234. Novel Ketones from Roman Camomile Oil

by **Alan F. Thomas** and **Jean-Claude Egger**

Firmenich SA, Research Laboratories, 1211 Geneva 8, Switzerland

(26.VIII.81)

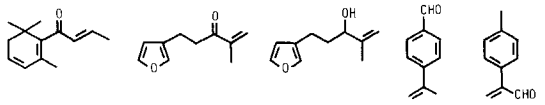
Summary

β-Damascenone (**1**) has been identified in the fraction of Roman camomile *(Anthemis nobilis)* oil that contains homologues of carvotanacetone. 5-(3-Furyl)-2-methyl-1-penten-3-one (**2**), (*E*)-1-(2,6-dimethylphenyl)-2-buten-1-one (**8**), 4-isopropenylbenzaldehyde (**4**), were also identified and synthesized.

During a routine analysis of the oil of Roman camomile *(Anthemis nobilis)*, capillary gas chromatography (GC.)/mass spectrometry (MS.) coupling experiments revealed a substance suspected to be β-damascenone (**1**), and a larger amount of oil was worked up in order to isolate this ketone. This paper describes some novel substances found in the same region of b.p. and polarity as damascenone.

The isolation of the products was carried out by a combination of distillation and chromatography (see exper. part). The β-damascenone (**1**) thus obtained was identical in all respects with authentic material [1].

Somewhat before **1** by GC. on a silicone oil column there was eluted the novel monoterpenoid ketone **2**, which we propose to call 'lepalone', the corresponding alcohol **3** having been isolated from *Ledum palustre* oil and called lepalol [2]. Lepalol (**3**) was synthesized by *Kondo* [3] from myrcene, and we prepared lepalone by manganese dioxide oxidation of this alcohol. On comparing the properties of lepalol (**3**; retention time on thin-layer chromatography and GC.) with corresponding regions of our extracts from Roman camomile, we were able to demonstrate that **3** also occurs in this oil.



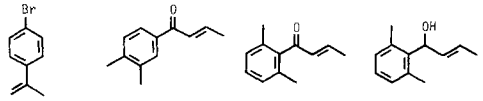
1 **2** **3** **4** **5**

Also with a slightly shorter retention time on silicone oil columns than β-damascenone (**1**), 4-isopropenylbenzaldehyde (**4**) was eluted. This was identified from the mass spectrum, and the fact that the signal in the ^{1}H-NMR. spectrum for

[1]) This statement is based on the positions of the methyl signals in α-methylstyrene (2.13 ppm) and 4,α-dimethylstyrene (2.14 and 2.34 ppm).

0018-019X/81/7/2393-04$01.00/0

the methyl group was at 2.16 ppm. The alternative 4-methylphenyl substituted acrolein **5** would have had the methyl signal at lower field[1]). Compound **4** has been described in older literature [4], but only once recently together with its spectra [5], where the MS. was clearly incorrect. We therefore repeated the preparation of **4** from 2-(4-bromophenyl)-1-propene (**6**; readily available from 1,4-dibromobenzene [6]) by a *Grignard* reaction with dimethylformamide, and found it to be identical with the natural product (corrected spectra in the exper. part).



6 **7** **8** **9**

GC./MS. coupling of the tail of the damascenone peak from the silicone oil column revealed several known compounds, 2-dodecanone, isobutyl benzoate, phenylethyl isobutyrate and phenylethyl propionate, the mass spectra and retention times of which were identical with authentic material. A further substance in this fraction had a MS. nearly identical with the known 1-(3,4-dimethylphenyl)-2-buten-1-one (**7**) [7]. Because of the presence of β-damascenone (**1**), we decided that the isomer 1-(2,6-dimethylphenyl)-2-buten-1-one (**8**) was a likely possibility for this compound[2]). With crotonaldehyde 2,6-dimethylphenyllithium gave the alcohol **9**, and this was oxidized with manganese dioxide to the desired ketone **8**. The latter had the same retention time as the unknown substance from Roman camomile on two different GC. columns, and its mass spectrum was identical with the natural product, so there is a very strong presumption that the structure **8** is that of the natural product.

Fractions of the natural material eluted later than this on silicone oil GC. columns contained the C_{12} and C_{13} homologues of carvotanacetone which we have already described [9].

Compound **3** has a smell reminiscent of mushrooms, while **2** is weaker and not specific. Compound **8** has a saffron note. The strongest smelling substance described here is the aldehyde **4**, which is like cuminaldehyde, but with a more pronounced almod note.

We thank Mr. *Christian Starkemann* for the synthesis of **4**.

Experimental Part

General remarks. See [9].

Isolation of natural products from oil of Anthemis nobilis. The oil (purchased from *Bruce Stark & Co.;* 10 kg) was distilled at 10 Torr and then at 1 Torr until the b.p. reached 80°/1 Torr. There was obtained 8.870 g of distillate, and the residue was distilled on a *Leybold* short-path distillation apparatus at 45°/0.01 Torr. About 75% of the residue distilled under these conditions, and this distillate was chromatographed on silica gel using hexane to hexane/ether mixtures to pure ether to ether/methanol 98:2. Five crude fractions were taken, the second of which was eluted with hexane/ether 8:2, and

[2]) Two other isomers have been described [8].

weighed 30 g. This consisted of material intermediate in polarity (judged by TLC.) between hydrocarbons and tertiary alcohols. Careful redistillation yielded 5 g of a fraction with b.p. 60–65°/0.01 Torr. This distillate was fractionated by prep. GC. on silicone oil into six zones. From these zones, individual substances were obtained by rechromatographing on *Carbowax;* alternatively, complex mixtures were examined by GC./MS. coupling. Zone 1 consisted almost entirely of *5-(3-furyl)-2-methyl-1-penten-3-one* (**2**), identified by the following spectra. – ^{1}H-NMR. (90 MHz): 1.90 (*s*, 3 H); 2.86 (*m*, 4 H); 5.78 (*d*, J = 1, 1 H); 5.97 and 6.28 (2 *s*, each 1 H); 7.26 and 7.35 (2 *d*, each with J = 1.5, each 1 H). – MS.: 164 (43, M^+), 95 (100), 81 (46), 69 (35), 67 (16), 41 (68), 39 (23).

Zone 2, eluted just before the main component, was very complex, but *4-isopropenylbenzaldehyde* (**4**) was identified by ^{1}H-NMR. (90 MHz): 2.16 (*s*, 3 H); 5.22 and 5.48 (2 *s*, long-range coupling in former signal, each 1 H); 7.55 and 7.80 (2 *d*, each with J = 8, each 2 H); 9.94 (*s*, 1 H). – MS.: 146 (93, M^+), 145 (100), 117 (21), 115 (35), 91 (17), 77 (8), 51 (9), 39 (8).

Zone 3 was the largest, and consisted almost entirely of *β-damascenone* (**1**), the spectra (^{1}H-NMR., MS.) of which were identical with those of authentic material [1].

Zone 4 still contained some **1**, and GC./MS. coupling enabled the following to be identified from their MS. and retention times: *2-dodecanone, isobutyl benzoate, phenylethyl isobutyrate, phenylethyl propionate,* and the previously undescribed *(E)-1-(2,6-dimethylphenyl)-2-buten-1-one* (**8**). Insufficient **8** was available for determination of a ^{1}H-NMR., but the synthesis (below) supported the ascribed structure.

Zone 5 was almost homogeneous, consisting of *5-isopropyl-2-propyl-2-cyclohexenone* [9].

Zone 6 was less important than zone 5, and consisted mainly of *5-isopropyl-2-(2-methylpropyl)-2-cyclohexenone* [9].

Synthesis of 5-(3-furyl)-2-methyl-1-penten-3-ol (= *lepalol;* **3**). Photooxygenation of myrcene [3], followed by decomposition of the peroxide with ferrous sulfate [10] yielded **3**. Its acetate was prepared with acetic anhydride in pyridine and purified by GC. on *Carbowax*. – ^{1}H-NMR. (60 MHz): 1.68 and 2.01 (2 *s*, each 3 H); 2.2–2.6 (*m*, 4 H); 4.93 (br. *s*, 2 H, 2 H–C(1)); 5.18 (*t*, J = 6.5, 1 H); 6.26 and 7.24 (each 1 H). – MS.: 166 ($(M-42)^+$, tr), 148 (58), 133 (39), 119 (27), 105 (22), 82 (22), 81 (55), 53 (13), 43 (100), 41 (13).

Synthesis of 5-(3-furyl)-2-methyl-1-penten-3-one (= *lepalone;* **2**). A solution of 10 g of **3** in 200 ml of petroleum ether (b.p. 50–70°) was shaken with 100 g of manganese dioxide (*Merck*, activated for 1.5 h at 120°), then filtered through *Hyflo*. After concentration, the product (9.5 g) was distilled, b.p. 98–105°/10 Torr. – ^{1}H-NMR. and MS. identical with those of the neutral material.

Synthesis of 2-(4-Bromophenyl)-2-propanol (*cf.* [6]). A *Grignard* reagent was prepared from 55 g of magnesium and 576 g of 1,4-dibromobenzene (recryst. from hexane) in 1000 ml of abs. ether. Over 1.5 h was added to the stirred mixture a solution of 151 g of acetone (dried by percolation through alumina, neutral, act. I) in 600 ml of ether. Work-up (ice/ammonium chloride, washing, drying, concentrating) yielded 395 g of crude product. Distillation of half of this yielded first, 40 g of a mixture of 1,4-dibromobenzene and 2-(4-bromophenyl)propene, b.p. 90–110°/10 Torr, then 109.3 g of the title product, b.p. 134–135°/10 Torr, m.p. 52°.

Synthesis of 2-(4-bromophenyl)-1-propene (**6**). A solution of 110.7 g of 2-(4-bromophenyl)-2-propanol and 0.5 g of *p*-toluenesulfonic acid in 350 ml of toluene was heated at reflux with separation of the water formed. (Unlike 2-phenyl-2-propanol, which is dehydrated by refluxing toluene alone, the presence of acid is necessary.) The reaction was complete after 2 h, and the mixture was washed, dried, concentrated, and the residue distilled, b.p. 99°/10 Torr, yield 74 g (74%) of **6**.

Synthesis of 4-isopropenylbenzaldehyde (**4**). A *Grignard* reagent was prepared from 0.7 g of magnesium and 5 g of **6** in 30 ml of dry THF at reflux for 2 h. Over 10 min, 2 g of dimethylformamide was added, then the mixture was stirred for 2 h and poured onto ice. Acidification with 2N H_2SO_4 and extraction in pentane yielded, after the usual work-up, 3.5 g of material with b.p. 100°/0.01 Torr; yield 2.3 g. For analysis, this was further purified by chromatography on silica gel. – ^{1}H-NMR. (90 MHz) and MS.: identical with those of the natural product (above).

Semicarbazone of **4**, m.p. 240–242° (2-propanol)

$C_{11}H_{13}N_3O$ (203.18) Calc. C 65.00 H 6.45 N 20.68% Found C 64.88 H 6.49 N 20.55%

Synthesis of 1-(2,6-dimethylphenyl)-2-buten-1-ol (**9**). A suspension of 2.8 g (0.4 mmol) of lithium in small pieces in 25 ml of dry ether at 0° was stirred under N_2 while 30 g of 2,6-dimethylphenyl bromide (prepared from 2,6-dimethylaniline by the *Sandermann* reaction [11]) in 50 ml of ether was added over 1 h. The mixture was stirred for 2 h at 0°, then cooled to –70°, when 11.2 g (0.16 mol) of crotonaldehyde

was introduced over 30 min. The mixture was allowed to come to RT., then poured into ice/ammonium chloride. The usual ether work-up yielded material which was distilled to yield 13.8 g of material of b.p. 70–76°/0.001 Torr which was practically pure title product. For analysis it was further purified by GC. on *SP 1000*. – ^{1}H-NMR. (60 MHz): 1.12 (*d*, J=6 and further coupling, 3 H); 2.31 (*s*, 6 H); 5.4–5.8 (*m*, 3 H); 6.93 (*s*, 3 H). – MS.: 176 (1, M^+), 161 (32), 158 (10), 143 (36), 133 (100), 128 (20), 119 (10), 107 (10), 105 (33), 91 (24), 77 (10), 55 (20).

1-(2,6-Dimethylphenyl)-2-butenyl acetate was prepared with acetic anhydride in pyridine. – ^{1}H-NMR. (60 MHz): 1.42 (*d*, J=6.5, 3 H); 2.07 (*s*, 3 H); 2.26 (*s*, 6 H); 5.4–5.9 (*m*, 2 H); 6.35–6.8 (*m*, 1 H); 7.03 (*s*, 3 H). – MS.: 218 (1.5, M^+), 174 (7), 159 (48), 158 (50), 144 (19), 143 (100), 141 (13), 129 (17), 128 (49), 117 (14), 115 (18), 105 (13).

Synthesis of 1-(2,6-dimethylphenyl)-2-buten-1-one (**8**). The alcohol **9** (10 g) was shaken with 100 g of manganese dioxide (*Merck*, activated at 120° for 1.5 h) in 250 mol of ether for 12 h. Filtration and concentration yielded 5 g of material which consisted mainly of the desired **8**. The latter was purified by prep. GC. (silicone oil). – ^{1}H-NMR.: 1.91 (*d*, J=5.5, 3 H); 2.18 (*s*, 6 H); 6.27 (*d*, J=15) superimposed on 6.51 (*d*×*qa*, J=15 and 5.5, resp.); 6.9–7.3 (*m*, 3 H). – MS.: 174 (26, M^+), 160 (12), 159 (100), 145 (23), 144 (9), 133 (35), 131 (14), 105 (35), 77 (15), 69 (17), 41 (12). Diagnostic differences with 1-(2,4-dimethylphenyl)-2-buten-1-one (**7**) [7] are: the relative intensity of M^+ (18 in the case of **7**) and the pair *m/z* 144 (14) and 145 (13). The MS. of **8** was identical with that of the natural product, as were the retention times on a *UCON* capillary column and a silicone oil packed GLC. column.

REFERENCES

[1] *E. Demole, P. Enggist, U. Säuberli, M. Stoll & E. sz. Kováts*, Helv. Chim. Acta *53*, 541 (1970).
[2] *N.S. Mikhailova, K.S. Rybalko & V.I. Sheichenko*, Khim. Prir. Soedin, *1979*, 322; Chem. Abstr. *92*, 3176 (1980).
[3] *K. Kondo & M. Matsumoto*, Tetrahedron Lett. *1976*, 391; *M. Matsumoto & K. Kondo*, J. Am. Chem. Soc. *40*, 2259 (1975).
[4] a) *L. Tomaszewska & W. Zacharewicz*, Roczniki Chem. *35*, 1597 (1961); b) *S. Tanimoto, T. Kunitomo & R. Oda*, Nippon Kagaku Zasshi *86*, 947 (1965); *C. Nakashima, S. Tanimoto & R. Oda*, ibid. *87*, 267 (1966).
[5] *R.G. Salomon & J.M. Reuter*, J. Am. Chem. Soc. *99*, 4372 (1977).
[6] *R. Arshady*, Chem. and Ind. *1981*, 250.
[7] *M. Winter & V. Rautenstrauch*, Swiss Pat., 583, 083.
[8] *D.V. Hertzler, J.M. Behrdahl & E.J. Eisenbraun*, J. Org. Chem. *33*, 2008 (1968).
[9] *A.F. Thomas, J.-C. Egger and M. Schouwey*, Helv. Chim. Acta *64*, 1488 (1981).
[10] *J.A. Turner & W. Herz*, J. Org. Chem. *42*, 1900 (1977).
[11] *E.A. Coulson*, J. Chem. Sob. *1937*, 1298.