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ITALICENE AND ISOITALICENE, NOVEL SESQUITERPENE HYDROCARBONS FROM HELICHRYSUM OIL[1)]

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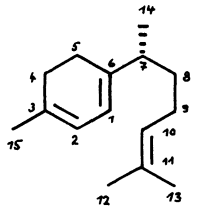
From Helichrysum oil two new sesquiterpene hydrocarbons, italicene and isoitalicene were isolated. Their structure was confirmed by spectral data, degradation reactions and unambiguous synthesis starting from m-bromoanisole.

Helichrysum oil from the Mediterranean region (France, Italy, Yugoslavia) is widely used in perfumery.[2)] Though many of the polar compounds of Helichrysum italicum were identified[3)] the composition of the sesquiterpene hydrocarbon fraction remained unknown. We reexamined this fraction, and we discovered via GC/MS coupling[4)] 14 known sesquiterpene hydrocarbons[5)] e.g. γ-curcumene (1, 10.4% relative amount), α-curcumene (4.0%), and two new compounds 2 (4.0%) and 3 (1.5%) with MS very similar to 1 but not comparable with any other known sesquiterpene hydrocarbon. For the isolation of 2 and 3 we first removed α-pinene (22%) and some other monoterpenes by distillation (46-68 °C/15 Torr) from the original Helichrysum oil (from Yugoslavia). After liquid-liquid distribution of the residue the nonpolar fraction was distilled at a slit-tube column (80-94 °C/3 Torr). Thus some fractions contained about 40% 2 and 20% 3 (+ caryophyllene, α-copaene, bergamotene). Column chromatography on silica gel, repeated on silica gel containing 25% $AgNO_3$ yielded fractions with almost pure 2 and 3, further purification (up to 98%) of which is possible by preparative GC.

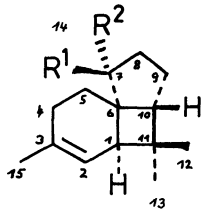
The structures of 2 and 3 were elucidated by ^{1}H-NMR spectra (Table 1) and ^{13}C-NMR data (Table 2). Extended spin decoupling (in $CDCl_3$, C_6D_6, CD_3COCD_3) led to the structure formula 2 and 3 resulting from [2+2]cycloaddition of 1. The skeleton of 2 and 3, which we called italicene and isoitalicene, seems to be hitherto unknown for naturally occurring compounds.[6)] The assignment of (-)-italicene[7)] to structure 2 and (+)-isoitalicene[7)] to 3 is also based on the NMR spectra. The allylic 4-CH_2 group (δ 1.77) of 2 is shifted upfield in comparison to that of 3 (δ≈ 1.94), because it is shielded by the 7-Me group. Likewise the ^{13}C-NMR spectrum of 2 shows the shielding effect of the 7-Me-group on C-5 (cis-position) and further γ-effects on C-9 and C-10. Dreiding models also explain the upfield shift of C-1 by the 7-Me group in 3. To confirm these structures 2 was treated with OsO_4 to give the cis-diol 4 (mp 114 °C), which was transformed via a ketoaldehyde to the acetal 6 by oxidation with HIO_4 in methanol. The ^{1}H-NMR spectra of 4, and particularly of the ketoacetal 6 with clearly separated signals

substantiated the proposed structures. Similarly, 3 was converted via diol 5 (mp 126 °C) to the ketoaldehyde 7.

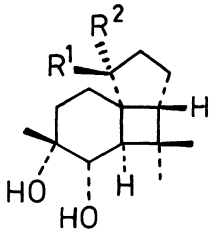
For the synthesis of 2 and 3 enone 8[6,8] (prepared from m-bromoanisole) was methylated (LDA/THF/-78 °C/MeI/-78 °C → 20 °C) to give enone 9.[9] Irradiation of 9 (125 W Hg-lamp, Pyrex filter, CH_2Cl_2, 4 h, room temp) yielded the cyclobutane photoadducts 10 and 11 (2:1), each as a mixture of diastereomers.[9] 10 and 11 were separated by silicagel chromatography followed by preparative GC. Since subsequent reduction and elimination of water will destroy the chirality at C-3 the synthetic work could be carried out with the unseparated mixture of 10 resp. 11. $LiAlH_4$ reduction of 10 resp. 11 furnished 12 resp. 13 selectively.[9] Configuration of the 2-OH function must be trans to 1-H since the Dreiding model shows only in this quasi-1,3-diaxial position of 2-OH and Me-12 this Me group could be downfield shifted to δ 1.35. This configuration is in agreement with the hydride attack to 10 resp. 11 from the less hindered side. After reaction of 12 resp. 13 with Burgess reagent[10] racemic 2 resp. 3 were isolated, whose data (MS, ^{1}H-, ^{13}C-NMR, GC retention time) were identical with the natural products.



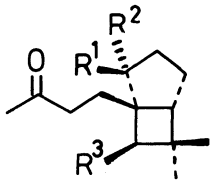
1



2, 3

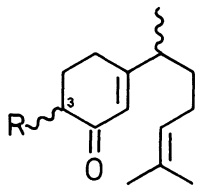


4, 5



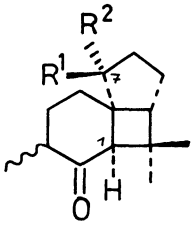
6: R^3 = $CH(OMe)_2$

7: R^3 = CHO

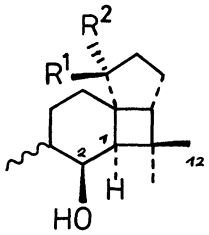


8: R = H

9: R = Me



10, 11



12, 13

	R^1	R^2
2, 4, 6, 10, 12	Me	H
3, 5, 7, 11, 13	H	Me

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Table 1. ^{1}H-NMR data (400 MHz, δ, $CDCl_3$) of italicene (2), isoitalicene (3), and the derivatives 4 - 7

	2	4	6[a)]	3	5	7
1-H	mc 1.88	d 1.52	d,br. 1.85	mc 2.00	dd 1.60	d,br. 2.33
2-H	mc 5.32	d 3.77	d 4.52	mc 5.38	d 3.61	d 9.89
4-H	AB 1.77		ddd 2.43	ddd 1.97		ddd 2.36
4'-H			ddd 2.82	ddd 1.91		ddd 2.44
5-H	ddd 1.64		ddd 2.18	ddd 1.82		ddd 2.09
5'-H	ddd 1.84		ddd 1.78	ddd 1.63		ddd 2.15
7-H	dq 1.71	dq,br. 2.07	dq 1.82	m		dq,br. 1.60
8-H	dd,br. 1.46	dd,br. 1.47	dd,br. 1.44	1.37-1.60		ddd,br. 1.35
8'-H	dddd 2.02	dddd 2.03	dddd 2.01	(4 H)		ddd,br. 1.82
9-H	dddd 1.64		dddd 1.65	m		ddd,br. 1.44
9'-H	dd,br. 1.55	dd,br. 1.55	dd,br. 1.56	1.67-1.78		dd,br. 1.65
10-H	d 1.72	d,br. 1.77	d,br. 1.72	(2 H)	d,br. 1.75	d,br. 1.95
12-H	s 0.96	s 0.97	s 0.87	s 0.90	s 0.94	s 0.98
13-H	s 0.91	s 1.18	s 1.14	s 0.89	s 1.05	s 1.35
14-H	d 0.77	d 0.73	d 0.78	d 0.82	d 0.95	d 0.86
15-H	s 1.71	s 1.29	s 2.14	s 1.72	s 1.25	s 2.17

a) 2 s: 3.22, 3.28 (2 MeO).

J [Hz] 2: 1,2 = 3.5; 4,5' = 5; 4',5' = 3; 5,5' = 12; J(7-10) cf. 6.
4: 1,2 = 9; J(7-10) cf. 6.
6: 1,2 = 9.5; 4,4' = 18; 4,5 = 4',5' = 11; 4,5' = 4',5 = 5; 5,5' = 15; 7,8' = 7,14 = 8,9 = 8',9' = 7; 7,8 = 8,9' = 9',10 = 1.5; 8,8' = 8',9 = 12.5; 9,9' = 13.5; 9,10 = 8.5.
3: 1,2 = 4.5; 4,4' = 16.5; 4',5 = 9.5; 4,5 = 4,5' = 4',5' = 5; 5,5' = 13; 7,14 = 6.5.
5: 1,2 = 4.5; 1,10 = 1; 7,14 = 6.5; 9,10 = 8.
7: 1,2 = 2.5; 1,10 = 1; 4,4' = 17; 4,5 = 9; 4,5' =7,8' = 5.5; 4',5 = 7; 4',5' = 9.5; 5,5' = 14; 7,14 = 8',9' = 6.5; 8,8' = 12; 8,9 = 9,9' = 13; 7,8 = 8,9' = 9',10 = 1.5; 9,10 = 8.

Table 2. ^{13}C-NMR data (CFT-20, $CDCl_3$, off resonance) of 2 and 3

		2	3			2	3
C-1	d	48.1	45.0	C-9	t	24.8	26.4
C-2	d	121.1	121.8	C-10	d	51.6	53.6
C-3	s	135.9	135.6	C-11	s	34.8	35.1
C-4	t	28.0	28.6	C-12	q	24.8*	24.3*
C-5	t	27.7	33.1	C-13	q	27.1	27.1
C-6	s	45.4	43.9	C-14	q	16.4	13.3
C-7	d	39.9	41.1	C-15	q	24.2*	24.0*
C-8	t	35.0	36.2			* exchangeable	

References

1) Terpenes and Terpene Derivatives, XIV; presented (P. W.) partly at the 9th International Congress of Essential Oils, Singapore (1983).

2) E. Gildemeister and F. Hoffmann, "Die ätherischen Öle," Akademie Verlag, Berlin (1961) Vol. VII, p. 599.

3) R. Hänsel, E.-M. Cybulski, B. Çubukçu, A. H. Meriçli, F. Bohlmann, and C. Zdero, Phytochemistry, 19, 639 (1980); L. Peyron, J. Acchiardi, B. Bruni, J. C. Rossi, and R. Granger, Perfum. Flavor., 3, 25 (1978); P. Manitto and D. Monti, Phytochemistry, 11, 2112 (1972).

4) Varian MAT 711 (70 eV) via GC with 25 m FS-WCOT-FFAP column.

5) Identification by MS and ^{1}H-NMR (400 MHz). Comparison with authentic samples or reference data. Full details will be reported later.

6) A C_{14}-ketone with an analogous ring conjunction prepared by photocycloaddition of enone 8 is described as precursor of the spirocyclic acorane skeleton: T. R. Hoye, S. J. Martin, and D. R. Peck, J. Org. Chem., 47, 331 (1982); with a correction of M. Fetizon, S. Lazare, C. Pascard, and T. Prange, J. Chem. Soc., Perkin Trans. 1, 1979, 1407 and D. D. Khac Manh, J. Ecoto, M. Fetizon, H. Colin, and J.-C. Diez-Masa, J. Chem. Soc., Chem. Commun., 1981, 953.

7) 2: $[\alpha]_D^{25}$ -53.8° (c 3.0 in $CHCl_3$); 3: $[\alpha]_D^{25}$ +35.4° (c 1.4 in $CHCl_3$).

8) W. Oppolzer, F. Zuttermann, and K. Bättig, Helv. Chim. Acta, 66, 522 (1983).

9) Spectral data of 9 - 13 (diastereomeric mixtures) are as follows:
9: IR (CCl_4) 1680, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.05/1.06 (2 d, J = 7 Hz, 7-Me), 1.12 (d, J = 7 Hz, 3-Me), 1.56, 1.67 (2 s,br, Me-12, -13), 5.06 (t,br, J = 7 Hz; 10-H), 5.84 (s,br, 1-H); ^{13}C-NMR ($CDCl_3$) δ 15.2 (q, C-15), 18.9/19.1 (2 q, C-14), 17.7, 25.7 (2 q, C-12, -13), 25.9, 26.5/26.6, 31.2, 34.9 (5 t, C-4, -5, -8, -9), 41.1, 41.2 (2 d, C-3, -7), 123.9, 124.7/124.8 (3 d, C-1, -10), 132.0 (s, C-11), 169.5/169.7 (2 s, C-6), 202.6 (s, C-2); MS m/e 220.183 ($C_{15}H_{24}O$, M^+, 67%), 164 (23), 151 (69), 138 (67), 82 (100).
10: IR (CCl_4) 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.82/0.87 (2 d, J = 7 Hz, 7-Me), 1.00, 1.02, 1.05, 1.09 (4 s, Me-12, -13), 1.10/1.11 (2 d, J = 7 Hz, 3-Me), 2.17/2.19 (2 s,br, 1-H); MS m/e 220.183 ($C_{15}H_{24}O$, M^+, 46%), 192 (23), 178 (21), 162 (33), 151 (69), 138 (70), 96 (45), 82 (100).
11: IR (CCl_4) 1695 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.88/0.90 (2 d, J = 6.5 Hz, 7-Me), 0.97, 1.00, 1.04, 1.09 (4 s, Me-12, -13), 1.08/1.09 (2 d, J = 7 Hz, 3-Me), 2.31/ 2.32 (2 s,br, 1-H); MS m/e 220.183 ($C_{15}H_{24}O$, M^+, 48%), 192 (20), 178 (17), 164 (27), 162 (27), 151 (69), 138 (72), 96 (43), 82 (100).
12: IR (CCl_4) 3620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.76/0.78 (2 d, J = 7 Hz, 7-Me), 0.96/0.99 (2 d, J = 6.5 Hz, 3-Me), 0.97, 1.36 (2 s, Me-12, -13), 3.31 (dd, J = 11 and 8 Hz/3.94 (dd, J = 6 and 2 Hz, 2-H); MS m/e 222.198 ($C_{15}H_{26}O$, 2%), 85 (43), 82 (100).
13: IR (CCl_4) 3620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.85/0.91 (2 d, J = 7 Hz, 7-Me), 0.95/0.97, 1.34/1.35 (4 s, Me-12, -13), 0.98/1.00 (2 d, J = 6.5 Hz, 3-Me), 3.26 (dd, J = 11 and 8 Hz)/3.99 (dd, J = 7.5 and 4.5 Hz, 2-H); MS m/e 222.198 ($C_{15}H_{26}O$, M^+, 7%), 93 (47), 82 (100).

10) $Et_3\overset{+}{N}SO_2\overset{-}{N}CO_2Me$: E. M. Burgess, H. R. Penton, and E. A. Taylor, J. Org. Chem., 38, 26 (1973).

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