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A Study on the Structure/Odour Relationship of Norpatchoulenol and Patchoulol, II [1]

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Summary. In continuation of studying structure/odour relationships of odourous compounds, the tricyclic patchouli-system is degraded to bicyclic structures by cutting the C_6-C_7 bond (**8** and **9**) or by omitting the methylene group of C_{11} (**12**). The olfactory properties are studied and described by using the key odour descriptors – woody, earthy, and camphoraceous.

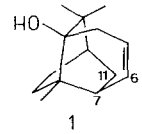
Keywords. Structure/odour relationships; Norpatchoulenol; Patchoulol; Ultrasound.

Untersuchung über Struktur/Geruchs-Beziehungen bei Norpatchoulenol und Patchoulol, 2. Mitt.

Zusammenfassung. In Fortführung der Untersuchungen über Struktur/Geruchs-Beziehungen wird das tricyclische Patchouli-Gerüst durch Lösen der C_6-C_7 Bindung (in **8** und **9**) bzw. durch Entfernung der C_{11}-Methylen-Gruppe (in **12**) auf ein bicyclisches System reduziert. Die Geruchseigenschaften werden mit Hilfe der Hauptgeruchsmerkmale – holzig, erdig und camphrig – beschrieben.

Introduction

In the preceeding study on patchouli compounds the influence of the bridge head bonded methyl group and of the C_5-C_6 double bond to the odourous character was studied [1]. It is known that excessive degradation of the tricyclic patchouli system leads to a loss of the harmonious playing together of the woody, earthy, and camphoraceous notes [2, 3]. These three key odour descriptors are characteristic for patchouli odour. Therefore in this study a moderate degradation to bicyclic partial structures is realized by cutting the C_6-C_7 bond in norpatchoulenol (**1**) and patchoulol (**2**). Besides that a bicyclic structure is obtained by omitting the methylene group of C_{11} in norpatchoulenol (**2**). The consequences of these structural modifications have been studied and the olfactory properties of these compounds discussed.



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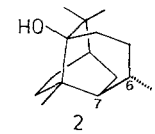

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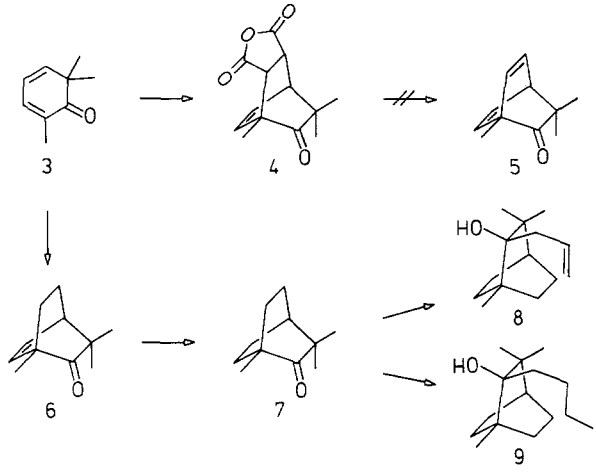
Results and Discussion

Syntheses of the C_6-C_7 seco Patchouli Compounds

As key substance for the syntheses of the C_6-C_7 *seco* Patchouli derivatives **8** and **9** served the bicyclic ketone **7** for which the Diels-Alder adduct **4** [4] of 2,6,6-trimethylcyclohexadienone (**3**) [5] seemed to be a good starting compound. However, neither lead tetraacetate [6] nor bis-triphenylphosphin-dicarbonyl-nickel, a very potent catalyst for decarboxylation reactions [7–9], could enforce an oxidative decarboxylation yielding **5** which should be hydrogenated in the following to **7**. But by Diels-Alder reaction of **3** with ethylene [10] and subsequent hydrogenation the desired ketone **7** was obtained in high yields. Further reaction with allyllithium (in situ prepared from allyltriphenyltin and phenyllithium) [11] or butyllithium furnished the desired carbinols **8** and **9**.



Synthesis of Norpatchoulol Analogue by Omitting C_{11}

The structure of the bicyclic compound **12** is adequate to norpatchoulenol missing the C_{11} methylene group. The synthesis of **12** started from the commercially available 2,6,6-trimethylcyclohexanone (**10**), which was α-alkylated by *cis*-1,4-dichlorobutene to **11**. The following crucial step was the ultrasonic promoted Barbier like cyclisation with lithium [12]. The sterically hindrance of the axially bonded methyl groups at C_2 and C_6 in **11** and also the somewhat rigid *cis*-butenechloride group let expect the formation of the *cis* annellated product **12**. Indeed after sonification a 0.1 *m* solution of chloroketone **11** in *THF* in the presence of 4 equivalents of lithium (wire) for 45 minutes only one isomere could be detected by GC/MS monitoring. Nevertheless the yield of **12** was reduced by retro-reactions furnishing educt **10** and by the formation of polymerisation byproducts.

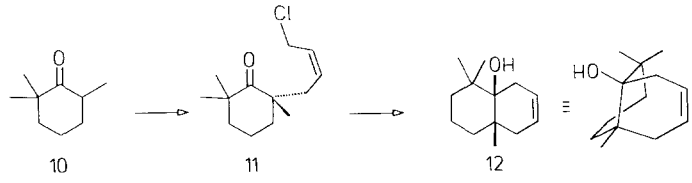


Table 1. Odour properties of compounds (+)-**1**, (−)-**2**, and (±)-**8**, **9**, **12**

	Woody	Earthy	Camphoraceous
(+)-**1**[a]	+ + +	+ + +	+ + +
(−)-**2**[a]	+ + +	+ +	+ + +
(±)-**8**	(+)	+ + +	+ +
(±)-**9**	+ + + +	(+)	+ +
(±)-**12**	+	−	+ + + +

[a] see [2]

Organoleptic Analyses

The C_6-C_7 cutting of the tricyclic norpatchoulenol system (**8**) leads to a decline of the woody odour, the total impression is a "hard" above all earthy odour with a strong camphoraceous bynote. Contrary to this, **9** exhibits a pleasant intense woody odour with nearly no earthy and only a bit camphoraceous bynote.

Compound **12** imparts predominantly an intense camphoraceous odour with a weak woody bynote. The results are summarized in Table 1 and compared to norpatchoulenol and patchoulol [2].

Experimental Part

Ultrasound reactions were carried out in an Elma T 480/H-2 cleaning bath with 35 kHz at room temperature. Proton magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker-AC-80-Spectrometer. Chemical shifts are quoted in δ values (ppm) with tetramethylsilane (*TMS*) as an internal standard. Infrared spectra (IR) were recorded on a Perkin Elmer-298-Spectrometer (values in cm^{-1}), mass spectra on a GC/MS-Hewlett Packard instrument (GC; 5890; MS: 5970). Chromatography was carried out on silica gel coated thin layer plates from Merck (13793).

1,3,3-Trimethylbicyclo[2.2.2]oct-5-en-2-one (**6**)

6.8 g (50 mmol) 2,6,6-trimethylcyclohexadienone (**3**) dissolved in 15 ml benzene are heated in an ethylene charged autoclave at 80 atm at 85°C for 2.5 h. The solvent is distilled off and the residue is purified by bulb to bulb distillation. Yield 7.5 g (91%); $C_{11}H_{16}O$ (164.25). ^{1}H-NMR ($CDCl_3$): 1.04 (s, 3 H), 1.08 (s, 3 H), 1.20 (s, 3 H), 2.50 (m, 2 H), 5.75 (m, 1 H), 6.50 (m, 1 H) . IR (NaCl; liquid film): 1715. MS (*m*/e; r. i.); 164 (M^+, 4), 121 (18), 94 (100), 93 (24), 91 (13), 79 (60), 77 (15), 72 (12).

1,3,3-Trimethylbicyclo[2.2.2]octan-2-one (**7**)

1.5 g (9 mmol) **6** is hydrogenated in ethyl acetate with palladium 10% on carbon. The catalyst is filtered off and the filtrate concentrated in vacuum. Yield 1.45 g (96%); $C_{11}H_{18}O$ (166.26). ^{1}H-NMR ($CDCl_3$): 0.91 (s, 3 H), 1.12 (s, 6 H), 1.4 − 2.0 (m, 9 H). IR (NaCl; liquid film): 1720. MS (*m*/e; r. i.): 166 (M^+, 16), 95 (44), 94 (100), 81 (18), 79 (15), 67 (19), 55 (16).

1,3,3-Trimethyl-2(2-propenyl)bicyclo[2.2.2]octan-2-ol (**8**)

A solution of 1.3 g (3.3 mmol) of allyltriphenyltin in 10 ml ether is treated under vigorous stirring with 0.67 ml (3.3 mmol) 2 *m* phenyllithium-solution (ether/hexane) and stirred for 30 min. After the

addition of a solution of 0.5 g (3 mmol) **7** in ether the resulting mixture is refluxed for 1 h. After cooling to room temperarure dist. water is added and the mixture extracted with ether, dried over $MgSO_4$, concentrated in vacuo and distilled in a Kugelrohr apparatus. Further purification is done by prep. *TLC* with ligroin/ethylacetate (80/20). Yield: 363 mg (58%); $C_{11}H_{24}O$ (208.34). ^{1}H-NMR ($CDCl_3$): 0.78 (s, 3 H), 0.97 (s, 3 H), 1.13 (s, 3 H), 5.07 (m, 1 H), 5.23 (m, 1 H), 5.84–6.37 (m, 1 H). IR (NaCl; liquid film): 3 58O, 1 635. MS (*m*/e; r. i.): 208 (M^+, 8), 167 (59), 149 (51), 121 (72), 95 (52), 94 (51), 81 (56), 55 (69), 43 (80), 41 (100).

2-Butyl-1,3,3-trimethylbicyclo[2.2.2]octan-2-ol (**9**)

A solution of 0.5 g (3 mmol) **7** in 5 ml ether is treated at 0°C a in argon atmosphere with 2.1 ml (3.3 mmol) 1.6 *m* buthyllithium-solution (hexane). After further stirring for 2 h at 0°C sat. NH_4Cl solution is added, the mixture extracted with ether, dried over $MgSO_4$ and concentrated in vacuo. The residue is purified by prep. *TLC* with ligroin/ethylacetate (80/20). Yield: 420 mg (62%); $C_{15}H_{28}O$ (224.38). ^{1}H-NMR ($CDCl_3$): 0.75 (s, 3 H), 0.94 (t, J=7.25 Hz, 3 H), 1.05 (s, 3 H), 1.10 (s, 3 H). IR (NaCl; liquid film): 3 600, 1 465. MS (*m*/e; r. i.): 224 (M^+, 6), 128 (76), 121 (100), 94 (62), 83 (85), 81 (58), 57 (56), 55 (55), 43 (67).

2,6,6-Trimethyl-2-(4-chlorobut-2(Z)-enyl)-cyclohexanone (**11**)

To a solution of 3.1 ml (22 mmol) diisopropylamine in 20 ml absol. ether are added under stirring at −78°C 13.75 ml 1.6 *m* buthyllithium-solution (hexane). After complete addition the solution is stirred at room temperature for 30 min, cooled to −78°C and treated with 2.8 g (20 mmol) 2,6,6-trimethyl-cyclohexanone (**10**). After stirring for 1 h at room temperature the solution is treated at −78°C with 2.6 ml (25 mmol) *Z*-1,4-dichlorobutene. The mixture is allowed to warm up to room temperature and after stirring for 16 h it is hydrolized by addition of a sat. NH_4Cl solution. After extraction with ether, drying over $MgSO_4$ and concentration in vacuo the residue is fractionated by bulb to bulb distillation. B. $p._1$ 100°C. Yield: 1.9 g (42%); ^{1}H-NMR ($CDCl_3$): 1.08 (s, 3 H), 1.13 (s, 6 H), 1.70 (m, 6 H), 2.33 (m, 2 H), 4.09 (d, J=8.3 Hz, 2 H), 5.30–5.90 (m, 2 H). IR (NaCl; liquid film): 1 695, 75O. MS (*m*/e; r. i.): 193 (M^+-Cl, 100), 109 (17), 97 (16), 95 (23), 81 (28), 69 (42), 55 (45). $C_{13}H_{21}ClO$ (228.76); calc. C 68.26, H 9.25, Cl 15.50; found C 68.15, H 9.43, Cl 15.21.

6,10,10-Trimethylbicyclo[4.4.0]dec-3-en-1-ol (**12**)

To a solution of 2.5 g (11 mmol) **11** in 110 ml absol. *THF* are added 0.3 g finely cut pieces of lithium wire. The mixture is sonificated with ultrasound for 45 min and subsequently filtered through glass wool, extracted with water, dried over $MgSO_4$ and evaporated. The residue is rectified by bulb to bulb distillation at 1 torr (forerun at 50°C, **12** at 95°C). The distillate is purified by prep. *TLC* with ligroin (5-fold development). Yield: 445 mg (21%); $C_{13}H_{22}O$ (194.32). ^{1}H-NMR ($CDCl_3$): 0.99 (s, 6 H), 1.03 (s, 3 H), 5.56 (m, 2 H). IR (NaCl; liquid film): 3 500, 1 670. MS (*m*/e; r. i.): 194 (M^+, 18), 140 (60), 125 (39), 110 (73), 109 (100), 95 (26), 55 (25), 43 (37).

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