235. The Occurrence of Some Novel Diesters in Roman Camomile Oil

by **Alan F. Thomas**

Firmenich SA, Research Laboratories, CH-1211 Geneva 8

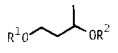
(26.VIII.81)

Summary

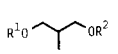
Three diols, 2-methylidene-1,3-propanediol, 2-methyl-1,3-propanediol and 1,3-butanediol, esterified on one hydroxyl group with isobutyric acid and on the other with angelic acid[1]), have been isolated from *Anthemis nobilis* oil (Roman camomile) and synthesized. The presence of homologous esters is very probable.

In previous publications [1] [2], we presented some of our results on the analysis of the oil of Roman camomile *(Anthemis nobilis)*. We now describe the isolation and synthesis of three diesters **1**–**3** (R^1 = angelyl[1]), $R^2 = (CH_3)_2CHCO$), and suggest that other similar esters are present, notably the homologue **1**, with R^1 = angelyl and $R^2 = CH_3CH_2CH(CH_3)CO$. These esters contribute to the odour of the oil.

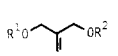
Work-up of the oil was described in the foregoing publication [2], and the diesters now described occurred in the fraction which was slightly more polar than the one containing the unsaturated ketones discussed there. All these compounds have approximately the same volatility, and **1**–**3** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$) were eluted in that order from a *Carbowax* gas chromatography (GC.) column.



1



2



3

Clearly **1** and **2** are chiral (when R^1 and R^2 are different in the case of **2**), and sufficient of **1** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$) was available to show that the natural product was laevorotatory. The identification of all the esters was by ^{1}H-NMR. and mass spectrometry (MS.; see exper. part). In the 360-MHz-^{1}H-NMR. spectrum of **3** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$) a doublet at 1.27 ppm was observed indicating the presence of an impurity. This doublet is at the same position as that of the methyl group in the butanediol part of **1** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$). In this impurity there appeared to be another methyl group giving rise to a triplet at 0.90, and we suggest that the presence of the homologue **1** (R^1 = angelyl,

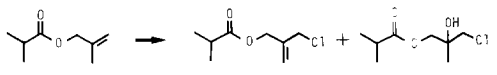
[1]) Angelyl = (*Z*)–$CH_3CH{=}C(CH_3)CO$, tiglyl = (*E*)–$CH_3CH{=}C(CH_3)CO$ ((*Z*)- resp. (*E*)-2-methyl-2-butenoic acid).

0018-019X/81/7/2397-04$01.00/0

$R^2 = CH_3CH_2CH(CH_3)CO$) would account for these observations. A peak observed during the GC./MS. coupling of this fraction gave an MS. (see exper. part) that corresponded to such a substance.

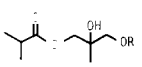
Synthesis of **1** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$) was achieved by partial esterification of 1,3-butanediol with angelic acid in the presence of *p*-toluenesulfonic acid. The desired ester **1** (R^1 = angelyl, R^2 = H) contained about 10% of the isomer **1** (R^1 = H, R^2 = angelyl), which was removed by careful distillation. Esterification of the secondary hydroxyl group with isobutyryl chloride in pyridine gave the desired ester **1** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$), contaminated by about 5% of the isomer **1** ($R^1 = (CH_3)_2CHCO$, R^2 = angelyl). Since we started with the pure primary ester, the impurity must be formed by transesterification, and it is very difficult to remove from the mixture.

Ester **3** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$) and the racemate of **2** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$) were synthesized from 2-methylallyl isobutyrate (**4**), itself a constituent of Roman camomile [3]. The *Wolinsky* reaction of **4** (using a two-phase solvent system and hypochlorous acid) yielded the chlorohydrin **5** as the major product, but the chloride **6** could be isolated from the mixture by distillation in about 25% yield. Believing that the favouring of the chlorohydrin was because of the increased water solubility of the esters over the hydrocarbons used by *Wolinsky* [4], we attempted to lower the solubility in the aqueous phase by adding salt, but there was a negligible effect on the yield of **6**. Treatment of **6** with tiglic acid and sodium ethoxide in ethanol at reflux gave slow conversion to the ester **3** (R^1 = tiglyl, $R^2 = (CH_3)_2CHCO$). To make the desired angelate, the same reaction conditions were used, taking care to have a slight excess of angelic acid present in order to avoid isomerization to **3** (R^1 = tiglyl, $R^2 = (CH_3)_2CHCO$). A trace of the hydroxy ester **7** (R = tiglyl or angelyl) was present in each case because of the presence of **5** in the chloride **6**, but this could easily be removed by distillation.



4 **5** **6**

2 R^1 = tiglyl or angelyl, $R^2 = (CH_3)_2CHCO$ ← **3** R^1 = tiglyl of angelyl, $R^2 = (CH_3)_2CHCO$



7

Catalytic hydrogenation of the angelate **3** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$) yielded the saturated ester **2** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$) in only about 50% yield under our conditions (Pt/C), the addition of hydrogen being accompanied by hydrogenolysis, since we detected over 20% each of isobutyric acid and angelic acid in the product.

I thank Mr. *Christian Starkemann* for assistance with the syntheses.

Experimental Part

General remarks. See [1].

Isolation of esters **1**–**3**. The fraction from the silica gel column immediately following the one containing the unsaturated ketones [2] was rechromatographed on silica gel to remove the remainder of the compounds of the previous fraction. The resulting mixture gave a single spot on TLC., and this material was separated into its components by GC. on *Carbowax*. There were eluted in order: *(–)-Butane-1,3-diyl 1-((Z)-2'-methyl-2'-butenoate) 3-isobutyrate* (**1**, R^1 = *angelyl*, $R^2 = (CH_3)_2CHCO$), $[\alpha]_D^{20} = -28°$ ($c = 1\%$, $CHCl_2$). – ^{1}H-NMR. (90 MHz): 1.16 (*d*, $J = 7$, 6 H, $(CH_3)_2CHCO$); 1.27 (*d*, $J = 6$, 3 H, 3 H–C(4)); 1.9–2.1 (*m*, 6 H); 2.50 (*qa*, $J = 7$, $(CH_3)_2CHCO$); 4.20 (*t*, $J = 7$, 2 H, 2 H–C(1)); 5.05 (*m*, 1 H, H–C(3)); 6.08 (*qa* + long-range coupling, H–C(3')). – MS.: 154 (40), 143 (12), 83 (59), 82 (60), 71 (52), 55 (100), 43 (65).

2-Methylpropane-1,3-diyl 1-((Z)-2'-methyl-2'-butenoate) 3-isobutyrate (**2**, R^1 = *angelyl*, $R^2 = (CH_3)_2CHCO$): ^{1}H-NMR. (360 MHz): 1.03 (*d*, $J = 7$, 3 H, H_3C–C(2)); 1.17 (*d*, $J = 7$, 6 H, $(CH_3)_2CHCO$); 1.89 (*qa*, $J = 1$, 3 H, 3 H–C(4')); 1.98 (*d* × *qa*, $J = 7$ and 1, 3 H); 2.22 (6 lines, 1 H, H–C(2)); 2.56 (5 lines, 1 H, $(CH_3)_2CHCO$); 4.04 and 4.10 (each *d*, $J = 6$, each 2 H, 2 H–C(1), 2 H–C(3)); 6.07 (*qa* + long-range coupling, H–C(3')). – MS.: 154 (27), 143 (30), 100 (8), 83 (75), 82 (100), 71 (63), 55 (50), 43 (65).

2-Methylidenepropane-1,3-diyl 1-((Z)-2'-methyl-2'-butenoate) 3-isobutyrate (**3**, R^1 = *angelyl*, $R^2 = (CH_3)_2CHCO$): ^{1}H-NMR. (360 MHz): 1.19 (*d*, $J = 7$, 6 H, $(CH_3)_2CHCO$); 1.91 (3 H) and 1.99 (3 H); 2.60 (5 lines, 1 H, $(CH_3)_2CHCO$); 4.63 and 4.69 (each *s*, each 2 H, 2 H–C(1), 2 H–C(3)); 5.28 (*d*, 2 H, H_2C=C(2)); 6.10 (*qa* + long-range coupling, H–C(3')). – MS.: 152 (32), 141 (43), 83 (100), 82 (58), 71 (65), 55 (56), 43 (88).

In the ^{1}H-NMR. **3** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$) were visible the following signals, corresponding to *butane-1,3-diyl 1-((Z)-2'-methyl-2'-butenoate) 3-(2''-methylbutyrate)* (**1**, R^1 = *angelyl*, $R^2 = CH_3CH_2CH(CH_3)CO$): 0.90 (*t*, $J = 7$, 3 H–C(4'')); 1.00 (*d*, $J = 7$) and 1.27 (*d*, $J = 7$); 4.20 (*m*); 5.05 (*m*). GC./MS. coupling showed the presence of a small amount of this substance with slightly longer retention time than the main product **3** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$), and which had the following MS.: 157 (12), 154 (48), 85 (30), 83 (53), 82 (76), 71 (65), 57 (53), 55 (100), 43 (73). The fragment with the highest *m/z* value is at 14 mass units above that observed for **1** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$), and the fragment at *m/z* 57 is characteristic for the group $CH_3CH_2CH(CH_3)CO$.

Reaction of 2-methyl-2-propenyl isobutyrate (= 2-methylallyl isobutyrate; **4***) with hypochlorous acid.* Into a stirred mixture of 24 g of **4** (prepared by esterification of 2-methylallyl alcohol with isobutyric acid), 60 ml of water, and 300 ml of dichloromethane at 0° were added simultaneously a solution of sodium hypochlorite (commercial bleach) and glacial acetic acid in such a way that the pH in the solution was maintained at 8 (pH meter). After dropwise addition over 1 h, GC. showed that there were present mainly two new substances to the extent of 25% (shorter retention time on *silicone* oil) and 66% (longer retention time). After a further 1 h, the former remained unchanged, but the latter had slightly increased. Distillation yielded two fractions which were fairly pure: 8.8 g of *3-chloro-2-methylidenepropyl isobutyrate* (**6**), b.p. 84/10 Torr. – ^{1}H-NMR. (60 MHz): 1.18 (*d*, $J = 7$, 3 H); 2.60 (5 lines, 1 H); 4.10 (*s*, 2 H); 4.69 (*s*, 2 H); 3.00 (*d*, 2 H, H_2C=C). – MS.: 141 (**40**), 89 (4; C_4H_6Cl, isotope fragment at *m/z* 91), 71 (45), 53 (19), 43 (100), 41 (20).

The second fraction (17.9 g) had b.p. 110°/10 Torr, and was identified as *3-chloro-2-hydroxypropyl-2-methyl isobutyrate* (**5**). – ^{1}H-NMR. (60 MHz): 1.20 (*d*, $J = 7$, 3 H); 1.32 (*s*, 3 H); 2.60 (5 lines, 1 H); 3.54 and 4.08 (each *s*, 2 H). – MS.: 179 (trace, $M^+ - 15$), 163 (trace, $M^+ - 41$), 145 (5, $M^+ - CH_2Cl$), 102 (30), 93 (11), 87 (26), 71 (73), 58 (12), 43 (100), 41 (20).

Synthesis of 2-methylidenepropane-1,3-diyl 1-((E)-2'-methyl-2'-butenoate) 3-isobutyrate (**3**, R^1 = *tiglyl*, $R^2 = (CH_3)_2CHCO$). A mixture of 3.7 g of **6**, 2.7 g of tiglic acid (= (*E*)-2-methyl-2-butenoic acid) and sodium ethoxide (prepared from 0.46 g of sodium) in 50 ml of ethanol was refluxed for 3 h. The mixture was diluted with water and the products extracted in pentane. After washing, drying and concentrating, the residue was distilled. At first 1.5 g of unchanged **6** distilled, followed by 1.3 g of a fraction that was largely the title product, b.p. 74–85°/0.001 Torr. For analysis, this was purified by GC. on *Carbowax*. – ^{1}H-NMR. (90 MHz): 1.20 (*d*, $J = 7$, 6 H); 1.83 (*d*), superimposed on 1.86 (*s*) (together 6 H); 2.60 (5 lines, 1 H); 4.63, 4.67, 5.26 (each *s*, 2 H); 6.88 (*qa* + long-range coupling, 1 H). – MS.: 240 (trace, M^+), 153 (8), 152 (8), 141 (7), 83 (100), 71 (32), 55 (40), 43 (60), 41 (11), 39 (11).

The major impurity was a little *2-hydroxy-2-methylpropane-1,3-diyl 1-((E)-2'-methyl-2-butenoate) 3-isobutyrate (7, R = tiglyl)* eluted later from the GC. – ^{1}H-NMR. (90 MHz): very similar to the previously described ^{1}H-NMR., but with the following differences: 1.28 (*s*, 3 H); 4.06 and 4.10 (each *s*, 2 H), the other signals at 4.6–5.3 being absent. – MS.: 240 (1, $M^+ - 18$), 157 (7), 145 (18), 99 (7), 83 (100), 71 (57), 55 (39), 43 (58), 41 (12).

The (*Z*)-isomer **3** (R^2 = angelyl, $R^2 = (CH_3)_2CHCO$) was similarly prepared from 11.1 g of **6**, 8.2 g of angelic acid (= (*Z*)-2-methyl-2-butenoic acid) and sodium ethoxide (from 1.4 g of sodium) in 100 ml of ethanol. It distilled at b.p. 50–71°/0.001 Torr, and weighed 5 g. After purification by GC. on *Carbowax*, it had identical spectra with those of the natural product (see above). The impurity, *2-hydroxy-2-methylpropane-1,3-diyl 1-((Z)-2'-methyl-2'-butenoate) 3-isobutyrate (7, R = angelyl)*, was characterized as follows. – ^{1}H-NMR. (60 MHz): 1.18 (*d*, $J = 7$, 6 H); 1.28 (*s*, 3 H); 4.06 and 4.11 (each *s*, 2 H); 6.10 (*qa*, 1 H). – MS.: 240 (4, $M^+ - 18$), 157 (7), 145 (14), 83 (100), 82 (32), 71 (69), 55 (43), 43 (69), 41 (10). The presence of the fragment at *m/z* 82 is characteristic of angelates but not tiglates [5].

Synthesis of **2** *(R^1 = angelyl, $R^2 = (CH_3)_2CHCO$).* The compound **3** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$; 2 g) obtained above was hydrogenated in ethanol over 10% Pt/C. The theoretical amount of H_2 for 1 mol-equiv. was absorbed in 50 min. The solution was filtered, evaporated, and the product purified by prep. GC. on *Carbowax*. The mixture contained 23% of isobutyric acid and 24% of angelic acid (^{1}H-NMR. and comparison with authentic samples), and 43% of the title product, having spectra identical with the naturally occurring ester **2** (R^1 = angelyl, $R^2 = (CH_3)_2CHCO$).

Synthesis of (±)-butane-1,3-diyl 1-(Z)-2-methyl-2-butenoate 3-isobutyrate (**1**, *R^1 = angelyl, $R^2 = (CH_3)_2CHCO$).* A solution of 18 g of 1,3-butanediol, 15 g of angelic acid, and 0.1 g of *p*-toluenesulfonic acid was heated at reflux with separation of water formed for 24 h. After washing ($NaHCO_3$, water) and evaporating the solvent, the product was distilled, b.p. 51–56°/0.001 Torr to give 5.0 g of *(±)-3-Hydroxybutyl (Z)-2-methyl-2-butenoate* (**1**, R^1 = angelyl, R^2 = H) contaminated with *ca.* 10% of the isomer **1** (R^1 = H, R^2 = angelyl). – ^{1}H-NMR. (90 MHz): 1.20 (*d*, $J = 6.5$); 1.9–2.1 (*m*, 8 H); 3.5–4.6 (*m*, 3 H); 6.08 (*qa*, 1 H); the isomer **1** (R^1 = H, R^2 = angelyl) was responsible for signals at 1.30 (*d*, $J = 7$) and 5.15 (*m*). The pure ester **1** (R^1 = angelyl, R^2 = H) was obtained by preparative GC. *(Carbowax)* and had MS.: 172 (M^+, trace), 154 (3), 100 (57), 83 (70), 82 (65), 55 (100).

To a solution of 1 g of **1** (R^1 = angelyl, R^2 = H, purified by GC.) in 0.5 g of pyridine was added 0.67 g of isobutyryl chloride. After the usual work-up, the title product was purified by GC. on *Carbowax*. The ^{1}H-NMR. spectrum was practically identical with that described above for the natural product, but GC./MS. coupling showed the presence of *ca.* 5% of the isomer **1** ($R^1 = (CH_3)_2CHCO$, R^2 = angelyl) having a similar MS., but with *m/z* 154 (20) and 143 (25) instead of the values given above.

REFERENCES

[1] *A. F. Thomas, M. Schouwey & J.-C. Egger*, Helv. Chim. Acta *64*, 1488 (1981).
[2] *A. F. Thomas & J.-C. Egger*, Helv. Chim. Acta *64*, 770 (1981).
[3] *A. F. Thomas*, unpublished work.
[4] *S. G. Hedge, M. K. Vogel, J. Saddler, T. Hrinyo, N. Rockwell, R. Haynes, M. Oliver & J. Wolinsky*, Tetrahedron Lett. *21*, 441 (1980).
[5] *A. F. Thomas & B. Willhalm*, Org. Mass Spec. *11*, 831 (1976).