An unusual intramolecular hydrogen transfer during the hydrolysis of a chloroacetoxy ester

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An intramolecular hydrogen transfer from the chloroacetoxy group has been shown to occur in the hydrolysis of the sesquiterpenoid derivative, 5β-chloroacetoxy-15-norpanasinsan-8-one leading to the formation of 5ββ,8α-dihydroxy-15-norpanasinsane.

Keywords: panasinsane, hydrogen transfer, hydrolysis, sesquiterpenoid

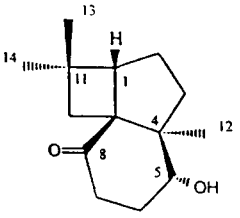
Transannular intramolecular hydride rearrangments leading to the reduction of ketones are relatively rare because of the geometrical requirements imposed by the relationship between the hydrogen donor and the ketone. In a study of intramolecular hydride shifts in 4-hydroxycyclohexanones, Warnhoff reported[1] a base-catalysed intramolecular hydrogen transfer in the interconversion of 5α-hydroxy-15-panasinsan-8-one **1** and its 8α-hydroxy-5-keto isomer. Whilst preparing[2] some sesquiterpenoid panasinsane derivatives for evaluation as biosynthetically-patterned fungistatic agents against *Botrytis cinerea*, we have observed a further intramolecular hydride transfer in this series. This rearrangment forms the subject of this paper.

5α-Hydroxy-15-norpanasinsan-8-one **1** was obtained by the literature procedure[3-5] which involved treating the norcaryophyllene epoxy-ketone, kobusone, with ethanolic potassium hydroxide. Its stereochemistry, particularly at C-5 has been thoroughly established.[4] In order to prepare the 5β-epimer of this alcohol, we carried out a Mitsunobu reaction[6] on the 5α-alcohol. Chloroacetic acid has been recommended[7] as a better nucleophile than acetic acid for this process. Treatment of the ketol with dry chloroacetic acid, triphenylphosphine and diethyl azodicarboxylate in toluene gave 5β-chloroacetoxy-15-norpanasinsan-8-one **2** in 40% yield. In comparison to the starting material, the 5-H proton resonance had changed from a double-doublet, *J*=4.2 and 11.8 Hz, to a double-doublet, *J*=3.2 and 5.6 Hz. However, molecular models showed that the cyclohexane ring of the panasinsane ring system could exist in two twisted chair conformations allowing both the 5α and 5β (and corresponding 8β and 8α) substituents to take up equatorial conformations. Hence coupling constant measurements alone may not be a reliable indicator of stereochemistry. However the stereochemistry at C-5 and C-8 can be established by nOe studies. Irradiation of the C-4α methyl signal (H-12, δ_H0.90) produced a 10.9% enhancement of the signal at δ_H 4.90 assigned H-5α. The chloroacetoxy group in **2** has, as anticipated, the 5β-configuration.

Hydrolysis of the chloroacetate ester with methanolic potassium carbonate at room temperature for 24 hours gave a diol in 79% yield instead of the anticipated ketol. The diol was assigned the structure 5β,8α-dihydroxy-15-norpanasinsane **4**. The two C**H**(OH) resonances (δ_H 3.23 and 3.30) were double-doublets, (both *J*=4.4 and 11.9 Hz). Irradiation of the 4α-methyl group resonance (H-12, δ_H 0.75) gave a 3.1% enhancement of the signal at δ_H 3.30 which was therefore assigned to the 5α-H. Confirmation of the stereochemistry at C-8 came via identification of the signal assigned to the 1β-H. Irradiation of the 11β-methyl group signal (δ_H 1.19) gave a 5.9% enhancement to a double-doublet (*J*=1.7 and 7.9 Hz) at δ_H 2.11 which was assigned to the 1β-H. Irradiation of this signal gave a 0.9% enhancement to the other C**H**(OH) resonance (δ_H 3.23) which was therefore assigned to the 8β-H. Hence the diol **4** has the 5β,8α-stereochemistry. The isomeric 5α,8β-dihydroxy-15-norpanasinsane **6**, which was prepared by the sodium borohydride reduction of the ketol **1**, possessed the 5β-H and 8α-H resonances at δ_H 3.32 and 3.38 (*J*=4.2 and 12.0 Hz).

In order to demonstrate that the chloroacetoxy group was the source of the hydrogen for the reduction, the Mitsunobu reaction was repeated with benzoic acid as the nucleophile. This gave the 5β-benzoate **3** (δ_H 5.24, triplet, *J*=4.0 Hz, 5α-H). Hydrolysis of the benzoate with methanolic potassium carbonate gave a quantitative yield of 5β-hydroxy-15-norpanasinsan-8-one **5**.[1] The ^{1}H NMR spectrum possessed the 5α-H resonance at δ_H 3.63 (double-doublet, *J*=4.2 and 7.0 Hz). Since there was no diol found in this case, the source of the hydride must be the chloroacetoxy group.

We have been unable to find any prior report of a chloroacetoxy ester acting as a source of hydrogen for an intramolecular hydrogen transfer.



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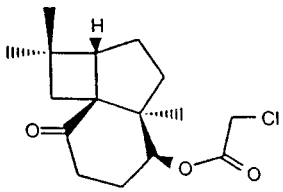

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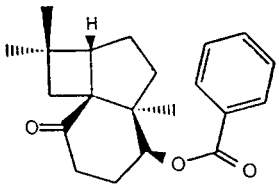

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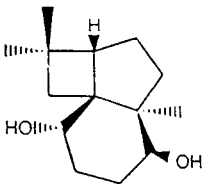

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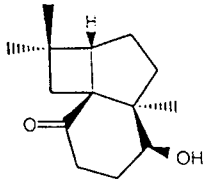

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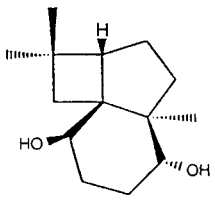

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* Correspondence.

Experimental

General experimental details: Silica for chromatography was Merck 9385. Light petroleum refers to the fraction b.p. 60–80°C. ^{1}H NMR spectra were determined at 500 MHz for solutions in deuteriochloroform. IR spectra were determined as nujol mulls. Mass spectra were determined on a Fisons Autospec mass spectrometer. Extracts were dried over sodium sulfate.

Preparation of 5β-chloroacetoxy-15-norpanasinsan-8-one **2**: 5α-Hydroxy-15-norpanasinsan-8-one **1** (450 mg), triphenylphosphine (1.07 g) and dry chloroacetic acid (385 mg) were dissolved in dry toluene (100 cm^3). Diethyl azodicarboxylate (0.65 cm^3) was added dropwise. The solution was left at room temperature for 24 h. The toluene was evaporated *in vacuo* and the residue chromatographed on silica. Elution with 10% ethyl acetate;light petroleum gave 5β-chloroacetoxy-15-norpanasinsan-8-one **2** (245 mg) as an oil, (Found: M^+ 298.1341 $C_{16}H_{23}ClO_3$ requires 298.1335); ν_{max}/cm^{-1} 1724, 1692; δ_H 0.83 (3H, s,), 0.90 (3H, s), 0.97 (3H, s), 1.36 (1H, d, *J*=12.7Hz, 10α-H), 2.17 (1H, dt, *J*=5.3 and 15.4 Hz, 7α-H), 2.43 (1H, dd, *J*=3.1 and 8.3 Hz, 1β-H), 2.46 (1H, dd, *J*=3.2 and 12.0 Hz, 10β-H), 2.69 (1H, ddd, *J*=6.4, 10.2 and 15.4 Hz, 7β-H), 4.06 (2H, s, CH_2Cl), 4.90 (1H, dd, *J*=3.2 and 5.6 Hz, 5α-H). Further elution with 25% ethyl acetate:light petroleum gave the starting material (115 mg), m.p.147–149°C (lit.,[3] 148–149°C) identified by its NMR spectrum.

*Hydrolysis of 5β-chloroacetoxy-15-norpansinsan-8-one***2**: 5α-Chloroacetoxy-15-norpanasinsan-8-one **2** (180 mg) in dry methanol (30 cm^3) was treated with dry potassium carbonate (500 mg) at room temperature for 24 h. Acetic acid (10 cm^3) was added and the solution was stirred for 30 min. The methanol was evaporated *in vacuo* and the residue was taken up in ethyl acetate. The organic layer was washed thoroughly with aqueous sodium hydrogen carbonate, water, brine and dried. The solvent was evaporated to give 5β,8α-dihydroxy-15-norpanasinsane **4** (107 mg) which crystallised from chloroform as needles, m.p. 180–182°C, (lit.,[1] 181–182°C); ν_{max}/cm^{-1} 3658; δ_H 0.72 (3H, s,), 0.75 (3H, s), 1.12 (3H, s), 2.11 (1H, dd, *J*=1.7 and 7.9 Hz, 1β-H), 3.23 (1H, dd, *J*=4.4 and 11.9Hz, 8β-H), 3.30 (1H, dd, *J*=4.4 and 11.9 Hz, 5α-H).

Preparation of 5β-benzoyloxy-15-norpanasinsan-8-one **3**: 5α-Hydroxy-15-norpanasinsan-8-one **1** (350 mg), triphenylphosphine (1.65 g) and dry benzoic acid (770 mg) were dissolved in dry toluene (100 cm^3). Diethyl azodicarboxylate (1.2 cm^3) was added dropwise. The solution was left at room temperature for 24 h. The toluene was evaporated *in vacuo* and the residue chromatographed on silica. Elution with 7.5% ethyl acetate;light petroleum gave 5β-benzoyloxy-15-norpanasinsan-8-one **3** (120 mg) as an oil, (Found: M^+ 326.1874 $C_{21}H_{26}O_3$ requires 326.1881); ν_{max}/cm^{-1} 1717, 1697; δ_H 0.91 (3H, s,), 1.04 (3H, s), 1.10 (3H, s), 1.41 (1H, d, *J*=12.1Hz, 10α-H), 2.32 (1H, dt, I 5.3 and 15.4 Hz, 7α-H), 2.54 (1H, dd, *J*=3.1 and 8.3 Hz, 10β-H), 2.62 (1H, dd, *J*=2.7 and 9.2 Hz, 1β-H), 2.69 (1H, ddd, *J*=7.7, 9.1 and 15.6 Hz, 7β-H), 5.24,(1H,t, *J*=5.3 Hz, 5α-H), 7.48 (2H, d, *J*=7.4 Hz, Ar-H), 7.60 (1H,t *J*=7.4 Hz, Ar-H), 8.03 (2H, d, *J*=7.4 Hz, Ar-H).

Hydrolysis of 5β-benzoyloxy-15-norpansinsan-8-one **3**: 5β-Benzoyloxy-15-norpanasinsan-8-one **3** (110 mg) in dry methanol (30 cm^3) was treated with dry potassium carbonate (500 mg) at room temperature for 24 h. Acetic acid (10 cm^3) was added and the solution was stirred for 30 min. The methanol was evaporated *in vacuo* and the residue was taken up in ethyl acetate. The organic layer was washed thoroughly with aqueous sodium hydrogen carbonate, water, brine and dried. The solvent was evaporated to give 5β-hydroxy-15-norpanasinsan-8-one **5** (69 mg) which crystallised from light petroleum as needles, m.p. 87–89°C, (lit.,[1] 92°C); ν_{max}/cm^{-1} 3534, 1677; δ_H (300 MHz), 0.89 (3H, s,), 0.90 (3H, s), 1.01 (3H, s), 1.0–2.4 (overlapping multiplets), 3.63 (1H, dd, *J*=4.2 and 7.0Hz, 5α-H).

Reduction of 5α-hydroxy-15-norpanasinsan-8-one with sodium borohydride: A solution of 5α-hydroxy-15-norpanasinsan-8-one **1** (250 mg) in methanol (20 cm^3) was cooled in an ice-bath and treated with sodium borohydride (50 mg) in portions. The mixture was left for 12 h. at room temperature and then acetic acid (2 cm^3) was added. The solution was concentrated and then diluted with ethyl acetate. The organic phase was washed with aqueous sodium hydrogen carbonae, water, brine and dried. The solvent was evaporated to give 5α,8β-dihydroxy-15-norpanasinsane **6** (239 mg) which crystallised from acetonitrile as fine white needles, m.p. 160–162°C (lit.,[1] 162.5–163°C); ν_{max}/cm^{-1} 3390; δ_H (300 MHz), 0.80 (3H, s,), 0.89 (3H, s), 1.15 (3H, s), 1.1–2.0 (overlapping multiplets), 2.17 (1H, dd, *J*=2.0 and 7.0 Hz, 1β-H), 3.32 (1H, dd, *J*=4.2 and 12.0 Hz,5β-H), 3.38 (1H, dd, *J*=4.1 and 12.0 Hz, 8α-H).

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