[Contribution from the Applied Chemistry Department, Indian Institute of Technology]

CONFORMATION OF TERPENES. II. PINOCAMPHEOLS AND PINOCARVEOLS[1]

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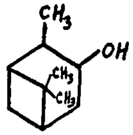
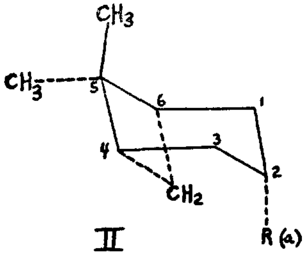
Pinocampheol (I) should exist as four stereoisomeric *dl*-pairs by virtue of its four centers of asymmetry two of which are connected by a methylene bridge. All these isomers are known and Schmidt (1) has derived their configuration partly on the basis of Auwers-Skita rules. Since these rules have been shown to be without validity in the case of several 1,3-disubstituted cyclohexane derivatives (2), it seems desirable to examine the stereochemistry of pinocampheols on the basis of the concept of axial and equatorial bonds. This concept has been successfully applied to the study of the stereochemistry of several types of compounds (3–5) including terpenes like menthols (3) and carvomenthols (6).

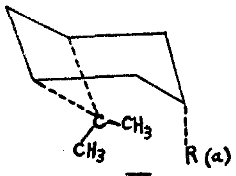
Of the two conformations II and III possible for the fused ring system of pinane and its derivatives, II should be preferred as it places a methylene group rather than a bulky *gem*-dimethyl group in a position that is hindered by the axial substituent at carbon atom 2. (Solid lines indicate substituents above the puckered plane of the chair form of the cyclohexane ring; broken lines indicate substituents below the plane.)



I



II



III

Equilibration of either pinocamphone (IV) or isopinocamphone (V) in the presence of sodium alkoxide leads to a mixture containing about 77% of IV (7). The more stable conformation IV should therefore be assigned to pinocamphone.

Sodium and alcohol reduction of pinocamphone leads to pinocampheol but catalytic reduction affords the epimer neopinocampheol (1). It is known that the reduction of a ketone with sodium and alcohol leads predominantly to the more

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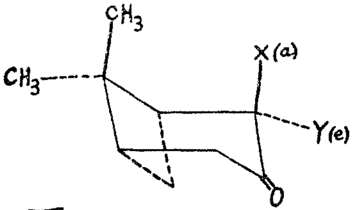
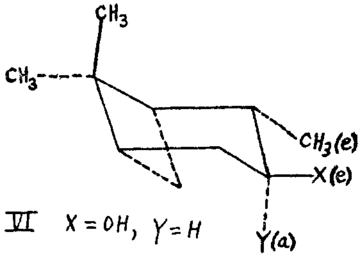
[1] For Part I see *Experientia*, **8**, 458 (1952).

stable epimer of the alcohol (8, 3). The hydroxy group should therefore be equatorial in pinocampheol (VI) and axial in neopinocampheol (VII).

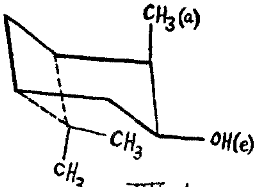




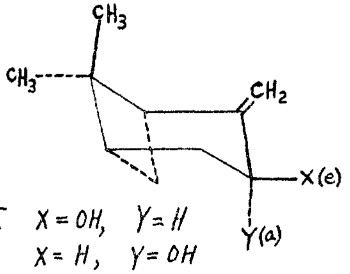
IV $X = H$, $Y = CH_3$
V $X = CH_3$, $Y = H$

VI $X = OH$, $Y = H$
VII $X = H$, $Y = OH$

Schmidt (9) has reported that of the two epimeric alcohols, (−)-*trans*-pinocarveol, m.p. 5°, and (+)-*cis*-pinocarveol, m.p. 51°— the former is esterified more rapidly than the latter and the acetate of the former is saponified faster than the acetate of the latter. It has been established that an equatorial substituent is sterically less hindered than the corresponding axial substituent (3, 4). The hydroxy group should therefore occupy an equatorial position in *trans*-pinocarveol (VIII) and an axial position in *cis*-pinocarveol (IX). The observation (9) that IX is dehydrated by sulfuric acid to a hydrocarbon whereas the same reagent hydrates VIII lends support to this assignment of conformation, because, it has been shown (3, 4) that ionic elimination of a group takes place more readily when it is in the axial position than when it is in the equatorial position.



VII b

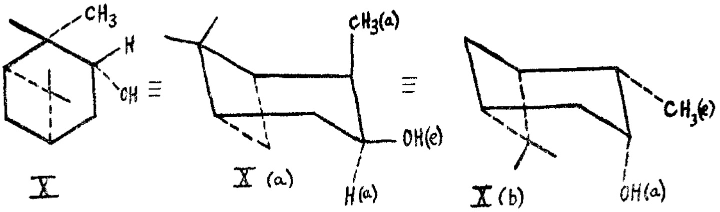


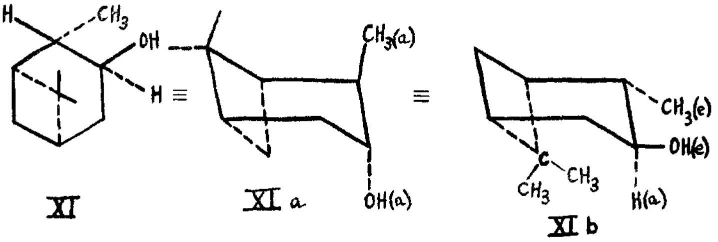
VIII $X = OH$, $Y = H$
IX $X = H$, $Y = OH$
XV $X = Y = H$

The catalytic reduction of VIII leads to isopinocampheol and of IX to neoisopinocampheol (1). Both these isomers yield isopinocamphone on oxidation.

From the conformation VIII for *trans*-pinocarveol, it is seen that the *gem*-

dimethyl group and the hydroxy group are *cis* to each other. Since the relative positions of these groups should be unaffected by the reduction of VIII to isopinocampheol, we can assign the configurations X and XI to isopinocampheol and neoisopinocampheol respectively.





For each of the configurations X and XI there are two possible conformations. It is possible to decide which of them are the preferred conformations if it be known whether the hydroxy group is axial or equatorial.

Isopinocampheol has been prepared by the sodium and alcohol reduction of 2-oxypinocamphone (10). The nature of the reducing agent used suggests that the hydroxy group should be equatorial in isopinocampheol. Delepine and Badoche (11) have stated that the sodium and alcohol reduction of (+)-isopinocamphone affords crystalline (+)-pinocampheol and an oil that in their opinion is a mixture of (+)-pinocampheol and (−)-isopinocampheol. This is reminiscent of the production of both menthol and isomenthol by the sodium and alcohol reduction of isomenthone (or menthone) (12). The hydroxy group in both menthol and isomenthol has been assigned the equatorial orientation (3). By analogy the hydroxy group in isopinocampheol also should be in the equatorial position.

Schmidt (1) has reported the following observations on the equilibration of pinocampheols by heating with sodium at 160°:

Alcohol		$[\alpha]_D$ of equilibrium mixture
Pinocampheol	66°	52°
Neopinocampheol	−17°	42°
Isopinocampheol	−32°	−23° (50° on prolonged heating)
Neoisopinocampheol	36°	54°

It is evident that pinocampheol is the most stable isomer because all others can be transformed into it. The observation that under less drastic conditions the rotation of isopinocampheol changes from −32° to −23° may mean that the equilibrium mixture consists of 87% of isopinocampheol and 13% of its isomer neoisopinocampheol. Since a substituent in the equatorial position is more stable than the same substituent on the same carbon atom in the axial position (3), VI with both the methyl and hydroxyl groups in the equatorial position is expected to be the most stable of the four isomers. The equilibration data therefore strongly support the conformations assigned to pinocampheol and neopinocampheol and indicate the equatorial orientation for the hydroxy group in isopinocampheol.

The following yields of crude ester have been reported on the acetylation of isomeric pinocampheols under identical conditions (1):

Pinocampheol	92%	Neopinocampheol	67%
Isopinocampheol	85%	Neoisopinocampheol	56%

When 0.5 g. of the acetate of the pinocampheols is treated with 10 ml. of 0.5 *N* potassium hydroxide solution for one hour, the extent of hydrolysis is as follows (1):

Pinocampheol acetate	86%	Neopinocampheol acetate	19.6%
Isopinocampheol acetate	89%	Neoisopinocampheol acetate	38%

It has been established that a hydroxy group is more easily acylated and the corresponding ester is more easily saponified when the hydroxy group is in the equatorial orientation than when it is in the axial orientation (3). The data quoted above constitute strong evidence in favor of the equatorial conformation for the hydroxy group in pinocampheol and isopinocampheol. The appreciably higher rate of hydrolysis of neoisopinocampheol acetate compared to that of neopinocampheol acetate parallels the relative rates of esterification of neoisomenthol and neomenthol[2] (13).

According to Eliel (14) the hydroxy group in neoisomenthol (XII) and neomenthol (XIII) has to assume the equatorial position before acylation. This involves conformational inversion from XII to XIIa and XIII to XIIIa. The change from XIII to XIIIa will be less facile than that from XII to XIIa, since in the former two alkyl groups have to be forced into the crowded axial position, in the latter only one. Therefore, making the reasonable assumption that XIIa and XIIIa are of the same order of reactivity, XII should be esterified more readily than XIII (14).

Eliel's idea may be used to compare the reactivity of the acetates of neoisopinocampheol and neopinocampheol if we assume XIa and VIIa to be the stable conformations of these two alcohols. Before acylation VIIa has to be converted to VIIb and XIa to XIb so as to place the hydroxy groups in the more accessible equatorial positions. Conversion of XIa (axial methyl, axial hydroxy) to XIb (equatorial methyl, equatorial hydroxy) would be expected to require less energy than the conversion of VIIa to (equatorial methyl, axial hydroxy) to VIIb (axial methyl, equatorial hydroxy); neoisopinocampheol should therefore react faster than neopinocampheol. Schmidt's data show that these two alcohols have the

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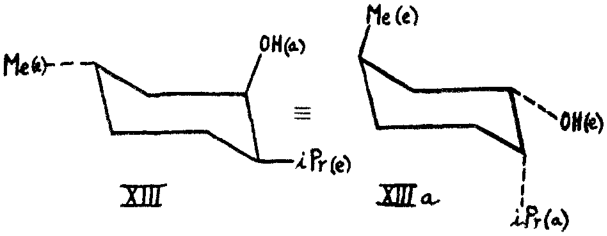
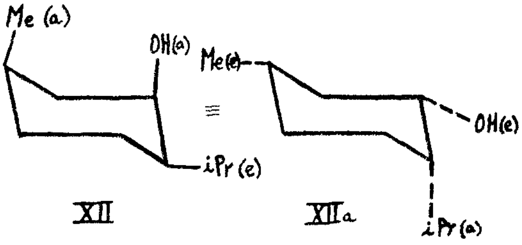
[2] The author is thankful to one of the referees for pointing out this analogy and suggesting the application of Eliel's idea to neoisopinocampheol.

same order of reactivity, but their acetates differ appreciably in reactivity and in the expected direction.



XIII XIIIa



XII XIIa

The following data on the behavior of the p-toluenesulphonates of pinocampheols have been reported by Schmidt (14):

Alcohol	Yield of Tosylate, %	Products Obtained from Tosylate and Sodium Ethoxide		
		Alcohol, %	Ethyl ether, %	Hydrocarbon,%
Pinocampheol	60	30	33	37
Neopinocampheol	40	Nil	Nil	Only product
Isopinocampheol	80	21	Nil	79
Neoisopinocampheol		5	Nil	95

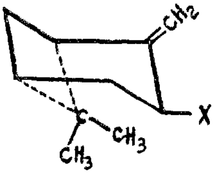
An axial substituent is known to be more favorably situated for ionic elimination reactions than a corresponding equatorial substituent (3). The very high yield of hydrocarbons and the negligible yield of alcohols in case of the tosylates of neopinocampheol and neoisopinocampheol indicate clearly that the hydroxy group in these two isomers are in the axial position.

The ease of formation of the tosylate of pinocampheol and the appreciable substitution reactions that take place in competition with elimination reactions when the tosylate is treated with sodium ethoxide are indicative of the equatorial position of the hydroxy group in pinocampheol.

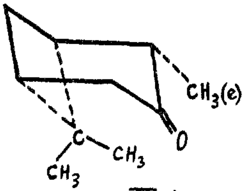
Isopinocampheol is tosylated with great ease. This observation and the 21% yield of alcohol in the reaction of the tosylate with alkali point to the possibility of the hydroxy group being equatorial in orientation. On the other hand, the high yield of hydrocarbons is compatible with the axial orientation of the hydroxy group. The marked difference toward the elimination reaction between pinocampheol and isopinocampheol can, however, be satisfactorily explained without assigning an axial hydroxy group to isopinocampheol.

Ionic elimination reactions take place best when the two neighboring carbon atoms involved and the two substituents that are eliminated are all in one plane (16). Therefore it may be assumed that for elimination reaction to occur, the tosyl group should be in the axial orientation (through conformational inversion if necessary). If VI and Xa represent the stable conformation of pinocampheol and isopinocampheol respectively, conformational inversion will be required before elimination will take place. Such inversion will be easier for isopinocampheol than for pinocampheol, because in the case of the former, an axial methyl group will be transformed into a less hindered equatorial group, whereas in the case of the latter, an equatorial methyl group will be forced to an axial orientation. This facility of conversion will be expected to result in greater elimination.

The data presented so far seem to indicate that pinocampheol and neopinocampheol can be adequately represented by conformations VI and VII and that isopinocampheol and neoisopinocampheol appear to be mostly Xa and XIa with some contribution from Xb and XIb respectively. If Delépine and Badoche's (11) contention that the sodium and alcohol reduction of isopinocamphone affords isopinocampheol as one of the products be correct, then the conformation V and not Vb is indicated for isopinocamphone.



XIV X = OH
XVI X = H



V b

According to Schmidt (15), the hydrocarbons obtained from the *p*-toluenesulphonate of isopinocampheol by reaction with sodium ethoxide are mostly α-pinene and camphene. The hydrocarbons obtained similarly from the tosylate of neoisopinocampheol consist largely of α-pinene. This work needs reinvestigation because only the lowest-boiling fractions of hydrocarbon mixtures were analyzed for their α-pinene content. The observation that large amounts of α-pinene are obtained from both isopinocampheol and its epimer neoisopinocampheol indicate that *trans* elimination must be accompanied by side reactions. No inference regarding the configuration of pinocampheols can safely be drawn from these elimination experiments.

Schmidt (1) prepared the xanthate from pinocampheol and isopinocampheol by carrying out the first part of the preparation (reaction of the alcohol with sodium) at a comparatively low temperature to prevent isomerization before xanthate formation. Pyrolysis of pinocampheol xanthate afforded a mixture of hydrocarbons, 55% of which was α-pinene. The hydrocarbon from isopinocampheol xanthate was found to be essentially pure α-pinene. Since the Chugaev reaction is known to take place through *cis*-elimination, methyl and hydroxy groups should be *trans* to each other in both pinocampheol and isopinocampheol, provided no rearrangement had occurred during xanthate formation.

Conformational analysis and the Chugaev reaction, therefore, yield contradictory results in the case of isopinocampheol and neoisopinocampheol. One of the referees has pointed out that the conformation XIb for isopinocampheol accounts for the Chugaev reaction and also the equatorial nature of the hydroxy group.

If the conformation XIb be accepted for isopinocampheol, neoisopinocampheol should be represented by Xb or its inverted form Xa, and *trans*-pinocarveol should have the conformation XIV instead of VIII. In view of the severe steric hindrance in Xb, the preferred conformation should be Xa and neoisopinocampheol should show the properties of an equatorial hydroxy group, but, it does not. Further, it is difficult to see why β-pinene should prefer the more hindered conformation XV to XVI (*Cf.* 17).

It is evident that more data are required before a choice between the configurations X and XI for isopinocampheol can be made with certainty. Experimental work is in progress in this laboratory to determine unequivocally the steric relationship between the methyl and the hydroxy groups in isopinocampheol.

SUMMARY

The concept of axial and equatorial bonds has been used for examining the stereochemistry of pinocarveols and pinocampheols. The conformations derived for pinocarveols, isopinocampheol, and neoisopinocampheol are at variance with the configurations assigned to them by Schmidt partly on the basis of Auwers-Skita rules. The conformations deduced for pinocampheol and neopinocampheol lead to configurations identical with those indicated by Schmidt.

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