COMMUNICATIONS

An Improved Synthesis of *trans*-5,6-Dihydroxy-1,3-cyclohexadiene (*trans*-1,2-Dihydroxy-1,2-dihydrobenzene)

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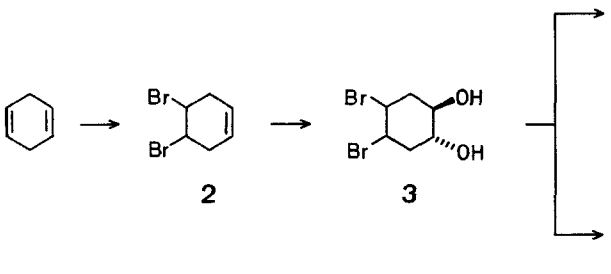
Benzene is metabolised by mammalian species predominantly to phenol and conjugates derived therefrom, but to some extent also to *trans*-5,6-dihydroxy-1,3-cyclohexadiene (*trans*-1,2-dihydroxy-1,2-dihydrobenzene **1**)[1]. The latter is then further metabolised by a NADP-dependent dehydrogenase to catechol[2]. The remarkable organ selectivity of benzene toxicity[3] may be due to the presence of different enzymes or enzyme forms involved in benzene metabolism in susceptible versus resistant organs. The study of *trans*-1,2-dihydroxy-1,2-dihydrobenzene dehydrogenase required a synthetic source of **1**.

Of the many attempts to prepare **1**, some failed[4,5] and some succeeded, but with yields of less than 8%[6,7].

We therefore developed a five-step synthesis starting with 1,4-cyclohexadiene which affords **1** in an overall yield of 51%.



1,4-Cyclohexadiene (Merck, Darmstadt) was brominated in chloroform at −70° to give 4,5-dibromocyclohexene **2**[8] in 92% yield. This product **2** was transformed to **3** by the action of performic acid in formic acid followed by acidic methanolysis.

All attempts to dehydrobrominate **3** to **1** quantitatively using numerous bases (potassium hydroxide, sodium methoxide, triethylamine, pyridine) and solvents (water, ethanol, ether, acetonitrile, tetrahydrofuran, benzene) were unsuccessful.

Only 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) in tetrahydrofuran (60°, 6 h) produced small amounts (5%) of **1**. Even when the hydroxy groups were protected by formation of a dibenzoate **4a**[9] the dehydrobromination to **5a** with DBN in ether or tetrahydrofuran at 5° did not work satisfactorily.

Finally the dehydrobromination of *trans*-1,2-diacetoxy-4,5-dibromocyclohexane (**4b**) with lithium chloride and lithium carbonate in hexamethylphosphoric triamide led to a complete conversion to **5b** as described for a similar compound[10,11].

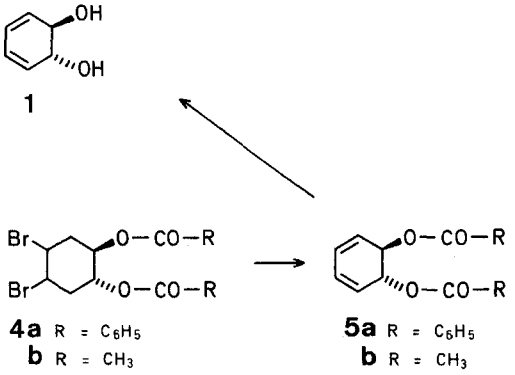
The formation of phenyl acetate, a by-product in this dehydrobromination, can be kept to a minimum by optimisation of reaction temperature and time. When **5b** was purified by distillation no further aromatisation was observed. In the final step, **5b** was reduced to **1** by treatment with lithium tetrahydroaluminate in ether at −3°.

***trans*-1,2-Dihydroxy-4,5-dibromocyclohexane (3):**
A solution of 4,5-dibromocyclohexene **2** (20.2 g, 84.2 mmol) in chloroform (15 ml) is dropped at 30° in the course of 60 min with vigorous stirring to a solution of 30% hydrogen peroxide (12 ml) in 98% formic acid (50 ml). Stirring is continued for an additional 12 h and then the volatile components are removed under reduced pressure. Methanol (150 ml) and *p*-toluenesulphonic acid (40 mg) are added and the mixture is heated under reflux for 1 h. The methanol is removed and the residue recrystallised from chloroform to give **3** as white needles; yield: 19.8 g (86%); m.p. 124°.

$C_6H_{10}Br_2O_2$ (274.0) calc. C 26.31 H 3.68; found 26.43 3.73

^{1}H-N.M.R. (60 MHz, CD_3COCD_3): δ = 2.2–2.5 (m, 4H), 3.6–4.0 (m, 2H), 4.2 (d, 2H) 4.4–4.8 ppm (m, 2H).

***trans*-1,2-Diacetoxy-4,5-dibromocyclohexane (4b):**
Compound **3** (17.0 g, 62.1 mmol) is acetylated with acetyl chloride in pyridine and affords (after recrystallisation from ethanol) **4b** as off-white crystals; yield: 20.7 g (93%); m.p. 110°.



$C_{10}H_{14}Br_2O_4$ (358.0) calc. C 33.55 H 3.94; found 33.74 3.88

^{1}H-N.M.R. (60 MHz, $CDCl_3$): δ = 2.0 (s, 6H), 2.3–2.7 (m, 4H), 4.3–4.6 (m, 2H), 5.0–5.5 ppm (m, 2H).

***trans*-5,6-Diacetoxy-1,3-cyclohexadiene (5b):**
The diacetate **4b** (17.1 g, 47.8 mmol), lithium chloride (5.7 g), and lithium carbonate (9.0 g) in freshly distilled hexamethylphosphoric triamide (150 ml) are stirred under nitrogen at 100° for 2.5 h. Ether (200 ml) is added followed by the slow addition of 7% hydrochloric acid (150 ml). The lower phase is extracted 3 times with ether (3 × 100 ml). The combined ether phases are washed with water (200 ml) and 2.5% sodium hydrogen carbonate solution (160 ml). After drying (magnesium sulphate), the ether is evaporated and the residual oil distilled under vacuum to give **5b** as a colourless oil; yield: 7.5 g (80%); b.p. 74°/0.7 torr; Lit.[6] b.p. 112°/5 torr.

$C_{10}H_{12}O_4$ (196.2) calc. C 61.22 H 6.16; found 61.51 6.22

U.V. (ethanol): λ_{max} (log ε) = 258 nm (3.71); Lit.[6] λ_{max} (log ε) = 257.5 nm (3.69).

^{1}H-N.M.R. (60 MHz, CCl_4): $\delta = 2.0$ (s, 6H), 5.4 (d, 2H), 5.6–6.2 ppm (m, 4H).

***trans*-1,2-Dihydroxy-1,2-dihydrobenzene (1):**
A solution of **5b** (3.8 g, 19.4 mmol) in dry ether (40 ml) is dropped into a well-stirred suspension of lithium tetrahydroaluminate (1.0 g) in dry ether (70 ml) at −3° in the course of 45 min. Stirring is continued for an additional hour at −5°, then the reagent is decomposed by the dropwise addition of water followed by 10% sulfuric acid (60 ml). The water phase is continuously extracted with ether for 84 h. After drying (magnesium sulphate), evaporation, and recrystallisation from benzene, **1** is obtained as white platelets; yield: 1.9 g (87%); m.p. 77°; Lit.[7] m.p. 74–75°.

$C_6H_8O_2$	calc.	C 64.27	H 7.19
(112.1)	found	64.23	7.16

U.V. (ethanol): λ_{max} (log ε) = 262 nm (3.50); Lit.[6] λ_{max} (log ε) = 262 nm (3.49).

^{1}H-N.M.R. (60 MHz, $CDCl_3$): $\delta = 3.6$ (s, 2H), 4.5 (s, 2H), 5.9 ppm (s, 4H).

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[9] *trans*-1,2-Dibenzoyloxy-4,5-dibromocyclohexane (**4a**) forms white crystals from ethanol; m.p. 141°.

$C_{20}H_{18}Br_2O_4$	calc.	C 49.79	H 3.73
(482.2)	found	49.98	3.80

^{1}H-N.M.R. (60 MHz, CCl_4): $\delta = 2.3$–3.1 (m, 4H), 4.4–4.7 (m, 2H), 5.4–5.9 (m, 2H), 7.1–7.6 (m, 6H), 7.7–8.1 ppm (m, 4H).
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[11] We are indebted to Dr. J. D. White, Department of Chemistry, Oregon State University, Corvallis, Or. 97331, USA, for providing us with experimental details of this reaction.