156. A Study on the Odour/Structure Relationship of Patchoulol and Norpatchoulenol[1])

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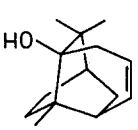
In continuation of studying structure/activity relationships of odorous compounds, the influence of the bridgehead-bonded Me group of (+)-norpatchoulenol (**1**) and (−)-patchoulol (**2**) and the olfactory properties of the corresponding unsaturated and saturated derivatives (±)-**3**, (±)-**4** and (±)-**5**, (±)-**6**, respectively, are studied. The key odour descriptors – wood, earth, and camphor – are used for classification.

Introduction. – Patchouli oil, which is obtained by steam destillation of the dried leaves of *Pogostemon* cablin, is an oil of considerable importance in the cosmetic industry. The harmonious playing together of the woody, earthy, and camphoraceous notes renders this essential oil to a favourite and important ingredient in perfume compounding. This fact is reflected by a world production of more than 500 tons per annum [1]. Moreover, there is no commercially available synthetic substitute for this essential oil.

The two sesquiterpenic alcohols norpatchoulenol (+)-**1** and patchoulol (−)-**2** are the principal cause of the typical patchouli odour. It is an astonishing fact that there exist only three detailed examinations dealing with structure/activity relationship of these two compounds [2]. *Näf et al.* studied the influence of chirality to the olfactive properties of **2**, exhibiting that only (−)-**2** produces a strong and typical patchouli scent, while (+)-**2** has a much weaker, nearly indefineable odour. *Mookherjee et al.* examined the question, which simplification of the tricyclic patchouli system is possible generating a patchouli-like aroma, successively degrading the tricyclic nucleus to a bicyclic and at least to a monocyclic partial structure. *Weyerstahl et al.* synthesized numerous compounds with a monocyclic partial structure of the tricyclic patchouli system. In this study, it was found that the size of the molecule, substitution pattern, existance of a hindered tertiary group, and the rigidity of structure are similarity determinations of the patchouli-aroma character. In the following examination, the influence of the bridgehead-bonded Me group of (+)-**1**



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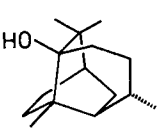

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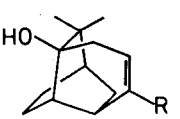
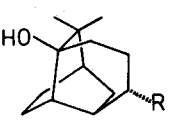


3 R = H
4 R = CH_3



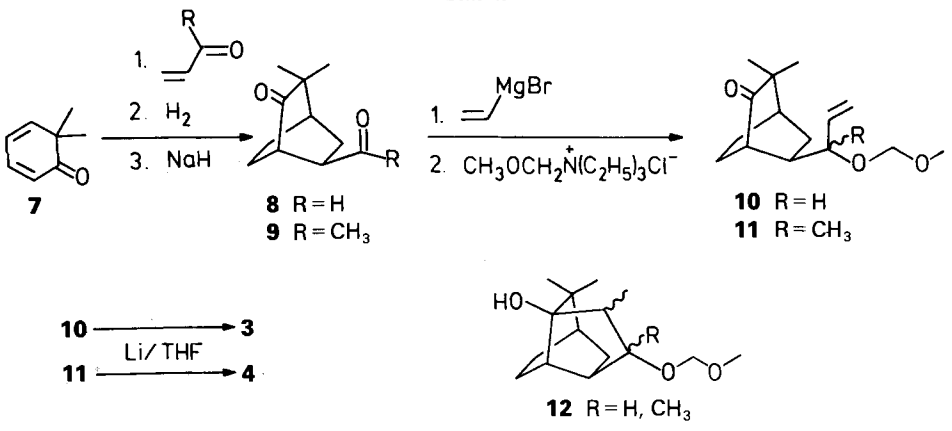
5 R = H
6 R = CH_3

[1]) Presented in part at the '11th Congress of Essential Oils, Fragrances and Flavours', New Delhi, 12–16th November, 1989.

and (−)-**2** is studied, and the olfactory properties of the corresponding unsaturated and saturated derivatives (±)-**3**, (±)-**4** and (±)-**5**, (±)-**6**, respectively, are described.

Results and Discussion. – According to previous studies [3], a short route to (±)-**3**–(±)-**6** should be accessable by radical induced S_N2' cyclization [4]. Starting from dienone **7** [5], the hydrogenated *Diels-Alder* adducts had to be epimerized to the *syn*-compounds **8**/**9** (*Scheme*). Because of the last and crucial cyclization step, the conversion to a *syn*-oriented side chain was a necessity.

Scheme



Astonishing there was no great influence to the epimerization rate neither by the kind of base used nor by extending the reaction time. The *syn*/*anti*-ratio usually ranges at *ca.* 50%, but it was increased satisfactorily by unusual workup. Dropping the NaH/THF suspension into a buffered two-phase system Et_2O/H_2O raised the *syn*/*anti*-ratios in both cases to *ca.* 85–90%, furnishing **8**/**9** in high yields.

Grignard reactions of **8**/**9** followed by protection of the resulting tertiary alcohol as methoxymethyl ether leads to **10**/**11**.

The reaction of ketyls with double bonds is scarcely used [6]. Generating ketyls from **10**/**11** by using highly dispersed Li in THF solely yielded the desired products **3**/**4** resulting from a S_N2' reaction; no by-products like **12**, resulting from radical addition to the double bond, could be detected. However, a selective route leads to **12** by using Na in refluxing toluene [7]. Moreover, using Li gave far better yields of **3**/**4** than Na. In addition, GC/MS monitoring exhibited that both diastereoisomeric ethers of **10**, but only one of **11**, underwent cyclization.

The most remarkable and balanced odorous impression is displayed by the norpatchoulol analogue (±)-**3** and the patchoulol analogue (±)-**6**. The absence of the bridgehead-bonded Me groups lead in both cases to an increase of the woody character and to a decline of the camphoraceous note. Compound (±)-**3** has an intense odour – this is in accordance with results of *Mookherjee et al.* [2], because they demonstrated that the existence of a double bond located there would intensify the strength of odour – with a strong earthy and, above all, woody note, and only a weak camphoraceous by-note.

The patchoulol analogue (±)-**6** has a significantly weaker intense odour with a remarkable pleasant warm woody note, again only with a weak camphoraceous by-note.

The results are summarized in the *Table* where the key odour descriptors of (±)-**3**–(±)-**6** are compared with the naturally occurring terpenes (+)-**1** and (−)-**2**.

Table. *Odour Properties of Compounds* (+)-**1**, (−)-**2**, *and* (±)-**3**–(±)-**6**

	Wood	Earth	Camphor
(+)-**1**[a])	+++	+++	+++
(−)-**2**[a])	+++	++	+++
(±)-**3**	++++	+++	+
(±)-**4**	++	+++	+
(±)-**5**	+	+++	++++
(±)-**6**	++++	++	+

[a]) See [2].

I am indepted to Mr. *D. Braun*, chief perfumer of *Dragoco-Vienna* for the organoleptic analyses of all new compounds. I also acknowledge with gratitude the kindly interest of *Dragoco-Vienna* in this work. I wish to thank Dr. *J. Zak* (Inst. of Phys. Chemistry) for the microanalyses and Doz. Dr. *A. Nikiforov* (Inst. of Org. Chemistry) for recording the mass spectra.

Experimental Part

General. S. [8].

syn-*5,5-Dimethyl-6-oxobicyclo[2.2.2]octane-2-carbaldehyd* (**8**). 1. anti-*8,8-Dimethyl-7-oxobicyclo[2.2.2]oct-5-ene-2-carbaldehyd.* A mixture of 14.52 g (0.12 mmol) of *6,6-dimethylcyclohexa-2,4-dienone* (**7**) [5] and 13.44 g (0.24 mol) of acroleine in 12 ml of benzene were refluxed for 3 h in the presence of a small amount hydrochinone. After concentration under reduced pressure, the residue was distilled in a *Kugelrohr* apparatus at 76°/0.01 Torr yielding 19.0 g (89%). IR (NaCl, liquid film): 1715, 1730. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.08 (*s*, 3H); 1.13 (*s*, 3H); 1.83 (*m*, 1H); 2.23 (*m*, 1H); 2.73 (*m*, 1H); 2.90 (*m*, 1H); 3.57 (*m*, 1H); 6.03 (*m*, 1H); 6.60 (*m*, 1H); 9.57 (*s*, 1H). MS: 178 (12, M^+), 122 (14), 121 (22), 107 (29), 79 (100), 77 (28), 70 (74), 43 (68). Anal. calc. for $C_{11}H_{14}O_2$ (178.23): C 74.13, H 7.92; found: C 73.90, H 8.08.

2. anti-*5,5-Dimethyl-6-oxobicyclo[2.2.2]octane-2-carbaldehyd.* The adduct (9.82 g, 55 mmol) was hydrogenated in AcOEt with Pd/C yielding 9.35 g (94%) of product. Bp. 116°/0.5 Torr. IR (NaCl, liquid film): 1715, 1725. ^{1}H-NMR (90 MHz, $CDCl_3$): 1.20 (*s*, 6H); 2.73–3.0 (*m*, 2H); 9.73 (*s*, 1H). MS: 180 (28, M^+), 107 (49), 86 (38), 79 (100), 70 (58), 67 (64), 43 (64). Anal. calc. for $C_{11}H_{16}O_2$ (180.25): C 73.30, H 8.95; found: C 73.00, H 9.01.

3. Hydrogenated adduct (9.0 g, 50 mmol) dissolved in 15 ml of THF, was added to a suspension of 1.40 g (60 mmol) of NaH in 20 ml of THF at 0° and refluxed for 2 h. The cooled mixture is added dropwise to a slow stirred mixture of 300 ml of Et_2O and 362 ml of H_2O containing 48 g of KH_2PO_4 and 54.5 g of Na_2HPO_4. Extraction with Et_2O and concentration yielded after distillation 7.38 g (82%) of **8** (*syn/anti* 89:11). IR (NaCl, liquid film): 1720. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.04 (*s*, 3H); 1.14 (*s*, 3H); 9.59 (*s*, 1H). MS: 180 (29, M^+), 81 (62), 79 (57), 69 (54), 67 (78), 55 (50), 43 (49), 41 (100). Anal. calc. for $C_{11}H_{16}O_2$ (180.25): C 73.30, H 8.95; found: C 73.30, H 9.00.

*6-*syn-*Acetyl-3,3-dimethylbicyclo[2.2.2]octan-2-one* (**9**). Compound *anti*-**9** (16.30 g, 84 mmol) [4] was treated with 3.37 g (140 mmol) of NaH in 60 ml of THF and worked up as described above: 16.1 g (98%) of **9** (*syn/anti* 86:14). Spectral data: see [3]. Anal. calc. for $C_{12}H_{18}O_2$ (194.27): C 74.17, H 9.34; found: C 74.03, H 9.41.

*6-*syn-*[1-(Methoxymethoxy)prop-2-enyl]-3,3-dimethylbicyclo[2.2.2]octan-2-one* (**10**). Compound **8** (7.0 g, 39 mmol) in 10 ml of THF was treated with 50 ml of 1M (50 mmol) vinyl magnesium bromide soln. in THF for 1 h at r.t. After usual workup, the obtained product was dissolved in 150 ml of MeCN and 15.4 g (85 mmol) of triethyl(methoxymethyl)ammonium chloride (Chlor-TEMMA [9]) were added and afterwards refluxed for 24 h. The cooled mixture was extracted with Et_2O, dried, and concentrated *in vacuo*, yielding 6.16 g (63%) of crude product which was purified by chromatography on silica gel (ligroin/AcOEt 90:10): 4.1 g (42) of pure **10**. IR (NaCl,

liquid film): 1705, 1135, 1080, 1010. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.14 (*s*, 6H); 1.4–2.3 (*m*, 9H); 3.37 (*s*, 3H); 3.42 (*s*, 2H); 4.36–4.8 (*m*, 2H); 5.1–5.7 (*m*, 2H). MS: 252 (1, M^+), 123 (18), 81 (15), 79 (13), 67 (34), 55 (10), 45 (100). Anal. calc. for $C_{15}H_{24}O_3$ (252.35): C 71.39, H 9.59; found C 71.24, H 9.64.

2,2-Dimethyltricyclo[5.3.1.0^{3,8}]undec-5-en-3-ol (**3**). Compound **10** (1.26 g, 5 mmol) was refluxed in 15 ml of THF containing 175 mg (25 mmol) of finely dispersed Li for 2 h. To the cooled suspension, H_2O is added cautiously. After all Li is destroyed, the mixture is extracted with Et_2O, washed with dil. HCl, and sat. $NaHCO_3$ soln., dried, and concentrated. The residue is chromatographed an silica gel (ligroin/Et_2O 80:20) yielding 605 mg (63%) of **3**. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.1 (*s*, 6H); 5.4–5.9 (*m*, 2H). MS: 192 (42, M^+), 131 (33), 123 (31), 108 (100), 95 (44), 91 (31), 79 (32), 55 (33). Anal. calc. for $C_{13}H_{20}O$ (192.30): C 81.20, H 10.48; found: C 80.91, H 10.58.

2,2-Dimethyltricyclo[5.3.1.0^{3,8}]undecan-3-ol (**5**). Compound **3** (250 mg, 1.3 mmol) was hydrogenated with Pd/C in AcOEt yielding 220 mg (87%) of **5**. ^{1}H-NMR (80 MHz, $CDCl_3$): 1.1 (*s*, 6H), 1.1–2.2 (*m*, 9H). MS: 194 (72, M^+), 151 (100), 133 (99), 110 (91), 97 (82), 91 (91), 84 (92), 55 (76). Anal. calc. for $C_{13}H_{22}O$ (194.32): C 80.35, H 11.41; found: C 80.12, H 11.67.

2,2,6-Trimethyltricyclo[5.3.1.0^{3,8}]undecan-3-ol (**6**). *2,2,6-Trimethyltricyclo[5.3.1.0^{3,8}]undec-5-en-3-ol* (**4**; 155 mg, 0.75 mmol) [3] was hydrogenated with Pd/C in AcOEt yielding 130 mg (83%) of **6**. ^{1}H-NMR (80 MHz, $CDCl_3$): 0.86 (*d*, $J = 6$, 3H); 1.12 (*s*, 6H). MS: 208 (74, M^+), 147 (69), 124 (66), 111 (64), 98 (100), 91 (64), 83 (72), 55 (77). Anal. calc. for $C_{14}H_{24}O$ (208.35): C 80.71, H 11.61; found: C 80.78, H 11.74.

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