

2,4-Dihydroxyphenanthrene, a Phenanthrene Analogue of *cis*-Pinosylvin

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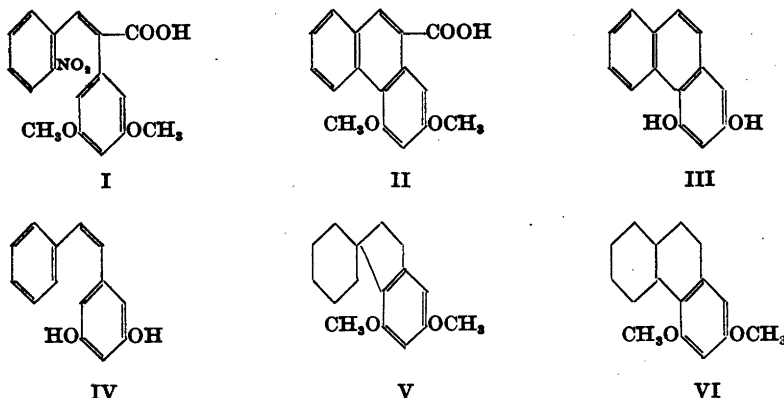
2,4-Dihydroxyphenanthrene has been prepared and was found to be less toxic than pinosylvin against certain wood-rotting fungi. The synthesis was performed according to the Pschorr procedure. The method of Cook and Hewett was not found to be satisfactory in this particular case.

Pinosylvin, 3,5-dihydroxy-*trans*-stilbene, and its monomethylether are the main toxic principles of the heartwood of pines. Their physiological properties have been studied by several authors¹⁻⁶. 2,4-Dihydroxyphenanthrene (III) embodies the skeleton of *cis*-pinosylvin (IV) and it was considered to be desirable to prepare this phenanthrene derivative in order to compare its toxicity against wood-rotting fungi with that of pinosylvin. Similar products obtained from cheap starting materials such as resin acids might possess technical potentialities and it is interesting to note that several phenolic diterpenes have been isolated from the heartwood of various conifers⁷.

2,4-Dihydroxyphenanthrene has been synthesised by a somewhat modified Pschorr procedure. 3,5-Dimethoxybenzoyl chloride was transformed by the Arndt-Eistert method into 3,5-dimethoxyphenylacetic acid (previously prepared by Mauthner⁸ by a different route) and the latter compound was then condensed with *o*-nitrobenzaldehyde. The resulting *o*-nitro- α -(3,5-dimethoxyphenyl)-cinnamic acid (I) was reduced to the corresponding amino acid which after diazotisation and cyclisation yielded 2,4-dimethoxyphenanthrene-10-carboxylic acid (II). This compound, on decarboxylation followed by demethylation with pyridinium chloride, furnished 2,4-dihydroxyphenanthrene (III).

An attempt was also made to prepare 2,4-dihydroxyphenanthrene according to the method of Cook and Hewett. The crude tertiary alcohol from the reaction of 3,5-dimethoxy- β -phenyl-ethyl magnesium bromide with *cyclohexanone* was cyclised by treatment with a sulphuric-acetic acid mixture and various dehydrogenation experiments were carried out on the product. In no case, however, could any recognisable products be isolated apart from un-

changed starting material. This result is almost certainly due to the fact that the spirane (V) and not the desired octahydro-phenanthrene (VI) is produced in the cyclisation reaction (cf. Cook *et al.*⁹ and Barnes¹⁰).



The toxicity of 2,4-dihydroxyphenanthrene and pinosylvin to some fungi has been studied by Docent E. Rennerfelt, Statens Skogsforskningsinstitut, Stockholm, to whom I am much indebted. In agar cultures no growth of the mycelia was observed with the following substances and organisms. Pinosylvin: 0.005 %, *Peniophora gigantea* and *Polyporus annosus*; 0.01 %, *Polyporus abietinus*; 0.02 %, *Fusarium culmorum* and *F. oxysporum*. (*Ophiostoma pini* was not inhibited at this concentration.) 2,4-Dihydroxyphenanthrene: 0.01 %, *Fusarium culmorum* and *Peniophora gigantea*; 0.02 %, *Fusarium oxysporum*. (*Ophiostoma pini*, *Polyporus abietinus* and *P. annosus* were not inhibited at this concentration.) It is thus apparent that 2,4-dihydroxyphenanthrene is a weaker fungicide than pinosylvin.

EXPERIMENTAL *

ω-Diazo-3,5-dimethoxyacetophenone. A solution of 3,5-dimethoxybenzoyl chloride (20 g) in absolute ether (300 ml) was slowly added with mechanical stirring to an excess of diazomethane in ether (prepared from 50 g of nitrosomethylurea in 600 ml of ether and dried over potassium hydroxide) at -5° . The solution was then allowed to stand for 4 hours, filtered from a small amount of a gummy impurity and evaporated *in vacuo* at about 30° . The yellow residue was dried in a vacuum desiccator. The diazo ketone could be crystallized from benzene-petroleum ether forming yellow needles melting at $72-73.5^{\circ}$ without appreciable decomposition (the melt crystallized on cooling). At about 90° , however, decomposition took place. Yield 20.2 g. (Found: OCH_3 30.01.)

ω-Chloro-3,5-dimethoxyacetophenone. To a solution of *ω*-diazo-3,5-dimethoxyacetophenone (200 mg) in ethanol (2 ml) was added conc. hydrochloric acid (0.3 ml). When the evolution of nitrogen had ceased the solution was heated and diluted with hot water. The chloro-ketone separated on cooling and was crystallized from ethanol (leaflets), m.p. $72.5-73.5^{\circ}$. (Found: Cl 16.5; OCH_3 29.13. Calc. for $\text{C}_{10}\text{H}_{11}\text{O}_3\text{Cl}$ (214.7): Cl 16.2; OCH_3 28.91.)

* All melting points uncorrected.

3,5-Dimethoxyphenylacetic acid. A solution of *o*-diazo-3,5-dimethoxyacetophenone (20 g) in absolute ethanol (300 ml) was heated on a waterbath to 55–60° and silver oxide (from 30 ml of a 10 % silver nitrate solution) added in small portions with mechanical stirring during 3–4 hours. The solution was then boiled for one hour, filtered through a thin layer of animal charcoal and evaporated *in vacuo*. The residual ester was distilled yielding a colourless oil (17.4 g) b.p. 164–166°/8 mm. The ester was boiled for one hour with sodium hydroxide (100 ml: 2 *N*) and after cooling and filtering the solution was acidified and the precipitate collected (15 g) and crystallized from water. M.p. 102–103°, Mauthner⁸ gives 99–100°.

***o*-Nitro-*a*-(3,5-dimethoxyphenyl)-cinnamic acid (I).** A solution of 3,5-dimethoxyphenylacetic acid (12 g), *o*-nitro-benzaldehyde (9.5 g) and triethylamine (8.9 ml) in acetic anhydride (30 ml) was heated on a waterbath for 24 hours, water (6 ml) was carefully added and the heating continued for 0.5 hour. The mixture was then poured into dilute hydrochloric acid (500 ml) and the precipitated gum dissolved in dilute sodium hydroxide. After shaking with ether the alkaline solution was acidified giving a brownish yellow precipitate which was collected, dried and triturated with cold benzene (3 × 50 ml) giving a crystalline product. After one crystallization from benzene (50 ml) the yellow product (7.1 g) melted at 153–160°. It was used for the next step without further purification. After repeated crystallizations from ethanol the yellow prisms melted at 179.5–180.5°. (Found: OCH₃ 18.93. Calc. for C₁₇H₁₅NO₄ (329.3): OCH₃ 18.85.)

***o*-Amino-*a*-(3,5-dimethoxyphenyl)-cinnamic acid.** The *o*-nitro-*a*-(3,5-dimethoxyphenyl)cinnamic acid (6 g) was dissolved in aqueous ammonia (conc. ammonia 20 ml, water 30 ml) and the solution added to a hot mixture of ferrous sulphate (45 g FeSO₄ · 7 H₂O) and ammonia (conc. ammonia 160 ml, water 250 ml). The mixture was heated on a waterbath for 1.5 hours and after cooling the solution was filtered and carefully made slightly acid with hydrochloric acid. The greenish yellow precipitate (3.9 g) crystallized from ethanol in yellow prisms, m.p. 189–190°. (Found: OCH₃ 20.39. Calc. for C₁₇H₁₇NO₄ (299.3): OCH₃ 20.74.)

2,4-Dimethoxyphenanthrene-10-carboxylic acid (II). The *o*-amino-*a*-(3,5-dimethoxyphenyl)-cinnamic acid (3 g) was dissolved in sodium hydroxide solution (20 ml; 2 *N*) and precipitated with sulphuric acid (120 ml; 2 *N*). The mixture was cooled to about 0° and an aqueous solution of sodium nitrite (15 ml containing 0.8 g of sodium nitrite) was added dropwise with stirring. The stirring was continued for 4 hours and the excess of nitrite was then destroyed with urea. The yellow solution was filtered and the filtrate heated on a waterbath until it gave no colour reaction with *α*-naphthol. The precipitated acid was collected (2.6 g) and crystallized from ethanol (long needles), m.p. 225.5–226°. (Found: OCH₃ 22.16. Calc. for C₁₇H₁₄O₄ (282.3): OCH₃ 21.99.)

2,4-Dimethoxyphenanthrene. 2,4-Dimethoxyphenanthrene-10-carboxylic acid (2 g) was heated with Adkin's copper chromite catalyst (80 mg) in quinoline (10 ml). The evolution of carbon dioxide started at 210° and ceased after 1.5 hours at 220°. The mixture was cooled, poured into dilute hydrochloric acid and extracted with ether. The ethereal layer was washed successively with hydrochloric acid, dilute sodium hydroxide and water, dried over calcium chloride and evaporated. An oil was obtained which crystallized when triturated with a little methanol. The product (1.6 g) was distilled *in vacuo* and crystallized from ethanol (needles), m.p. 75.5–76.5°. (Found: OCH₃ 25.8. Calc. for C₁₆H₁₄O₂ (238.3): OCH₃ 26.05.)

2,4-Dihydroxyphenanthrene (III). 2,4-Dimethoxyphenanthrene (1 g) was heated with pyridinium chloride (3 g) at 180° for 2 hours and the mixture poured into dilute hydrochloric acid. A precipitate was formed which was dissolved in ether, washed with hydrochloric acid and filtered through aluminium oxide. After evaporation of the ether a light brownish residue (0.7 g) was obtained which was crystallized from water (animal charcoal) giving a slightly pink coloured product melting at 156.5–157°. (Found: C 80.35; H 4.79. Calc. for C₁₄H₁₀O₂ (210.2): C 79.98; H 4.79.)

2,4-Diacetoxyphenanthrene was prepared from 2,4-dihydroxyphenanthrene using acetic anhydride in pyridine. The product crystallized from ethanol in prisms, m.p. 136–137°. (Found: C 73.35; H 4.88. Calc. for C₁₆H₁₄O₄ (294.3): C 73.46; H 4.79.)

2,4-Dibenzoyloxyphenanthrene prepared from 2,4-dihydroxyphenanthrene by the Schotten-Baumann method crystallized from ethanol in prisms, m.p. 184–184.5°. (Found: C 80.23; H 4.38. Calc. for C₂₈H₁₈O₄ (418.4): C 80.37; H 4.34.)

3,5-Dimethoxy- β -phenylethyl alcohol. A solution of ethyl 3,5-dimethoxyphenylacetate (16 g) in absolute ether (100 ml) was slowly added with mechanical stirring to a slurry of lithium aluminium hydride (4 g) in dry ether (400 ml) at a rate sufficient to keep the solution boiling. The mixture was boiled for an additional 0.5 hour and the excess of hydride then destroyed by careful addition of water (15 ml) with cooling. Sulphuric acid (175 ml, 10 %) was added and the ethereal layer washed with water, dried over anhydrous sodium sulphate and the ether evaporated. The residue, distilled *in vacuo*, gave 3,5-dimethoxy- β -phenylethyl alcohol as a colourless oil (12 g), b.p. 126–130°/1–2 mm. The 3,5-dinitrobenzoate, prepared by heating the alcohol with 3,5-dinitrobenzoyl chloride in dry pyridine for a short time, crystallized from benzene-ligroin as yellow needles, m.p. 141.5–142°. (Found: OCH₃ 15.33. Calc. for C₁₇H₁₆N₂O₆ (376.3): OCH₃ 16.49.)

3,5-Dimethoxy- β -phenylethyl bromide. To a solution of 3,5-dimethoxy- β -phenylethyl alcohol (10 g) in carbon tetrachloride (20 ml) at 60° was added phosphorus tribromide (8 g) in one portion and the mixture refluxed for 45 minutes. The solution was washed with sodium carbonate solution followed by water, dried over anhydrous sodium sulphate and the solvent evaporated. The residue was distilled *in vacuo* yielding a colourless oil (8.2 g), b.p. 125–128°/1–2 mm. Redistillation followed by cooling of the distillate gave 3,5-dimethoxy- β -phenylethyl bromide as a solid, m.p. 20–22°. (Found Br 32.3; OCH₃ 25.3. Calc. for C₁₆H₁₄O₂Br (245.1): Br 32.6; OCH₃ 25.3.) The bromide when refluxed with the silver salt of 3,5-dinitrobenzoic acid in dry benzene for 12 hours gave 3,5-dimethoxy- β -phenylethyl-3,5-dinitrobenzoate m.p. 144–145°, undepressed on admixture with a sample of the compound prepared from the alcohol as previously described.

1- β -(3,5-Dimethoxyphenyl)-ethylcyclohexanol. A mixture of 3,5-dimethoxy- β -phenylethyl bromide (7.5 g), magnesium turnings (0.8 g), a crystal of iodine and absolute ether (30 ml) was boiled until most of the metal had passed into solution. Cyclohexanone (3.5 ml) in ether (10 ml) was then slowly added with cooling when a heavy oil separated. The reaction mixture was decomposed with ammonium chloride solution, the ethereal layer washed with sodium bisulphite solution followed by water and dried over anhydrous sodium sulphate. Evaporation of the ether followed by distillation gave 1- β -(3,5-dimethoxyphenyl)-ethylcyclohexanol (3.2 g) as a viscous, slightly yellowish oil, b.p. 165–170°/1–2 mm.

Cyclisation of 1- β -(3,5-dimethoxyphenyl)-ethylcyclohexanol. 1- β -(3,5-Dimethoxyphenyl)-ethylcyclohexanol (2 g) was refluxed for 1 hour with a mixture of glacial acetic acid (20 ml) and concentrated sulphuric acid (2 ml). The reaction mixture was poured into water, the product extracted with ether and the ethereal solution washed with sodium carbonate solution followed by water and dried. Evaporation of the ether gave a thick brownish yellow syrup containing some crystals. Distillation *in vacuo* (12 mm) afforded a colourless oil which immediately crystallized. Recrystallization from ethanol gave the substance as colourless prisms, m.p. 95–96°. (Found: C 78.0; H 9.07. Calc. for C₁₆H₂₂O₂ (246.3): C 78.01; H 9.00.)

Dehydrogenation experiments. (a) Sulphur. A mixture of cyclisation product (225 mg) and sulphur (115 mg) was heated to 210° when evolution of hydrogen sulphide commenced. After one hour at 220° the reaction mixture was distilled *in vacuo* but only a dark tar was obtained. A similar result was obtained when the reaction was carried out by heating *in vacuo* (200 mm) for one hour at 170° and then for an additional 0.5 hour at 200°.

(b) Selenium. Cyclisation product (200 mg) was heated with selenium (250 mg) at 290–300° for 12 hours. Hydrogen selenide was evolved but no recognisable product could be isolated from the reaction.

(c) Catalytic dehydrogenation. A 10 % palladium-carbon catalyst was employed under varying conditions — with the catalyst alone or with naphthalene or tetralin as solvent or with cinnamic acid as hydrogen acceptor. In all experiments either the substance was recovered unchanged or else intractable material was produced.

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