Stereospecific Synthesis of 2,3-Disubstituted 1,4-Benzodioxans

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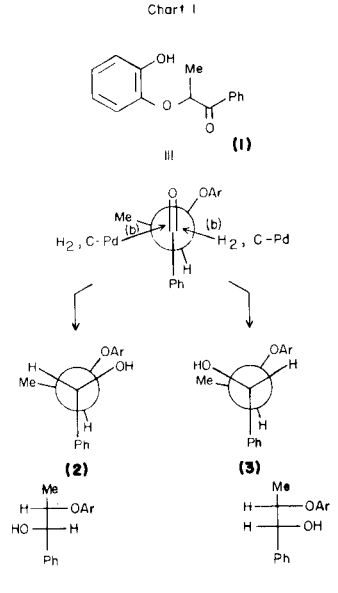
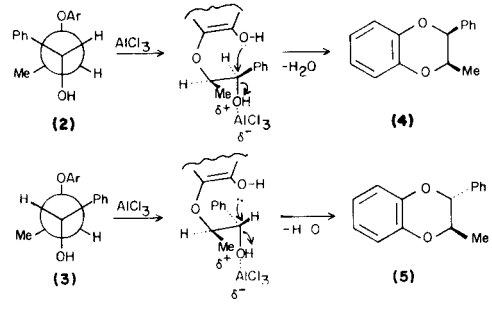
The synthesis of *cis*- and *trans*-2-methyl-3-phenyl-1,4-benzodioxans **4** and **5**, from 1-phenyl-2-[2-(hydroxy)-phenoxy]propanols *threo* **2** and *erythro* **3** are described.

J. Heterocyclic Chem., **18**, 415 (1981).

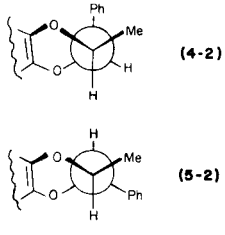
In connection with a project involving the synthesis of natural compounds containing the benzodioxane ring (1), we needed a method for the stereospecific synthesis of *cis*- and *trans*-2,3-disubstituted 1,4-benzodioxans. We now report that 2-methyl-3-phenyl-1,4-benzodioxans *cis* **4** and *trans* **5** have been obtained, respectively, by cyclization of 1-phenyl-2-[2-(hydroxy)phenoxy]propanols *threo* **2** and *erythro* **3**. Compounds **2** and **3** were obtained by catalytic hydrogenation of 1-benzoyl-1-[2-(hydroxy)phenoxy]ethane **1**. The *erythro* and *threo* diastereoisomers were obtained in the ratio 1.23:1, and were isolated by chromatography on silica gel. Each isomer was submitted to cyclization with aluminium chloride in benzene solution; after 10 minutes the mixture was worked up and the 1,4-benzodioxane was isolated. The *trans*-isomer **5** shows ^{1}H-nmr signals at δ 4.52 (d, 1H, C*H*Ph, J = 8) and δ 4.00 (m, 1H). From the $J_{2,3}$ value it is possible to deduce that compound **5** is in the most stable conformation **(5a)** (2) with the methyl and phenyl groups in *trans* diequatorial positions. The *cis* isomer **4** shows ^{1}H-nmr signals at δ 5.10 (d, 1H, J = 3) and at δ 4.51 (m, 1H). The first ^{1}H-nmr signal is attributable to an axial/equatorial coupling between the δ 2H and 3H, and it is possible to deduce that **4** is in the conformation **4a**. Cyclization of *erythro* **3** gives only the *trans* isomer **4**. Therefore, this cyclodehydration is stereoselective and we believe that it proceeds through the mechanism reported in the Chart 1.

Chart I





Scheme-I



EXPERIMENTAL

All melting points were taken with a Reichert thermovar micro melting point apparatus and are uncorrected. Ir spectra were determined using a Perkin Elmer 257 spectrophotometer. ^{1}H-nmr spectra were recorded with a Jeol-C-60-HL spectrometer using TMS as the internal standard. The chemical shifts and coupling constants are reported in δ and Hz, respectively. The mass spectra were measured with a Varian Matt-113 (75 eV, direct inlet systems) spectrometer.

Synthesis of 1-Phenyl-2-2-(hydroxy)phenoxypropanols (**2** and **3**).

1-Benzoyl-1-2-(hydroxy)phenoxyethane **1**, (5 g., 20 mmoles), prepared as previously described by A. Pelter (3), was dissolved in 50 ml. of methanol, and 0.5 g. of 10% palladium on carbon was added to the solution at room temperature. Hydrogen was passed through the stirred solution for 8 hours. The catalyst was removed by filtration through a small Hirsh funnel and the solvent was distilled under vacuum to give 4.62 g. of a yellow oily residue. This oil was divided in portions for further experimentation. Gas chromatography showed that the oily mixture contains two products in the ratio 1.23:1 corresponding to two isomers **2** and **3**. These two compounds were isolated by chromatography on silica gel H-60. Elution with hexane/ether 4:1 gave 75% of a crude oil that after further purification was identified as the pure *threo* isomer **2** (1.7 g., 34%); ir (carbon tetrachloride): 3350, 3050, 2950, 1260; nmr (deuteriochloroform): 1.05 (d, 3H, CH_3, J = 6), 3.25 (s, 1H, OH), 3.42 (d, 1H, C*H*OH), 4.58 (q, 1H, C*H*CH_3, J = 6), 5.50 (s, 1H, OH), 7.01 (s, 4H, C_6H_4),

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7.45 (s, 5H, C_6H_5).

On the contrary, elution with hexane/ether 1:1 gave 80% of a crude product that was further purified and identified as the pure *erythro* isomer **3** (2.18 g., 43%); ir (carbon tetrachloride): 3350, 3050, 2950, 1260; nmr (deuteriochloroform): 1.25 (d, 3H, CH_3, J = 7), 2.88 (s, 1H, OH), 3.00 (d, 1H, C*H*OH), 4.60 (q, 1H, C*H*CH_3, J = 7), 5.21 (s, 1H, OH), 7.00 (s, 4H, C_6H_4), 7.40 (s, 5H, C_6H_5).

Synthesis of Diastereoisomers 1,4-Benzodioxans (**4** and **5**).

The *threo* isomer **2** (1 g.) was dissolved in anhydrous benzene (20 ml.) and cooled to 0°. To the stirred solution was added 2 g. of aluminium chloride in portions over a period of 10 minutes, keeping the temperature at 20-25° with the aid of an ice water bath. The mixture was stirred for an additional hour. Hydrochloric acid (5%, 10 ml.) was then added to the reaction mixture and the organic layer was separated, washed with saturated sodium bicarbonate solution, dried over sodium sulphate and evaporated under vacuum to give 0.80 g. of a crude oily product. Gas chromatography showed the formation of only one compound corresponding to the *cis* isomer **4**, (1.29 g., 29%). Chromatography on silica gel with hexane gave crystals of **4**, m.p. 70-73°; ms: m/e 226 (M^+); ir (carbon tetrachloride): 3030, 2920, 1600, 1450, 1260; nmr (carbon tetrachloride): 1.07 (d, 3H, CH_3, J = 3), 4.51 (m, 1H, C*H*CH_3), 5.10 (d, 1H, C*H*C_6H_5, J = 3), 6.75 (s, 4H, C_6H_4), 7.27 (s, 5H, C_6H_5).

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.23. Found: C, 79.50; H, 6.23.

Under the same experimental conditions, the *erythro* isomer **3** gave only the *trans* isomer **5** (yield 52%), m.p. 90-91° ms: m/e 226 (M^+); ir (carbon tetrachloride): 3030, 2920, 1600, 1450, 1260; nmr (carbon tetrachloride): 1.10 (d, 3H, CH_3, J = 8), 4.00 (m, 1H, C*H*CH_3), 4.52 (d, 1H, C*H*C_6H_5, J = 8), 6.75 (s, 4H, C_6H_4), 7.27 (s, 5H, C_6H_5).

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.23. Found: C, 79.55; H, 6.23.

Acknowledgement.

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REFERENCES AND NOTES

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