Configurations and Conformations of Some 3-Acetoxy-*cis*-hexahydro-2(3*H*)-benzofuranones

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Catalytic hydrogenation of some 2-ethoxalylcyclohexanones afforded a mixture of isomeric 3-hydroxy-*cis*-hexahydro-2(3*H*)-benzofuranones. Three 5-*t*-butyl substituted diastereomers and two 5-unsubstituted epimers were separated and identified as acetates. The configurations were determined by 350 MHz ^{1}H-nmr analysis. The conformations of these fused-compounds are discussed.

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It is known that catalytic hydrogenation of 2-oxocyclohexylglyoxylic acid [1], 2-hydroxymandelic acid [2] or 2-ethoxalylcyclohexanone [3] afforded 3-hydroxyhexahydro-2(3*H*)-benzofuranone. However, this lactone was described either as a liquid [1] or as a crystalline compound [2,3]. The liquid lactone was probably a mixture of stereoisomers, whereas the isolated solid was a single isomer of unknown configuration. We report herein the synthesis of the lactone-alcohols **2-6** and their characterization as acetates **7-11** by catalytic hydrogenation (Raney nickel) of 2-ethoxalylcyclohexanones **1a,b**. Our aim was to assess not only to the configuration of these compounds, but also, by comparing the 5-*t*-butyl substituted derivatives with their 5-unsubstituted analogues, to know which conformation of the *cis*-fused isomers **7** and **8**, having a flexible skeleton is favoured. There is general agreement that the C-O-CO-C group is planar in γ-lactones [4,5] and that a *cis*-fused-five membered ring tends to flatten the chair conformation of the cyclohexyl ring [6].

Results and Discussion.

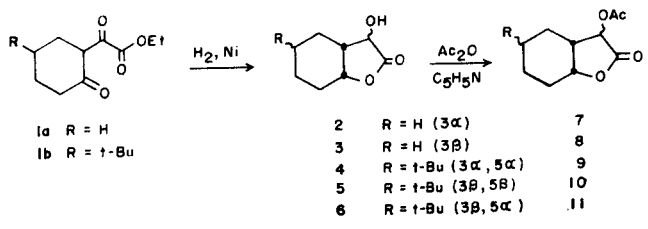
Catalytic hydrogenation (Raney nickel) of 2-ethoxalylcyclohexanones **1a,b** afforded a mixture of the *cis*-fused alcohols **2-6** as evidenced by the glc and ^{1}H-nmr examination in a synthetic mixture. However, by glc, the peaks were not well separated and in the ^{1}H-nmr spectra, direct analysis was hampered by overlap of the H-3 and H-7a protons. The signals for these hydrogens clearly separate off in the acetates of the alcohols **7-11**. Consequently, the alcohols were acetylated and the pure acetates were separated by gas chromatography and identified by ^{1}H-nmr spectral analysis. Compound **1a** (R = H) gave a mixture of the acetate 3α **7**, all *cis* and its 3β epimer **8** in a ratio of 65:35 respectively. Compound **1b** (R = *t*-Bu) afforded the isomeric acetates **9** (all *cis*), **10** and **11** in a ration of about 2:1:1 respectively.

"β" means on the same side of the ring as the hydrogen on C-3a. "α" means on the side opposite at this hydrogen.

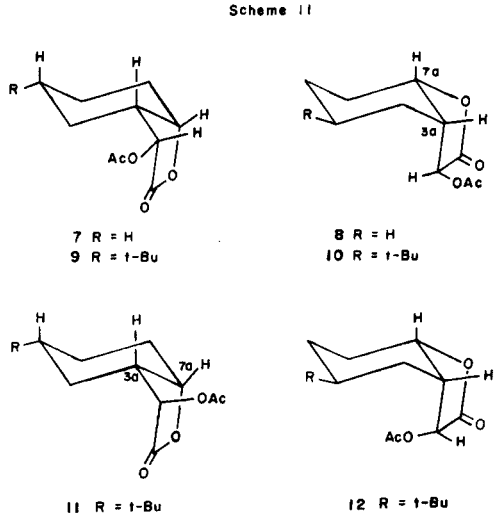
The assignment of the *cis* juncture for all the compounds **7-11** was deduced by means of ^{1}H-nmr investigation from the chemical shifts of the H-7a protons and the coupling constants H-7a,H-3a (3.2-7 Hz) determined by ^{1}H spin decoupling experiments. As expected for a *cis* stereochemistry, the H-7a proton showed a chemical shift of 4.54-4.76 ppm (Table I) close to those of the *cis*-fused lactones (~4.5 *vs* 3.9 for the *trans* isomers) [7-9]. Moreover, it is known that *cis*-hexahydro-2(3*H*)-benzofuranone is more stable than the *trans* isomer [7]. A *trans* juncture would lead to a coupling constant of 10-12 Hz [7,10-13].

In the case of the 5-substituted compounds, three out of the four possible diastereomers **9-11** were isolated. The 3α,5β isomer **12** was not obtained. A conformational rigidity is confered to these compounds by the 5-*t*-butyl group. The assignment of stereochemistry at C-3 and C-5 was

Scheme I



Scheme II



made on the basis of the coupling constants H-7a,H-7 and H-3,H-3a by referring to vicinal coupling constants in closely related compounds of known stereochemistry [7, 9, 12-15].

For the compounds **9** and **11**, the coupling constants H7a,H-7 with J values of 3.2 and 3.2 Hz were only consistent with a *cis* fusion of the rings with H-7a equatorial to the cyclohexane ring, consequently, the 5α-*t*-butyl position was inferred. The *cis* relationship of H-3 and H-3a for the compound **9** (all *cis*) was deduced from the coupling constant of 6.5 Hz, in analogy with the 3-methyl or 3-hydroxy-7-iodo analogues [14,15]. For the compound **11**, the magnitude of the coupling constant H-3,H-3a of 0 Hz is only consistent with a *trans* relationship of these protons with a dihedral angle H-3,C-3,C-3a,H-3a of 90° [13]. For the Compound **10**, the 3β position of the hydroxyl group is deduced from the coupling constant H-3,H-3a of 8.7 Hz, only compatible with a dihedral angle of 150-160° estimated from Dreiding model, according to literature assignment upon 3-substituted *cis*-fused lactones [14,15]. Thus, the *t*-butyl group and the C-7a-O bond are attached equatorially (the reverse situation at C-7a in compounds **9** and **11** in which the C-7a-O bond is axial). It is known that the magnitude of the vicinal coupling constant ax,eq or eq,ax is dependent upon the orientation of electronegative substituents [16], nevertheless, in this conformation, a flattening of the lactone ring and consequently of the cyclohexyl ring [17] could be expected to relieve the C-3, C-3a, C-5-H, C-7-H diaxial interactions. The vicinal coupling constants H-7a, H-7 with J values of 7 and 4.5 Hz may be related to smaller values of the dihedral angles than in a regular chair form.

Compounds **7** (3α) and **8** (3β) (R = H) could, a priori, exist in two interconvertible conformations. The remarkable similarity of the spectra of **7** and **9** and the close analogy of those of **8** and **10** suggest that these compounds were conformationally homogeneous. This comparison seems to show that the conformational equilibria of **7** and **8** are shifted towards the conformers having a pseudoequatorial hydroxyl group, thus the C-7a-O bond occupying an axial position in the isomer **7** 3α and an equatorial one in the isomer **8** 3β.

Table I

Pertinent ^{1}H-NMR Spectral Data of the Acetates **7-11**

Compound	δ H-3	δ H-7a	J, Hz H-3a,H-7a	J, Hz H-7a,H-7	J, Hz H-3,H-3a
7	5.53	4.54	3.2	3.2, 3.2	6.5
8	5.41	4.61	5.6	5.6, 8.4	8.8
9	5.59	4.50	3.2	3.2, 3.2	6.5
10	5.53	4.70	7.0	4.5, 7.0	8.7
11	4.87	4.76	3.2	3.2, 3.2	0

EXPERIMENTAL

Melting points were recorded on a Kofler hot plate. Boiling points are uncorrected. The ir spectra were recorded with a Beckman model Acculab 2 spectrometer. The ^{1}H-nmr spectra were recorded by using a Bruker WP-80 80 MHz or 350 MHz Cameca spectrometers. All spectra were obtained in deuteriochloroform as solvent and the chemical shifts are recorded in δ units in parts per million downfield from TMS. Gas chromatographic separations were performed on a Varian Aerograph 90P (TC detector) equipped with a 6 m × 4 mm column packed with 20% DEGS on 60/80 mesh Chromosorb W. Elemental analyses were determined by Microanalytical Laboratory, Centre National de la Recherche Scientifique 69390 Vernaison, France.

3-Hydroxy-*cis*-hexahydro-2(3*H*)-benzofuranones (**2-6**). General Procedure.

A mixture of 2-ethoxalylcyclohexanone **1a** [18], or **1b** [19] (50 mmoles, ethanol (75 ml)) and W4 Raney nickel (1 g) was hydrogenated at room temperature and an initial pressure of 100 atmospheres for 3 hours. The catalyst was filtered and the filtrate evaporated to give an oil which was distilled under reduced pressure, to yield a mixture of isomeric alcohols.

The mixture **2 + 3** was obtained in a 70% yield, bp 130-135° (15 mm Hg) [lit (0.01 mm Hg) [3], 171-173° (15 mm Hg) [1]].

The mixture **4 + 5 + 6** was obtained in a 80% yield, bp 155-160° (0.2 mm Hg); ir (film): 3350-3300, 1780 cm^{-1}.

Anal. Calcd. for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.85; H, 9.65.

The mixture of isomeric alcohols partly crystallized on standing.

3α-Hydroxy-*cis*-hexahydro-2(3*H*)-benzofuranone (**2**).

This compound was obtained by recrystallization of the solid material **2 + 3** from hexane in a 40% yield; mp 131-132° (lit 132-133° [2], 133-134° [3]; ^{1}H-nmr (80 MHz, deuteriochloroform): δ 1.0-2.8 (m, 10H with 1H deuterium oxide exchangeable), 4.48 (m, $W_{1/2}$ = 8 Hz, 1H), 4.59 (d, J = 6.5 Hz, 1H).

5α-*t*-Butyl-3α-hydroxy-*cis*-hexahydro-2(3*H*)-benzofuranone (**4**).

This compound was obtained by recrystallization of the solid material **4 + 5 + 6** from hexane in a 30% yield, mp 167°; ^{1}H-nmr (80 MHz, deuteriochloroform): δ 0.87 (s, 9H), 0.9-2.9 (m, 9H, with 1H deuterium oxide exchangeable), 4.52 (m, $W_{1/2}$ = 8 Hz, 1H), 4.75 (d, J = 6.5 Hz, 1H).

3-Acetoxy-*cis*-hexahydro-2(3*H*)-benzofuranones **7-11**. General Procedure.

A mixture of alcohols **2 + 3** or **4 + 5 + 6** (20 mmoles), anhydrous pyridine (40 ml) and acetic anhydride (53 mmoles, 5 ml) was refluxed for 15 minutes and poured onto ice-aqueous hydrochloric acid and extracted with ether. The organic layer was washed successively with 10% hydrochloric acid, 5% sodium bicarbonate and water and then dried. After elimination of the solvent, the residue was distilled under reduced pressure to give a mixture of isomeric acetates **7 + 8** or **9 + 10 + 11** which was analyzed by ^{1}H-nmr spectroscopy. The mixture **7 + 8** was obtained in a 80% yield, bp 125-130° (0.5 mm Hg); the **7:8** ratio was 65:35; ir (deuteriochloroform): 1795, 1750 cm^{-1}.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.80; H, 7.46.

The mixture **9 + 10 + 11** was obtained in a 90% yield, bp 150-155° (0.5 mm Hg); the **9:10:11** ratio was 2:1:1 respectively; ir (deuteriochloroform): 1800, 1755 cm^{-1}.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.32; H, 8.99.

A portion of the isomeric mixture was further chromatographed (glc DEGS, 200°) so as to separate the pure isomer. The elution order was **8** then **7** or **11**, **9** and **10**.

3α-Acetoxy-*cis*-hexahydro-2(3*H*)-benzofuranone (**7**).

This compound was isolated by glc from the mixture of compounds **7 + 8** in a 50% yield; n_D^{20} = 1.4767; ^{1}H-nmr (350 MHz, deuteriochloroform): δ 1.10-2.30 (m, 8H), 2.15 (s, 3H), 2.63-2.73 (m, 1H), 4.54 (q, J = 6.5 Hz, 1H).

3β-Acetoxy-*cis*-hexahydro-2(3*H*)-benzofuranone (**8**).

This compound was isolated by glc from the mixture of compounds **7** + **8** in a 25% yield; n_D^{20} = 1.4752; ^{1}H-nmr (350 MHz, deuteriochloroform): δ 1.30-2.30 (m, 8H), 2.17 (s, 3H), 2.52-2.61 (m, 1H), 4.61 (ddd, J = 5.6, 5.6 and 8 Hz, 1H), 5.41 (d, J = 8.8 Hz, 1H).

3α-Acetoxy-5α-*t*-butyl-*cis*-hexahydro-2(3*H*)-benzofuranone (**9**).

This compound was isolated by glc from the mixture of compounds **9** + **10** + **11** in a 40% yield, mp 123-124°; ^{1}H-nmr (350 MHz, deuteriochloroform): δ 0.85 (s, 9H), 0.80-2.35 (m, 7H), 2.19 (s, 3H), 2.65-2.74 (m, 1H), 4.50 (q, J = 3.2 Hz, 1H), 5.59 (d, J = 6.5 Hz).

3β-Acetoxy-5β-*t*-butyl-*cis*-hexahydro-2(3*H*)-benzofuranone (**10**).

This compound was isolated by glc from the mixture of compounds **9** + **10** + **11** in a 50% yield, mp 90-91°; ^{1}H-nmr (350 MHz, deuteriochloroform): δ 0.82 (s, 9H), 1.10-2.00 (m, 7H), 2.17 (s, 3H), 2.85-2.93 (m, 1H), 4.70 (ddd, J = 7.0, 7.0 and 4.5 Hz, 1H), 5.53 (d, J = 8.7 Hz).

3β-Acetoxy-5α-*t*-butyl-*cis*-hexahydro-2(3*H*)-benzofuranone (**11**).

This compound was isolated by glc from the mixture of compounds **9** + **10** + **11** in a 18% yield; 91-92°; ^{1}H-nmr (350 MHz, deuteriochloroform): δ 0.84 (s, 9H), 0.70-2.19 (m, 7H), 2.11 (s, 3H), 2.28-2.36 (m, 1H), 4.76 (q, J = 3.2 Hz, 1H), 4.87 (s, 1H).

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