[CONTRIBUTION FROM THE APPLIED CHEMISTRY DEPARTMENT, INDIAN INSTITUTE OF TECHNOLOGY]

CONFORMATION OF TERPENES. III. VERBANOLS, VERBENOLS, AND VERBANONES

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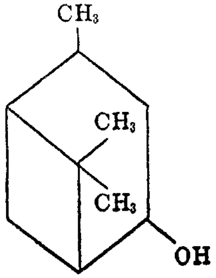
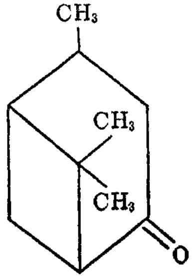
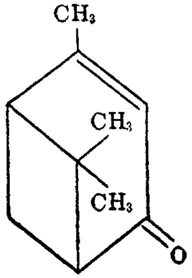
Verbanol (I) which possesses four centers of asymmetry two of which are connected by a methylene bridge, should be capable of existing as four stereoisomeric *dl*-pairs. Several verbanols have been reported in literature although their configurations have not been established (1). The precursors of these isomers are the verbanones (II), verbenone (III), and verbenols (IV).



I



II



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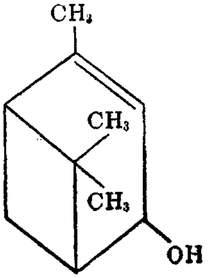
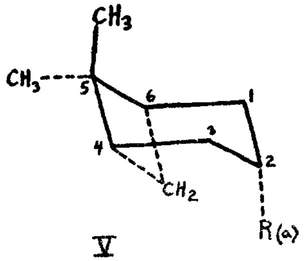


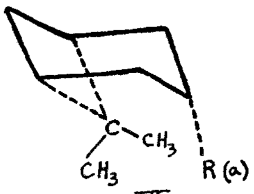
IV

Schmidt, Schulz, and Doll (2) have separated two stereoisomeric verbenols and have assigned to them configurations on the basis of the Auwers-Skita rules. Doubt has recently been cast on the validity of these rules when applied to 1,3-disubstituted cyclohexanes (3). It therefore seems to be of interest to examine the stereochemistry of the verbenols, verbanols, and verbanones 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 (4, 5) including terpenes like the menthols (4) and carvomenthols (6).

Of the two conformations (V and VI) possible for the fused ring system of pinane and its derivatives, V 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.)

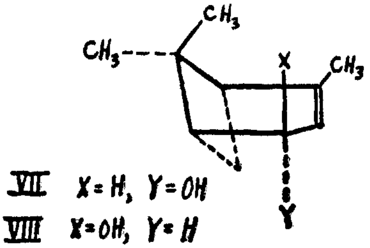


V



VI

Configuration of the verbenols. Of the two epimeric verbenols, m.p. 24° (VII) and m.p. 15.5° (VIII), obtained by the Meerwein-Ponndorf reduction of verbenone (III), the former shows a faster rate of esterification and therefore it must possess a less hindered hydroxy group than the latter. On making a molecular model of verbenol, it is found that carbon atoms 6, 1, 2, and 3 lie in one plane and the carbon atom 4 is not far from this plane. The methylene bridge and the *gem*-dimethyl group project above and below this plane in a more or less symmetrical manner. Hence, in verbenol, m.p. 24°, the hydroxy group should be *trans* to the bulky *gem*-dimethyl group; in verbenol, m.p. 15.5°, the hydroxy group and the *gem*-dimethyl group should be *cis* to each other.



VII X = H, Y = OH
VIII X = OH, Y = H

Conformation of the verbanones. Blumann and Zeitschel (7) obtained a verbanone (IX) by the oxidation of verbanol, m.p. 58°, in which the methyl group and the *gem*-dimethyl bridge are *trans* to each other (*vide infra*). The same ketone was prepared in a purer form by Wienhaus and Schumm (8) by the hydrogenation of verbenone (III) in the presence of palladium on animal charcoal. The Wolff-Kishner reduction of this ketone affords a pinane (8). Since the oxidation and reduction reactions at carbon 3 would not affect the steric position of the substituent on carbon 1, the conformation XIX can be assigned to this pinane.

Lipp (9) was the first to appreciate that pinane should exist as two stereoisomeric *dl*-pairs. He assigned the *cis* and *trans* configurations to isomeric pinanes on the basis of the rules of Auwers and Skita. Later Schmidt (10) derived the configurations of the pinanes and δ-pinenes from that of pinocamphone. The configuration of pinocamphone in its turn was assigned by Schmidt (11) on the basis of the rules of Auwers and Skita. From Table I it can be seen that the physical properties of the Wolff-Kishner reduction product of Blumann and Zeitschel's verbanone indicate it to be identical with the pinane to which the *trans* configuration

TABLE I

COMPARISON OF PHYSICAL CONSTANTS OF WOLFF-KISHNER REDUCTION PRODUCT AND PINANES

Substance	B.P., °C.	d_{20}	$[\alpha]_D$	n_D^{20}
Reduction product of IX (8)	168–170	0.8565	20.2	1.46058
trans-Pinane (10)	165–166.5	.8558	23.83	1.46181
cis-Pinane (10)	167–168	.8590	30.85	1.46325

TABLE II

COMPARISON OF VERBANONES

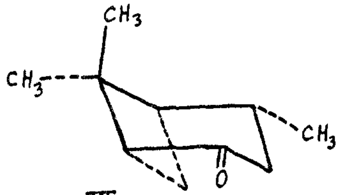
Compound	Verbanone			Verbanone Oxime		
	B.P., °C.	MM.	$[\alpha]_D$	B.P., °C.	MM.	$[\alpha]_D$
IX	104–105	20	+52.55	148–160 m.p. 88°	35	−30.5°[a] −23.76[b]
X	104–105	15	+68.80	138–139	15	10.25

[a] Before distillation. [b] After distillation.

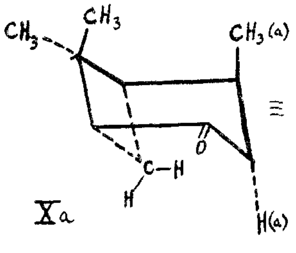
has been previously assigned. Auwers-Skita rules and conformational analysis, therefore, lead to the same configuration for pinanes.

Kahneman (12) prepared a verbanone (X) by the hydrogenation of verbenone (III) in presence of platinum black. A comparison of the properties of IX and X (see Table II) shows that they are distinct. Reduction of Kahneman's ketone X leads to the epimeric alcohols, isoverbanol and neoisoverbanol (*vide infra*)the xanthate of which affords a δ-pinene (XIV) which can be hydrogenated to *cis*-pinane (10). Therefore it is evident that Kahneman's ketone X is an impure sample of *cis*-verbanone and perhaps it should be renamed isoverbanone in keeping with the practice of naming isomeric ketones.

The conformation of *trans*-verbanone is illustrated by IX. For *cis*-verbanone two conformations Xa and Xb are possible. In our opinion Xa is to be preferred, because the steric interaction between the *gem*-dimethyl group and the axial hydrogen in Xb is likely to be greater than the steric interaction between the axial methyl groups in positions 1 and 5 in Xa.



IX



Xa

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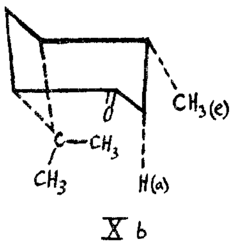
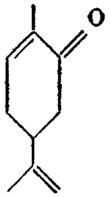


X b

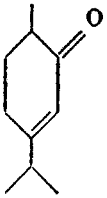
Conformation of verbanols. The reduction of (+)-verbenone (III) with sodium and moist ether or sodium and alcohol affords a verbanol of m.p. 58°, $[\alpha]_D$ 1.3°

(7). This type of reduction is known to yield predominantly the most stable of the isomers possible (4). The methyl and the hydroxy groups should therefore be assigned equatorial positions in the verbanol (XI) of m.p. 58°. Close analogies may be cited. Thus, the reduction of carvone (XV) with sodium and alcohol leads to (+)-dihydrocarveol (13) which can be hydrogenated to (+)-carvomenthol (14) in which the methyl and hydroxy groups occupy equatorial positions (6). On reduction with sodium and alcohol, carvenone (XVI) yields carvomenthol (15). Reduction of pulegone (XVII) with sodium and alcohol yields (−)-menthol (16) in which the isopropyl and the hydroxy groups are in equatorial positions (4). Hughson, Smith, and Read (17) reported that the sodium and alcohol reduction of *dl*-piperitone (XVIII) leads to a menthol of m.p. 39–41°. The fact that the m.p. of *dl*-menthol is 38° and that of *dl*-isomenthol is 53.5° seems to indicate that the reduction product was mainly *dl*-menthol. Read and Cook (18), however, isolated isomenthone in slight excess over menthone by oxidation of the crude reduction product. In view of their further observation that both isomenthone and menthone give predominantly menthol on reduction with sodium and alcohol, it is difficult to see how isomenthol and not menthol could be the major product in the sodium and alcohol reduction of piperitone. This work merits reinvestigation.

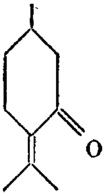
XIV



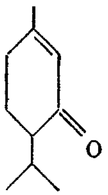
XV



XVI



XVII



XVIII

The observation that verbanol, m.p. 58°, is obtained in 63% yield by the sodium reduction of *trans*-verbanone IX (8) corroborates the assignment of the equatorial position to the hydroxy group in verbanol XI.

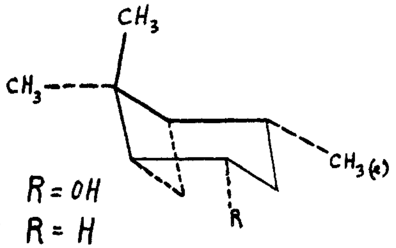
By the hydrogenation of verbanone X over platinum, Kahneman (12) obtained a (+)-*cis*-verbanol, m.p. 74–75°, $[\alpha]_D$ + 5.1° (hydrogen phthalate, m.p. 142–143°); by carrying out the reduction with sodium and alcohol he obtained a (+)-*trans*-verbanol, m.p. 69–70°, $[\alpha]_D$ + 11.7° (hydrogen phthalate, m.p. 163–164°). The hydroxy group should therefore be equatorial in *trans*-verbanol and axial in *cis*-verbanol. The observation (12) that the phthalate of Kahneman's *cis*-verbanol is saponified half as fast as the phthalate of *trans*-verbanol is in agreement with the conformation assigned.

By the hydrogenation of the verbenol (VII), m.p. 24°, Schulz and Doll (19) have obtained isoverbanol, m.p. 76°, $[\alpha]_D$ + 16° in benzene, which gives a *p*-nitrobenzoate, m.p. 95°, and a hydrogen phthalate, m.p. 190–191°. Similarly, from the verbenol (VIII), m.p. 15.5°, they have obtained neoisoverbanol, m.p. 74°, $[\alpha]_D$ + 5° in benzene (hydrogen phthalate, m.p. 142°). It has been pointed out that neoisoverbanol must be identical with Kahneman's (+)-*cis*-verbanol (1).

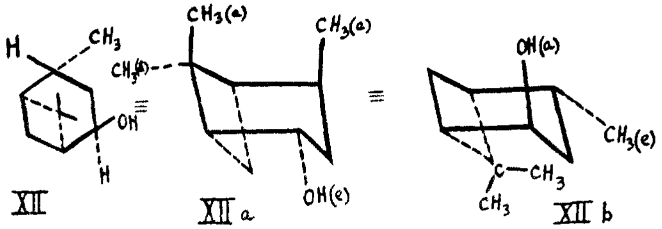
In our opinion, the (+)-*trans*-verbanol of Kahneman is an impure sample of isoverbanol. Since Kahneman's verbanone was probably contaminated with *trans*-verbanone, isoverbanol is likely to contain the verbanol (XI) as an impurity.

By catalytic hydrogenation in the presence of palladium, Wienhaus and Schumm (8) converted crude ( )-verbenol into a mixture of isomers of verbanol from which a crystalline phthalate, m.p. 127°, was separated, the steric purity of which was not established.

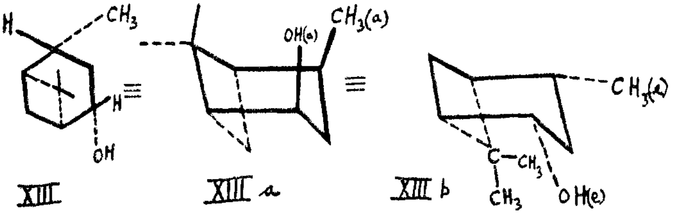
Since isoverbanol and neoisoverbanol are obtained by the reduction of *cis*-verbanone, the methyl group in these epimeric alcohols must be *cis* to the *gem*-dimethyl bridge. The relative configuration of the hydroxy and the *gem*-dimethyl group must be the same in isoverbanol as in the verbenol (VII), because the former is obtained by the catalytic reduction of the latter. For the same reason, the hydroxy group and the *gem*-dimethyl group must be *cis* to each other in both verbenol VIII and neoisoverbenol. The configuration of isoverbanol and neoisoverbanol can therefore be represented by XII and XIII respectively.



XI R = OH
XIV R = H



XII XIIa XIIb



XIII XIIIa XIIIb

For each of the configurations XII and XIII, there are two possible conformations. It has been already pointed out that the hydroxy group in isoverbanol should be equatorial in position. This rules out conformation XIIb for isoverbanol and consequently conformation Xb for *cis*-verbanone. If Xb did represent the conformation of *cis*-verbanone, sodium and alcohol reduction would have afforded an alcohol of conformation XIIIb in which the hydroxy group would have been equatorial and hence *cis* to the *gem*-dimethyl bridge. But, it has been deduced that the hydroxy group is *trans* to the *gem*-dimethyl bridge in isoverbanol—the sodium and alcohol reduction product of *cis*-verbanone. The conformation of *cis*-verbanone is therefore correctly represented by Xa.

More data, particularly (infrared) spectroscopic data, would be required for deciding between conformations XIIIa and XIIIb for neoisoverbanol.

(+)-Verbanol, m.p. 58°, (+)-isoverbanol, m.p. 76°, and (+)-neoisoverbanol, m.p. 74°, belong to three out of the four possible stereoisomeric pairs; the fourth—neoverbanol—seems to be unreported. It is possible, however, that the crystalline hydrogen phthalate, m.p. 127°, prepared by Wienhaus and Schumm (8) correspond to neoverbanol.

SUMMARY

The method of conformational analysis has been used for deducing the stereochemistry of the verbanols, verbenols, and verbanones. It has been inferred that the verbanone described by Blumann and Zeitschel is *trans*. It has further been suggested that Kahneman's verbanone is the impure *cis* form and his (+)-*trans*-verbanol is Schulz and Doll's isoverbanol contaminated with isomers. The presently accepted configurations of the verbenols and pinanes based on Auwers-Skita rules have been found to be in agreement with the conformations derived for them.

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