnesium bromide prepared by adding 1.6 g. of *n*-propyl bromide in 10 cc. of ether to 0.35 g. of magnesum ribbon. After all of the alcohol had been added the mixture was refluxed gently for one hour. Acetic anhydride (2.0 g. in 10 cc. of ether) was added slowly with cooling and the reaction mixture was allowed to stand for two days at room temperature. The product was removed by steam distillation of the reaction mixture and treated as described for the other acetate preparations. The partitioned acetate was shown to be bornyl acetate by its infrared spectrum and by its conversion to borneol by lithium aluminum hydride.

Acknowledgment.—The methylnopinol samples were provided by Professor Saul Winstein, to whom we are deeply grateful.

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COMMUNICATIONS TO THE EDITOR

FORMATION CONSTANTS OF METAL COMPLEXES CONTAINING OPTICALLY ACTIVE LIGANDS[1]

Sir:

It has been observed by other workers[2] that metals (M) when combining with optically active ligands (*l*-X) and (*d*-X) form complexes of the type $M(l\text{-X})_n$ and $M(d\text{-X})_n$ rather than the mixed complex $M(l\text{-X})_n(d\text{-X})_m$.

To demonstrate whether this favoring of non-mixed complexes occurs, at equilibrium, in solution the author has measured the formation constants of both types of complex. Two potentiometric titrations were made[3]: (1) the titration of a 2:1 mixture of *l*-asparagine and copper (II) with potassium hydroxide and (2) the titration of a 2:1 mixture of racemic-asparagine and copper(II) ion. In the first case the constant

$$K_1 = \frac{[Cu(l\text{-Asp})_2]}{[Cu(l\text{-Asp})^+][l\text{-Asp}^-]} \qquad (1)$$

(1) This investigation was supported in part by a research grant RG 5532 from the Division of General Medical Sciences, Public Health Service.

(2) Fred Basolo, "The Chemistry of the Coördination Compounds," Edited by John C. Bailar, Jr., Reinhold Publishing Corp., New York, N. Y., 1956, p. 313.

(3) The conditions were at a constant ionic strength of 0.1 (maintained by KCl) and at 25°.

Asp^- = negative ion of asparagine

could be calculated by conventional methods. In the second case the same calculations would give the constant

$$K_2 = \frac{[Cu(l\text{-Asp})_2] + [Cu(d\text{-Asp})_2] + [Cu(l\text{-Asp})(d\text{-Asp})]}{\{[Cu(l\text{-Asp})^+] + [Cu(d\text{-Asp})^+]\}\{[l\text{-Asp}^-] + [d\text{-Asp}^-]\}} \qquad (2)$$

It is to be expected that

$$[Cu(l\text{-Asp})_2] = [Cu(d\text{-Asp})_2]$$

and

$$[Cu(l\text{-Asp})^+] = [Cu(d\text{-Asp})^+] \qquad (3)$$

and

$$[l\text{-Asp}^-] = [d\text{-Asp}^-]$$

thus

$$K_2 = \frac{[Cu(l\text{-Asp})_2]}{2[Cu(l\text{-Asp})^+][l\text{-Asp}^-]} + \frac{1}{4}\frac{[Cu(l\text{-Asp})(d\text{-Asp})]}{[CuA^+][B^-]} \qquad (4)$$

where A^- = *l*-Asp^- if B^- = *d*-Asp^-

and A^- = *d*-Asp^- if B = *l*-Asp^-

The second term of (4) represents the formation constant of the mixed complex from the mixed