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SYNTHESIS OF GRISAN.

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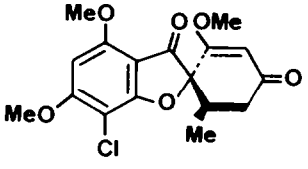
Abstract - Grisan (Spiro[benzofuran-2(3H)1'-cyclohexane], **2**) has been synthesized for the first time starting from cis-2-(2-hydroxybenzyl)-cyclohexanol (**7**).

Griseofulvin[1] (**1**) has a spiro- [benzofuran-2-(3H)1'-cyclohexane] skeleton **2**, which was named grisan by Grove et al.[2]. Although **1** and several of its derivatives were prepared in the past[3-7], the basic compound grisan itself has not yet been synthesized.

We realized this synthesis by chance during the course of the attempted preparation of the hexahydro-xanthenes **10** and **11**. The benzylidene derivative **4**, easily prepared by condensation of cyclohexanone with salicylaldehyde benzyl ether[8], served as starting material. Its catalytic hydrogenation should have resulted in a mixture of the cis- and trans- benzylcyclohexanols[9,11] **7** and **8**, which could cyclize to **10** and **11**. Instead of this the catalytic hydrogenation of **4** yielded 52% of trans-**9**[10], indicating the participation of the free hydroxyl in the formation of a hemiacetal structure.



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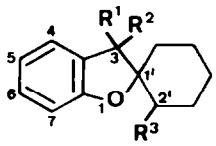
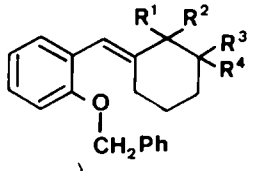


2: $R^1 = R^2 = R^3 = H$

2-D: $R^1 = H$, $R^2 = R^3 = D$

3: $\left.\begin{matrix}R^1\\R^2\end{matrix}\right\} = O$, $R^3 = H$

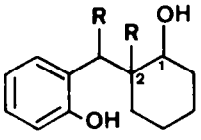


4: $\left.\begin{matrix}R^1\\R^2\end{matrix}\right\} = O$, $R^3 = R^4 = H$

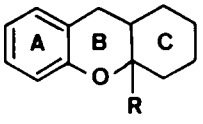
5: $\left.\begin{matrix}R^1\\R^2\end{matrix}\right\} = O$, $\left.\begin{matrix}R^3\\R^4\end{matrix}\right\}$ = E-2-Benzyloxybenzylidene

6: $R^1 = R^3 = R^4 = H$, $R^2 = OH$

This anomalous behaviour could, however, be avoided if **4** was first reduced with $NaBH_4$ in ethanol or with DIBAH in toluene at -65°C to the corresponding allylic alcohol **6**, the catalytic hydrogenation of which proceeded as expected to the desired cis- and trans- cyclohexanol derivatives **7** and **8**, easily separable by chromatography. Grisan (**2**) could be prepared from the cis-diol **7** by treatment with BF_3-OEt_2 in dichloromethane at room temperature, or with p-toluenesulfonic acid in boiling benzene. The structure of **2** was proved by its ^{1}H-and ^{13}C-NMR spectra as well as by its mass spectrum, and further supported by Jones oxidation[11] of **2** to the ketone **3** in acetic acid, confirming the presence of a benzylic methylene group. The trans-diol **8** did not react at all with BF_3-OEt_2; on treatment with p-toluenesulfonic acid it yielded instead a mixture of cis [10] - (**10**) and trans-hexahydroxanthene [12] (**11**) in a ratio of 6:1.

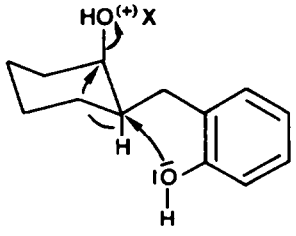


7: R = H, H - 1/H - 2 cis
7-D: R = D, H - 1/D - 2 cis
8: R = H, H - 1/H - 2 trans
8-D: R = D, H - 1/D - 2 trans

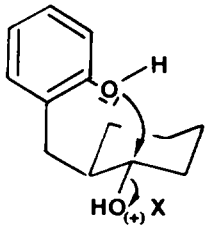


9: R = OH, B/C - trans
10: R = H, B/C - cis
11: R = H, B/C - trans

In order to rationalize the different reactivities of these two stereomers **7** and **8** we reacted the dideuterated derivative **7-D** in analogous manner and found that a 1,2-hydrogen shift has taken place leading to the spirocompound **2-D**. In the reaction of **8-D** on the other hand the two deuterium atoms retain their original positions. During the (formal) elimination of water only in **7** the XO-group and the neighbouring H-atom can adopt antiperiplaner positions which leads to this hydride shift (from C-2 to C-1) with concomitant attack of the phenolic OH at C-2. **8** cannot adopt a conformation necessary for such a hydride migration. The main product is formed under these S_N2-conditions by inversion leading to the thermodynamically less stable cis-compound **10**. Since the energy of this transition state is relatively high because it necessitates an axial arrangement of the benzylic group with attack of the phenolic OH from "inside the ring", the S_N1-type reaction can already compete and via this path appr. 15% of the trans-isomer **11** are formed. The ratio of 6:1 for the obtained mixture (**10/11**) does not depend on the reaction time, thus the formation of the trans-product during a consecutive ring-opening/ring-closure reaction can be excluded. In the ground state in both molecules **7** and **8** the benzylic group prefers the equatorial position as follows from the ^{1}H-NMR-spectra.



7



8

EXPERIMENTAL

M.p.s were determined on a Kofler hot stage and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were determined on a Varian XL 100 at 100 MHz or on a Perkin-Elmer R12 at 60 MHz with TMS as internal standard in $CDCl_3$. Mass spectra were recorded on a JEOL-0156-2 instrument (accelerating voltage 10 kV, ionization energy 75 eV). For work-up the solutions were dried with anh. magnesium sulfate and evaporated in vac.

2-(2-Benzyloxy)-benzylidene-cyclohexanone (4) and 2,6-Bis-(2-benzyloxy)-benzylidene-cyclohexanone (5):

4g Cyclohexanone and 4.2g 2-benzyloxy-benzaldehyde[8] were dissolved in 80ml ethanol, 5 ml piperidine were added and the solution was refluxed for 48 h. Partial evaporation gave 0.9g (15%) **5**, work-up of the mother liquor and chromatography on silica gel (benzene/2-butanone 20:1) gave 3g (51%) **4**, m.p. 80-83°C (from methanol).

4: IR(KBr): ν(CO) 1670cm^{-1}. UV(ethanol): λ_{max} (ε) 314i(7300), 282(10400), 227i(11200), 204(27600). ^{1}H-NMR: 1.50-2.20 (m, 4- and 5-CH_2), 2.42-2.98 (m, 3 and 6-CH_2), 5.12 (s, PhC$\underline{H}_2$), 6.79-7.66 (m, 9 arom. H), 7.80 (t, J=1.5 Hz, vinylic H). $C_{20}H_{20}O_2$ (292.4) Calc. C 82.15, H 6.89; Found C 82.04, H 6.86.

5: m.p. 141-142°C (from ethanol). IR (KBr): ν(CO) 1656cm^{-1}. UV (methanol) λ_{max} (ε) 328(5500), 307 (5400), 255(5200), 234(6500), 208(23900) nm. ^{1}H-NMR: 1.55-2.00 (m, 4-CH_2), 2.65-3.05 (m, 3- and 5-CH_2), 5.14 (s, 2 PhC$\underline{H}_2$), 6.80-7.70 (m,18 arom. H), 8.16 (bs, 2 vinylic H). $C_{34}H_{30}O_3$ (486.6) Calc. C 83.92, H6.21; Found C 83.42, H 6.11.

trans-4a-Hydroxy-1,2,3,4,4a,9a-hexahydro-xanthene (9)

Catalytic hydrogenation of 600mg **4** in 30ml methanol over 10%Pd-C gave after usual work-up 230mg (51%) **9**, m.p. 99-100°C (from n-hexane), lit[10]: 98°C. IR (KBr): ν(OH) 3480cm^{-1}.

2-(2-Benzyloxy)-benzylidene-cyclohexanol (6)

a) To the stirred solution of 450mg **4** in 45ml ethanol 150mg sodium borohydride were added in small portions. After 15 min a few drops of acetic acid were added to quench the excess of the reagent and on dilution with water the product was extracted with $CHCl_3$. Evaporation yielded 420mg (92%) **6** as a colourless oil.

b) To the solution of 292mg **4** in 20ml dry toluene a solution of 2.5mmol DIBAH in toluene was added at -65°C under argon atmosphere. After 0.5 h the usual work-up resulted in 264mg (90%) **6**.

IR (CCl_4): ν(OH) 3300cm^{-1}, ν(C=C) 1580 and 1600cm^{-1}. UV(methanol): λ_{max} (ε) 208(37700), 243(14100), 287(5100). MS:m/e (%) 294(100), 276(27.2), 203(67.2), 197(8.8), 185(86.4), 157(72.8), 144(18.4), 131(52.8), 115(28.8), 107(73.6), 92(47.2), 89(29.6), 77(33.6), 65(31.2), 63(30.4). Calc. for $C_{20}H_{22}O_2$ 294.161; Found 294.158. ^{1}H-NMR: 0.75-3.00 (bm, 3-, 4-, 5-, and 6-CH_2, and 1-OH), 4.15-4.48 (m, 1-H_{ax}), 5.15 (s, PhC$\underline{H}_2$), 6.65 (s, vinylic H), 6.79-7.66 (m, 9 arom H).

cis-2-(2-Hydroxybenzyl)-cyclohexanol (7) and trans-2-(2-Hydroxybenzyl)-cyclohexanol (8)

Catalytic hydrogenation of 420mg **6** in 50ml methanol over 400mg 10%Pd-C at r.t. resulted in 310mg of a mixture of **7** and **8**, which was separated on a silica gel column (benzene/2-butanone 5:1).

7: 117mg (40%), m.p. 124-126°C (from n-hexane/benzene), lit[11]: 123°C. IR(KBr): ν(OH) 3380 and 3100 cm^{-1},ν(C=C) 1605, 1595cm^{-1}. MS: m/e (%) 206(27.5), 188(28.2), 159(3.5). 145(10.2), 131(6.6), 120(10.7), 108(24.8), 107(100), 91(72), 81(29.8), 80(23.9), 79(12.3). ^{1}H-NMR: 1.30-1.90 (bm, 3-, 4-, 5-, 6-CH_2, and 2-CH), 2.40 and 2.82 (2 dd, PhC$\underline{H}_2$, J_{gem}=14Hz, $J_{2,vicH}$=4 and 10 Hz), 3.74 (bm, 1-H_{eq}, $J_{1,2}$=2Hz, $J_{1,6}$=2 and 3 Hz), 6.70-7.20 (m, 4 arom. H).

8: 37mg (12%), m.p. 96-97°C (from methylenechloride), lit[9]: 98°C. IR(KBr): ν(OH) 3400 and 3150cm^{-1}, ν(C=C) 1615, 1595cm^{-1}. MS: m/e (%) 206(32), 188(30.3), 159(3.9), 145(9.2), 131(6.7), 120(13.1), 108(24.9), 107(100), 91(8.4), 81(35.2), 80(20), 79(11.9). ^{1}H-NMR: 0.80-2.10 (bm, 3-, 4-, 5-, 6-CH_2, and 2-CH), 2.68 and 2.86 (2 dd, PhC$\underline{H}_2$, J_{gem}=14Hz, $J_{2,vicH}$=2.5 and 5Hz), 3.24 (m, 1-H_{ax}, $J_{1,2}$=10Hz, $J_{1,6}$=10 and 4Hz).

cis-[2-D]-2-[(2-Hydroxyphenyl)-[D]-methyl]-cyclohexanol (7-D) and trans-[2-D]-2-[(2-Hydroxyphenyl)-[D]-methyl]-cyclohexanol (8-D)

294mg 2-(2-Benzyloxy)-benzylidene-cyclohexanol in acetone were hydrogenated with D_2 as described for **7** and **8**. **7-D**: 120mg (57%), m.p. 123-125°C (from n-hexane). D-content (96.3%) was determined by MS based on the M^+-peak. $C_{13}H_{16}D_2O_2$ (208.01) Calc. C 74.99, H+D 9.62; Found C 74.74, H+D 9.59.

8-D: 42mg (20%), m.p. 94-95°C (from n-hexane). D-content: 97.2%. $C_{13}H_{16}D_2O_2$ (208.01) Calc. C 74.99, H+D 9.62; Found C 74.80, H+D 9.57.

Grisan (Spiro [benzofuran-2(3H),1'-cyclohexane]) (2)

a) To a solution of 450mg **7** in 25ml dry CH_2Cl_2 9ml BF_3.OEt_2 were added at r.t. After 100 h the reaction mixture was extracted with water to get a neutral solution, which was dried, evaporated, and purified on a silica gel column with n-hexane to give 330mg (80%) **2** as a colourless oil.

b) A solution of 100mg **7** and 25mg PTS in 10ml dry benzene was refluxed for 48 h. The work-up was similar to the one described in part a).

IR (CCl_4): ν(CH) 3040, 2910, 2850cm^{-1}, ν(C=C) 1610, 1598, 1485, 1460, 1455cm^{-1}.MS: m/e (%) 188(64), 159(4.6), 145(16), 131(14.6), 120(9.9), 108(24.5), 107(100), 94(5.2), 91(8.7), 81(54.1), 80(31.6), 79(12.5). Calc. for $C_{13}H_{16}O$ 188.119; Found 188.117. ^{1}H-NMR: 1.30-2.00 (bm, 2'-, 3'-, 4'-, 5'-, and 6'-CH_2), 2.91 (s, 3-CH_2), 6.65-7.15 (bm, 4 arom. H). ^{13}C-NMR: 23.06 (3'- and 5'-C), 25.26 (4'-C), 37.17 (2'- and 6'-C), 41.13 (3-C), 88.10 (1'-C), 109.50 (7-C), 119.72 (5-C), 125.10 (4-C), 126.66 (4a-C), 127.83 (6-C), 158.95 (7a-C).

2',3-D_2 -Grisan (Spiro [benzofuran-2(3D), 1'-[2'-D]-cyclohexane]) (2-D)

70mg **7-D** treated as described for the synthesis of **2** resulted in 35mg **2-D**. D-content 99.1%. Calc. for $C_{13}H_{14}D_2O$ 190.132; Found 190.133. ^{13}C-NMR 22.99 (3'-C), 23.08 (5'-C), 25.23 (4'-C), 36.82 (2'-C), 37.17 (6'-C), 40.70 (3-C), 88.24 (1'-C), 109.51 (7-C), 119.72 (5-C), 125.15 (4-C), 126.76 (4a-C), 127.85 (6-C), 158.92 (7a-C).

cis-1,2,3,4,4a,9a-Hexahydro-xanthene (**10**) and trans-1,2,3,4,4a,9a-Hexahydroxanthene (**11**)

A solution of 100mg **8** and 25mg PTS in 10ml dry benzene was refluxed for 160 h. After removal of the acid by extraction with water the solution was dried. Evaporation and chromatography of the residue (70mg) on silica gel plates (n-hexane/acetone 200:1) afforded **10** and **11**.

10: 42mg (46%), m.p. 71-72°C (from n-hexane), lit[10]: 74°C. ^{1}H-NMR: 1.20-2.20 (bm, 1-, 2-, 3-, and 4-CH_2), 2.50 and 3.00 (2 dd, 9-CH_2, J_{gem}=16Hz, $J_{9,9a}$=6 and 3Hz), 4.21 (m, 4a-CH_{eq}, $J_{4a,9a}$=2.5Hz, $J_{4,4a}$=2.5 and 4Hz), 6.70-7.15 (m, 4 arom H).

11: 7mg (8%), m.p. 76-77°C (from n-hexane), lit[12]: 78°C. ^{1}H-NMR: 0.80-2.40 (bm, 1-, 2-, 3-, and 4-CH_2), 2.57 and 2.70 (2 dd, 9-CH_2, J_{gem}=16Hz, $J_{9,9a}$=5.5 and 0.5Hz), 3.60 (m, 4a-CH_{ax}, $J_{4a,9a}$= 10Hz, $J_{4,4a}$ = 10 and 4Hz), 6.70-7.15 (m, 4 arom. H).

Spiro [benzofuran-2(3H),1'-cyclohexan]-3-one (**3**)

The solution of 60mg **2** in 3ml acetic acid was oxidized with Jones' reagent[11]. The usual work-up yielded 76mg crude product. Chromatography on silica gel plates (n-hexane/acetone 100:1) afforded 24mg (37%) **3** as a colourless oil. Calc. for $C_{13}H_{14}O_2$ 202.098; Found 202.096.

IR(CCl_4): ν(CO) 1710cm^{-1}. ^{13}C-NMR: 21.67 (3'- and 5'-C) 24.66 (4'-C), 31.65 (2'- and 6'-C), 89.65 (1'-C), 113.68 (7-C), 120.28(4a-C), 121.49(5-C), 124.79(4-C), 137.80(6-C), 171.22(7a-C), 204.10(3-C).

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