Synthesis and odor characteristics of some 6,6-dimethylbicyclo [3.1.0] hexane derivatives

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Monoterpenic compounds containing the bicyclo[3.1.0]hexane system, for example, sabinene, sabinene hydrate, thujone, thujyl alcohol, or umbellulone, are the substantial sensorial components of many essential oils of plants from the Cupressaceae, Compositae and Labiatae family.[1,2] Synthetic analogs of these compounds, and especially their odor qualities, are relatively little known. During several years of studies on the chemical transformations and stereochemistry of the carane system, some simple preparative methods of synthesis of bicyclo[3.1.0]hexane derivatives from 3-carene were elaborated.[3-7] Utilizing these methods and the standard means of extension of the side chains, a series of new compounds, containing the bicyclo[3.1.0]hexane system with various substituents at the 2- and 3-position, was synthesized.

The starting material for all syntheses was (+)-3-carene (1), which gave, through intermediate 3,4-dibromocarene, trans-3-acetyl-6,6-dimethylbicyclo[3.1.0]hexane (2),[3] the substrate for syntheses of further derivatives substituted at C-3. Ketone (2) was converted into acetate (3) by the Baeyer-Villiger oxidation, and (3) into alcohol (4). This alcohol gave 6,6-dimethylbicyclo[3.1.0]hexan-3-one (5)[4] by oxidation. The degradation of ketone (2) to acid (6)[3] and its reduction with lithium aluminium hydride (LAH) gave alcohol(7).[5]

The derivatives substituted at C-2 were obtained from 2-acetyl-6,6-dimethylbicyclo[3.1.0]hex-2-ene (9) which was also prepared from (+)-3-carene (1) accord-

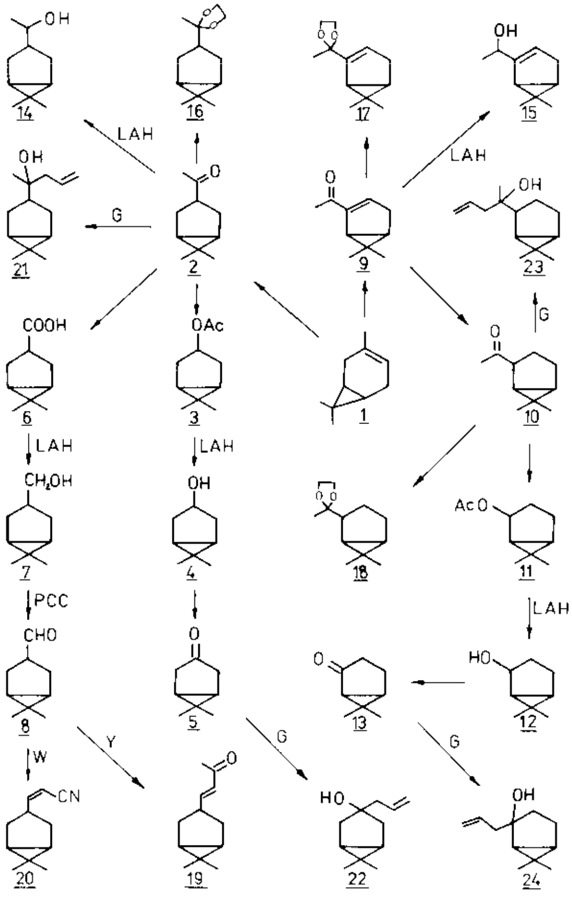
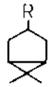
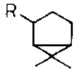
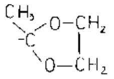


TABLE I

Odor characteristics of compounds from group of 2- and 3-substituted 6,6-dimethylbicyclo/3.1.0/hexane derivatives

Nr.	R		
1	$-OH$	4 $C_8H_{14}O$ M.w.126,2 intensive,camphor-like with leaf-green note	12 $C_8H_{14}O$ M.w.126,2 intensive,chemical with camphoric note
2	$-CH_2OH$	7 $C_9H_{16}O$ M.w.140,2 sharp, fatty with mildew-note	————
3	$-OCOCH_3$	3 $C_{10}H_{16}O_2$ M.w.168,2 intensive,fruity with raspeberry note	11 $C_{10}H_{16}O_2$ M.w.168,2 intensive,peppermint-fruity
4	$-COCH_3$	2 $C_{10}H_{16}O$ M.w.152,2 intensive, caraway-aniseed	10 $C_{10}H_{16}O$ M.w,152,2 intensive, menthone-like
5	$-CH(OH)CH_3$	14 $C_{10}H_{18}O$ M.w.154,3 medium-intensive, caraway-aniseed	————
6	$-CH=CHCN$	20 $C_{11}H_{15}N$ M.w.161,3 intensive,cumenic with aniseed note	————
7	$-CH=CHCOCH_3$	19 $C_{12}H_{18}O$ M.w.178,3 β-ionone-like with woody note	————
8	$CH_3\overset{\vert}{C}(OH)CH_2CH=CH_2$	21 $C_{13}H_{22}O$ M.w.194,3 medium-intensive, fungal, agreeable	23 $C_{13}H_{22}O$ M.w.194,3 intensive,similar to lupin flower with woody note
9		16 $C_{12}H_{20}O_2$ M.w.196,3 intensive, remarkably caraway	18 $C_{12}H_{20}O_2$ M.w.196,3 balsamic-camphoric, fresh

ing to Matsui and coworkers.[6] Ketone (9) gave a mixture of cis and trans(*) ketones (10) in a ratio of 9:1 by hydrogenation in the presence of Raney-nickel under pressure.[7] This mixture was converted into homogenous 6,6-dimethylbicyclo[3.1.0]-hexan-2-one (13) by a reaction sequence analogical to the transition from (2) to (5).[7]

Corresponding alcohols (14) and (15) were obtained in the yield of 95% from ketones (2) and (9), respectively, by reduction with LAH. From ketones (2), (9) and (10) corresponding ketals (16), (17) and (18), respectively, were obtained in the yield of ca 80% by the classical reaction with ethylene glycol in the presence of catalyst (p-toluenesulfonic acid). The oxidation of alcohol (7) with pyridine chlorochromate (PCC) gave trans-6,6-dimethylbicyclo[3.1.0]hexan-3-carboxaldehyde (8) in the 70% yield.[8] This aldehyde was used to carry out the modified Wittig reactions. By the application of a stereoselective method, (8) was converted into (E)-4-(trans-6,6-dimethylbicyclo-[3.1.0]hex-3-yl)-4-buten-2-one (19) means of acetonylidenetriphenylphosphorane (Y) in the yield of 40%.[8]

On the other hand, the Wittig-Horner reaction[9] of (8) with diethyl cyanomethanephospho-

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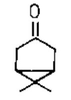
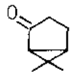
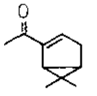
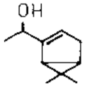
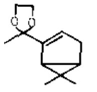
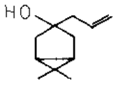
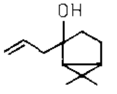
*Configuration cis and trans denotes the position in relation to the cyclopropane ring.

TABLE II

1		5 $C_8H_{12}O$ M.w.124,2 sharp, penetrating, camphoric
2		13 $C_8H_{12}O$ M.w.124,2 sharp, penetrating, camphoric-fruity
3		9 $C_{10}H_{14}O$ M.w.150,2 intensive, turpentine--resinous
4		15 $C_{10}H_{16}O$ M.w.152,3 medium-intensive,fruity with peppermint note
5		17 $C_{12}H_{18}O_2$ M.w.194,3 intensive, fresh with resinous note
6		22 $C_{11}H_{18}O$ M.w.166,3 fungal with floral note, agreeable
7		24 $C_{11}H_{18}O$ M.w.166,3 intensive,menthol--cineol-like

dnate (W) gave a mixture of (Z)- and (E)-2-(trans-6, 6-dimethylbicyclo[3.1.0]hex-3-yl)-2-ethen-1-carbonitrile (20), the yield being 71%.

Bicyclic ketones (2), (5), (10) and (13) were subjected to the Grignard reaction with allylmagnesium bromide. The synthesis carried out in the usual manner resulted in obtaining corresponding tertiary alcohols (21), (22), (23) and (24).

The course of all reactions and the purity of products obtained were controlled by means of TLC and GLC. Structure of the mentioned compounds was confirmed by the IR- and NMR-spectroscopic methods. The odor characteristics of the compounds were set together in Tables I and II.

Analysis and comparison of odors of the compounds placed in both tables bring to note some interesting relationships between structure and odor in the group of 6,6-dimethylbicyclo[3.1.0]hexane derivatives. Both bicyclic alcohols (4) and (12) reveal intensive chemically-green odors and are not interesting for perfumery—similarly alcohol (7).

Oxidation of the hydroxyl to carbonyl group causes a distinct change of odor of ketones (5) and (13) to penetrating, camphor-like odors—of little interest for perfumery. Acetates (3) and (10) have intensive fruity odors according to the expectations based on observations of other esters of acetic acid.[10]

Introduction of a chain containing two carbon atoms at C-3 to the 6,6-dimethylbicyclo[3.1.0]hexane system results in the marked change of the sensorial properties and in an arising remarkably caraway-aniseed odor with various notes in (2) and (14). However the same substituents introduced into the 2-position lead to compounds having a peppermint odor (10), (15).

Ethylenic ketals (16), (17) and (18) obtained from ketones (2), (9) and (10) are characterized by milder and more agreeable odors than the starting materials.

Further extension of the side chain (more than two carbon atoms) causes disappearance of the caraway-aniseed or peppermint note and appearance of floral-woody or fungal odors, mild, agreeable, medium-intensive with various notes. The most interesting among them is ketone (19) having a β-ionone-like odor with a well-marked woody note.

It can be generally stated that the odor of the compound group under investigation, containing 8-10 carbon atoms in the molecule, is strongly influenced by the 6,6-dimethylbicyclo[3.1.0]hexane system which decides their common characteristic camphoric-penetrating odor. This effect weakens with extension of the side chain and then the odor becomes markedly milder and the floral, fungal and woody notes appear.

The studies carried out allow speculation that some further interesting odoriferous compounds may be found in the group of 6,6-dimethylbicyclo[3.1.0] hexane derivatives.

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