Molecular Structures of Dimeric Reduction Products of Pulegone

Mitsuko KIKUCHI
College of Engineering, Nihon University, Koriyama, Fukushima 963

(Received December 14, 1991)

Synopsis. The molecular structures of "isobishydropulegone" and "Harries–Roeder ketol," isomers of "bishydropulegone," which are dimeric reduction products of pulegone, were determined as being (1*S*, 3′a*R*, 4*R*, 6′*R*, 7′a*S*)-7′a-hydroxy-2′,2′,3′,3′,4,6′-hexamethylspiro[cyclohexane-1,1′-octahydroinden]-2-one and (1*R*, 3′a*S*, 4*R*, 6′*R*, 7′a*S*)-7′a-hydroxy-2′,2′,3′,3′,4,6′-hexamethylspiro[cyclohexane-1,1′-octahydroinden]-2-one respectively by the analysis of the two-dimentional NMR spectra.

Pascual et al. reported a systematic investigation on the molecular structures of five hydroxy ketones obtained as dimeric reduction products of pulegone. However, the stereochemistry of the position at C3′a(H) and C7′a(OH) have not been fully elucidated.[1–3]

In our previous paper,[4] the molecular structure of bisydropulegone of the most stable product of (*R*)-(+)-pulegone was determined as being (1*R*, 3′a*R*, 4*R*, 6′*R*, 7′a*S*)-7′a-hydroxy-2′,2′,3′,3′,4,6′-hexamethylspiro[cyclohexane-1,1′-octahydroinden]-2-one by an X-ray crystallographic analysis.

Recently, Santelli et al.[5–7] proposed an anionic mechanism based on umpolung that was derived from a two-electron transfer to pulegone by a reductive dimerization of (+)-pulegone using the $TiCl_4$-Mg reagent,and five hydroxy ketones have been obtained in the reaction mentioned above. However, their molecular structures have not yet been characterized and the products only cited as Pascual's result.

As mentioned above, the stereochemistries of the isomers, except for bishydropulegone (**1**), have not yet been established. In this paper the author wishes to describe the stereostructures of isobishydropulegone (**2**) and "Harries–Roeder ketol" (**3**).

Experimental

The melting points were determined using a Mitamura melting-point apparatus (No. 8209) and are uncorrected. The IR spectra were recorded on a JEOL JIR 100FT-IR sepectrophotometer in CCl_4. The ^1H and ^{13}C NMR (δ) spectra were recorded on a Bruker AM 400 (400 MHz for ^1H and 100 MHz for ^{13}C) instrument in $CDCl_3$, CD_3OD, and $(CD_3)_2CO$. Each hydroxy ketone (15—20 mg) was dissolved in 0.3 ml of $CDCl_3$, CD_3OD, and $(CD_3)_2CO$ and placed in 5 mm sample tubes. Chemical shifts are expressed in δ (ppm) from internal TMS. The coupling constants (J) are given in Hz. GC was recorded on a shimadzu 7A Gas Chromatograph using capillary column SE-50 (20 m), a column temperature of 230 °C and an N_2 carrier gas flow rate of 50 ml min^{-1}.

(*R*)-(+)-pulegone and bishydropulegone (**1**) were as described in the first report concerning the molecular structure of a dimeric reduction product of pulegone.[4] Isobishydropulegone (**2**) was prepared through the isomerization of **1** according to the Pascual procedure.[8] The mixture of **1** (302 mg, 9.87×10^{-4} mol), anhydrous pyridine (3 ml) and 3,5-dinitrobenzoyl chloride (314 mg, 1.48×10^{-3} mol) was stirred in an oil bath at 105—110 °C for 9 h. Then, ice water (13 ml) was added into the reaction mixture under r.t. and with stirring. After it was allowed to stand overnight, deep wine-red crude crystals (300 mg) were collected by filtration. They were washed with water, and then dried under vacuum. They were then passed through a neutral alumina column (grade I) by eluting with hexane–Et_2O (10 : 1) to give a mixture of **1** and **2**. Mixed crystals of **1** and **2** were further separated by using preparative TLC developed twice with hexane–AcOEt (10 : 1) to give **1** (160 mg, 61% as crystals) and **2** (104 mg, 39%). **2** was further recrystallized from petroleum ether–EtOH (10 : 1); mp 136 °C; $[\alpha]_D^{21}$ +43.4° (*c* 0.206, $CHCl_3$); Found: *m*/*z* 306.2538. Calcd for $C_{20}H_{34}O_2$: M, 306.2520.

"Harries–Roeder ketol" (**3**) was prepared by the reduction of (+)-pulegone with Al-amalgam in Et_2O, as reported by Vogel,[9] which was first tried by Harries and Roeder[10] and was modified by Pascual.[11] Finely bended Al-foils (thickness: 0.05 mm, width: 10 mm, length: 100 mm, 1.3 g) were soaked into 10% NaOH at r.t. for 100 s. They were then washed with water to pH=7 (6 times) and with EtOH twice. After the Al-foils were slightly wiped using filter paper, they were amalgamated by soaking into 2%-Hg_2Cl_2 at r.t. for 2 min, and immediately washed with water four times and with EtOH twice. The Al-amalgam was added directly into the mixture of (+)-pulegone (1.5 g, 4.9×10^{-3} mol) and Et_2O (2 ml). The whole mixture was stirred at r.t. for 8 h. The mixture gradually changed to a brownish-gray viscous solution. Then, water (0.6 ml) and Et_2O (12 ml) were added, and the mixture was stirred for 30 min before being quenched. After the reaction mixture was filtered through celite, and was washed with Et_2O several times. Evaporation of the solvent afforded an oil (1.47 g) which was distilled to give a fraction (400 mg) boiling at 87—101 °C (bath temperature/3.0—1.0 mmHg, 1 mmHg=133.322 Pa) and a residual oil (709 mg). The residue was passed through a sillica-gel column by eluting with hexane–acetone (20 : 1) to give a hydroxy ketone (160 mg, 22.8%) as crystals. The crystals were recrystallized from petroleum ether–EtOH (10 : 1). Mp 114.5—115.5 °C; $[\alpha]_D^{20}$ +57.5° (*c* 1.045, $CHCl_3$). Found: C, 78.43; H, 10.83%. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18%. MS (EI 70 eV) Found: *m*/*z* 288.2454. (EI 20 eV) Found: *m*/*z* 288.2436. Calcd for $C_{20}H_{32}O$: M, 288.2452.

Isomerization of Bishydropulegone (1) to Isobishydropulegone (2). A solution of **1** (156 mg, 0.51 mmol) in THF (2.5 ml) was added into the mixture of *t*-BuOK (9.5 mg) and THF (2.5 ml) drop by drop, and was then stirred at r.t. for 2 h. After the addition of 10%-NH_4Cl (10 ml) to the reaction mixture, the product was extracted with Et_2O three times. The etherial solution of the product was washed with saturated brine twice. Removing the solvent afforded a crude product (156 mg), which was purified by sillica-gel column chromatography using 10% Et_2O–pentane as the solvent to give a fraction (144 mg), which crystallized upon standing. The area ratio of the GC (capillary column SE-50 20 m, column temperature; 230 °C, flow rate of N_2; 50 ml min^{-1}) of **1** (R_t; 8.90) and **2** (R_t; 11.66) in the fraction was 2.37 : 1.0.

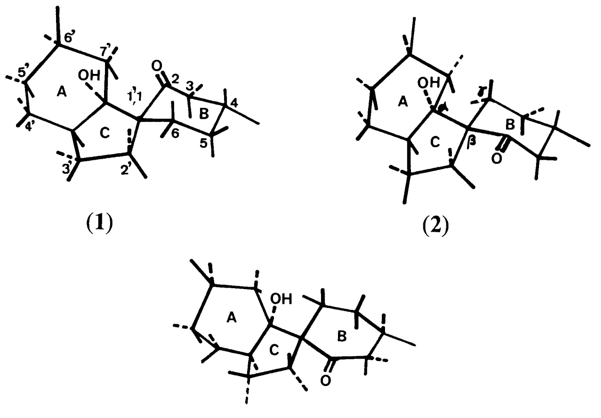
Results and Discussion

The stereostructures of **2** and **3** were elucidated by

Table 1. ^{13}C NMR Chemical Shift Data of **1**, **2**, and **3**

Carbon		Chemical shift (δ)			
		1$^{a)}$	**2**$^{a)}$	**3**$^{a)}$	**3**$^{b)}$
C1 (=C1′)		64.5	67.3	65.53	65.4
C2	C=O	219.7	215.7	219.1	218.9
C3	CH_2	52.2	51.3	52.8	52.5
C4	CH	34.4	28.6	31.0	30.7
CH_3–C4	CH_3	22.4	22.8	22.6	22.5
C5	CH_2	32.1	28.6	29.5	29.3
C6	CH_2	32.2	24.8	27.5	27.3
C2′	C	49.1	49.8	45.9	45.8
CH_3–C2′	CH_3	26.6	26.1	26.5	26.4
CH_3–C2′	CH_3	27.8	26.6	28.6	28.3
C3′	C	44.6	43.0	44.2	44.0
CH_3–C3′	CH_3	22.7	23.6	24.8	24.7
CH_3–C3′	CH_3	30.4	27.2	29.9	29.8
C3′a	CH	53.9	52.5	52.1	51.9
C4′	CH_2	21.5	21.8	22.0	21.7
C5′	CH_2	35.4	34.8	31.3	29.3
C6′	CH	27.9	28.4	26.7	26.6
CH_3–C6′	CH_3	22.5	22.3	23.2	23.1
C7′	CH_2	43.1	43.9	39.6	39.5
C7′a	C–OH	84.9	83.4	82.4	82.3

a) in $CDCl_3$. b) in CD_3OD.



(1) (2)

(3)

Fig. 1. Molecular Structures of Three Hydroxy Ketones (**1**), (**2**), and (**3**).

spectroscopic methods, mainly by 2D COSY NMR with an examination of the stereochemical correlations in the molecular models. The vicinal correlations of two *gem*-dimethyls attached to C2′ and C3′ were identified by the 2D NOESY spectra.

As is shown in Tables 1 and 2, the following partial connectivities were observed in **2**, except for the overlapping signals. The ^{13}C chemical shift of C6 (24.8) is at higher magnetic field than that of **1** (32.2), because of the close position of C6 to C7′ a spatially and the orientation at the γ-gausch position to the oxygen of the hydroxy group at C7′a. The large coupling constant (*J*, 12.8) between 3′aH- and 4′a protons clearly demonstrates a trans diaxial disposition of these protons. The 7′e proton exhibits a clear coupling pattern (*J*, 12.6 for 7′a, *J*, 3.8 for 6′H, and *J*, 1.8 for 5′e). These results supported the idea that **2** comprises the same rigid ring A with a stable trans ring junction as the structure of **1**. The ^{13}C chemical shift (215.7) of C2 in **2** shifted 4.0 ppm to a higher magnetic field compared with that of (219.7) in **1**. Also, no absorption band corresponding to an intramolecular hydrogen bond between the hydroxy group at C7′a and the carbonyl group at C2 was observed when the FT-IR spectrum of **2** was measured in a highly diluted solution (1.05×10^{-3} mol dm^{-3}) of **2** (3627 and 1695 cm^{-1}). The eventual **1**→**2** isomerization was confirmed by a GC-analysis of the product that treated **1** with *t*-BuOK/THF. From the 2D NOESY ^{1}H spectrum, cross peaks were observed belonging to correlations between protons at 2′Me (0.86) and 3′Me (0.98), and 3′Me (0.84) and 2′Me (1.08).

From these results, the molecular structure of isobishydropulegone (**2**) was determined as being (1*S*,3′a*R*,4*R*,6′*R*,7′a*S*)-7′a-hydroxy-2′,2′,3′,3′,4,6′-hexamethylspiro[cyclohexane-1,1′-octahydroinden]-2-one. Also, the molecular structure of isobishydropulegone **2** is depicted as the Figure with bishydropulegone (**1**) and "Harries–Roeder ketol" (**3**).

The FT-IR spectrum (3434 and 1678 cm^{-1}) of **3** in a highly diluted solution (3.02×10^{-3} mol dm^{-3}) shows an intramolecular hydrogen bond in **3** belonging to Group I (allo type) by Pascual et al. The ^{13}C chemical shift (219.1) of C2 in **3** is in excellent agreement with that (219.7) of **1**. The ^{1}H signal of 3′aH is in the lowest field among these three hydroxy ketones (2.57); further, the coupling pattern ($J_{3'aH\text{-}4'a}=J_{3'aH\text{-}4'e}$, 7.0) indicates a gauche conformation between the 3′aH and 4′-methylene protons (4′a and 4′e); the other W-type coupling pattern ($J_{3'aH\text{-}5'e}=J_{3'aH\text{-}7'e}$, 3.5) shows that the A/C ring system in **3** must be *cis* as well as the positions of C2(CO) and C7′a(OH) in **3**. In the 2D NOESY spectrum it was observed that there are cross peaks belonging to correlations between methyl protons (1.09) at C2′ (the opposite site to OH at C7′a and 3′aH) and 7′a, and 6e; between the vicinal methyl (0.90) at C3′ and 5′a; and between the other vicinal methyl (0.89) and 3a, especially the correlation between the methyl (0.97) at C3′ of the same site of the CO group and OH group and 3′aH.

From above results, the molecular structure of the "Harries–Roeder ketol" was determined as being (1*R*, 3′a*S*, 4*R*, 6′*R*, 7′a*S*)-7′a-hydroxy-2′,2′,3′,3′,4,6′-hexamethylspiro[cyclohexane-1,1′-octahydroinden]-2-one.

The author thanks emeritus Professor Akira Yoshikoshi of Tohoku University for his helpful discussion, and Mr. Takaaki Toyota of Takasago Perfumery Industrial Co., Ltd. for NMR measurements as well as his valuable advice. Thanks are also due to Mr. A. Aimi of the College of Science and Technology of Nihon University for High Mass spectral measurements.

References

1) Jose M. Front Cistero, *Rev. R. Acad. Cienc. Exactas, Fis. Nat. Madrid*, **66**, 455 (1972).

2) E. F. Flip, *Rev. R. Acad. Cienc. Exactas, Fis. Nat. Madrid*, **68**, 209 (1974).

3) E. Forne and J. Pascual, *J. Chem. Soc., Perkin Trans. 1*, **1978**, 288.

4) M. Kikuchi and Z. Taira, *Bull. Chem. Soc. Jpn.*, **59**, 3659 (1986).

5) J.-M. Pons and M. Santelli, *Tetrahedron Lett.*, **27**, 4153

Table 2. ^{1}H NMR Spectroscopic Data of Three Hydroxy Ketones (**1**, **2**, and **3**)

	1		**2**	
Proton	Chemical shift (δ)$^{a)}$	Coupling pattern and constant (Hz)	Chemical shift (δ)$^{a)}$	Coupling pattern and constant (Hz)
5′a	0.76	1H, qd ($J_{5'a-5'e}=J_{5'a-6'H}=J_{5'a-4'a}=12.5$, $J_{5'a-4'e}=3.8$)	0.81—0.91	2H
6′Me	0.86	3H, d ($J=6.7$)	0.86	3H, d ($J=6.4$)
4Me	1.02	3H, d ($J=6.4$)	1.01	3H, d ($J=6.9$)
7′a	1.11	1H, t ($J=11.8$)		
4′e	1.29	1H, d mul ($J_{4'e-4'a}=13.0$)	1.37—1.45	2H, mul
3′aH	1.25—1.35	1H, mul	2.05—2.11	1H, d mul ($J_{3'aH-4'a}=12.8$)
7′e	1.55—1.62	1H, mul	1.60	1H, ddd ($J=_{7'e-7'a}=12.6$, $J_{7'e-6'H}=3.8$, $J_{7'e-5'e}=1.8$)
4′a	1.58—1.70	1H, dd ($J_{4'a-4'e}=J_{4'a-5'a}=J_{4'a-3'aH}=13.1$, $J_{4'a-5'e}=3.9$)		
5a	1.56—1.69	2H, mul	1.40—1.45	1H, mul
5e			1.82—1.93	1H, mul
5′e	1.71—1.76	1H, broad d mul	1.67—1.75	1H, broad d mul
6a	1.81	1H, t d ($J_{6a-6e}=J_{6a-5a}=14.4$, $J_{6a-5e}=5.4$)	1.81—1.92	1H, mul
4H	1.74—1.85	1H, mul	1.97	6 lines
6e	1.96	1H, ddd ($J_{6e-6a}=14.4$, $J_{6e-5e}=J_{6e-5a}=4.4$)	2.10—2.18	1H, mul
6′H	1.94—2.07	1H, mul	1.64—1.74	1H, mul
3a	2.10	1H, t ($J_{3a-3e}=J_{3a-4H}=12.7$)	2.10	1H, dd ($J_{3a-3e}=15.2$, $J_{3a-4H}=10.9$)
3e	2.36	1H, ddd ($J_{3e-3a}=12.4$, $J_{3e-4H}=3.4$, $J_{3e-5e}=2.1$)	2.37	1H, ddd ($J_{3e-3a}=15.2$, $J_{3e-4H}=5.2$, $J_{3e-5e}=1.0$)
OH	4.98	1H, d ($J=1.9$)	1.23	1H, s

		3		
Proton	Chemical shift (δ)$^{a)}$	Coupling pattern and constant (Hz)	Chemical shift (δ)$^{b)}$	Coupling pattern and constant (Hz)
6′Me	0.87	3H, d ($J=6.7$)	0.89	3H, d ($J=6.6$)
4Me	0.99	3H, d ($J=6.4$)	0.99	3H, d ($J=6.2$)
5′a	0.82—0.99	2H, mul	0.97—1.08	1H, mul
7′a			1.07	1H, dd ($J_{7'a-7'e}=13.4$, $J_{7'a-6'H}=12.0$)
5a	1.31	1H, dd ($J_{5a-5e}=14.5$, $J_{5a-4H}=J_{5a-6a}=11.4$, $J_{5a-6e}=3.0$)	1.33	1H, qd ($J_{5a-5e}=14.4$, $J_{5a-4H}=J_{5a-6a}=11.4$, $J_{5a-6e}=3.0$)
5′e	1.47	1H, broad d ($J=14.4$)	1.46	1H, d mul ($J_{5'e-5'a}=11.4$)
4′e	1.56	1H, mul ($J_{4'e-4'a}=14.8$)	1.59	1H, d five lines ($J_{4'e-4'a}=14.7$, $J_{4'e-3'aH}=J_{4'e-5'e}=J_{4'e-5'a}=2.1$)
7′e	1.60	1H, d mul ($J_{7'e-7'a}=12.5$)	1.66	1H, d five lines ($J_{7'e-7'a}=13.3$, $J_{7'e-6'H}=J_{7'e-5'e}=1.8$)
4′a	1.75	1H, dd ($J_{4'a-4'e}=14.6$, $J_{4'a-3'aH}=J_{4'a-5'e}=2.9$)	1.66—1.78	1H, mul
6a	1.86	1H, dd ($J_{6a-6e}=14.4$, $J_{6a-5a}=\mathrm{J}_{6a-5e}=5.5$)	1.77—1.85	1H, mul
6′H	1.72—1.83	1H, broad mul	1.70—1.85	1H, mul
6e	2.02	1H, ddd ($J_{6e-6a}=14.4$, $J_{6e-5a}=J_{6e-5e}=5.9$)	1.96—2.07	1H, mul
5e	1.76	1H, t ($J_{5e-5a}=14.5$)	1.94—2.03	1H, mul
3a	2.07	1H, dd, ($J_{3a-3e}=14.6$)	2.07	1H, t ($J=10.1$)
4H	1.80—1.96	1H, broad mul	1.94—2.09	1 H, mul
OH	2.43	1H, broad s	2.15	1H, s
3e	2.47	1H, ddd ($J_{3e-3a}=14.3$, $J_{3e-4H}=4.9$, $J_{3e-5e}=2.0$)	2.43	1H, ddd, ($J_{3e-3a}=10.1$, $J_{3e-4H}=3.9$)
3′aH	2.57	1H, dd ($J_{3'aH-4'a}=J_{3'aH-4'e}=7.0$, $J_{3'aH-5'e}=J_{3'aH-7'e}=3.5$)	2.60	1H, d t ($J_{3'aH-4'a}=7.0$, $J_{3'aH-4'e}=1.9$)

a) in $CDCl_3$. b) in CD_3OD.

(1986).

6) M. Pierrot, J.-M. Pons, and M. Santelli, *Tetrahedron Lett.*, **29**, 5925 (1988).

7) J.-M. Pons and M. Santelli, *J. Org. Chem.*, **54**, 877 (1989).

8) F. Camps, A. Esquefa, H. Ferrer, F. Magrans, J. Pascual, and J. Sust, *An. R. Soc. Esp. Fis. Quim., Ser. B*, **57**, 791 (1961).

9) A. I. Vogel, "A Text-Book of Practical Organic Chemistry," 3rd ed, Longmans, London (1967), p. 198.

10) C. Harries and G. Roeder, *Ber.*, **32**, 3367 (1899).

11) J. Bartual, J. M. Font, E. Forne, J. Pascual, and J. Roque, *Ann. Quim.*, **68**, 483 (1972).