


Fungus Pigments

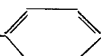
III. * The Synthesis of Two *ω-p*-Hydroxyphenylfatty Acids

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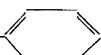
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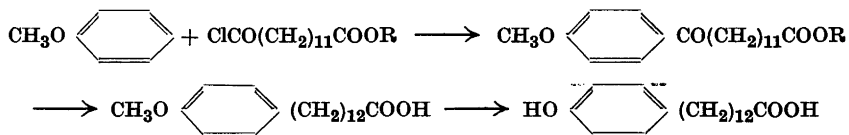
As outlined in the preceding paper¹ the two acids

HO- (CH₂)₁₂COOH, 13-*p*-hydroxyphenyltridecanoic acid and

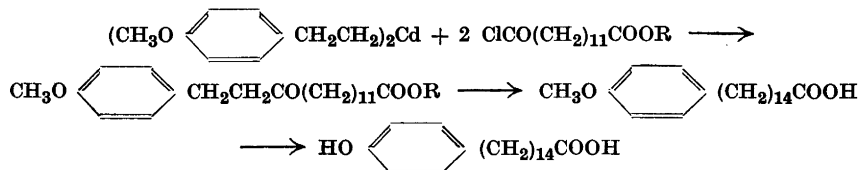
HO- (CH₂)₁₄COOH, 15-*p*-hydroxyphenylpentadecanoic acid were needed for comparison with the hydrogenation product of cortisalin.

A general method for the synthesis of acids of the type

HO- (CH₂)_{*n*}COOH has been worked out by Papa, Schwenk and Hankin², and this method was used for the synthesis of 13-*p*-hydroxyphenyltridecanoic acid which was obtained without difficulty according to the following scheme:



The synthesis of 15-*p*-hydroxyphenylpentadecanoic acid by a similar method would have required tridecandicarboxylic acid-(1,13) and its half ester which are not easily available. Instead the method of Cason³ was used, the synthesis being carried out as follows:



* Part II. *Acta Chem. Scand.* 6 (1952) 580.

Clemmensen reduction of 15-*p*-methoxyphenyl-13-ketopentadecanoic acid gave, in this case, a product which could not be obtained quite pure. As partial demethylation during the Clemmensen reaction could well account for the impurity obtained, the impure material was subjected to demethylation in the hope that this would give homogenous material. This was however not the case, and the impurities could not be removed by crystallisation. Although repeated crystallisation from different solvents gave a seemingly pure compound of a rather sharp m. p. 98–99° its analysis gave low carbon and hydrogen values. The impurities could be removed by chromatography on alumina from a benzene-ether solution, whereby the 15-*p*-hydroxyphenylpentadecanoic acid was retained on the column, the impurities being eluted. Elution with ether containing a small amount of acetic acid gave the pure 15-*p*-hydroxyphenylpentadecanoic acid with m. p. 99–100°.

EXPERIMENTAL

Methyl 13-p-methoxyphenyl-13-ketotridecanoate. Monomethyl brassylate (8.8 g) was converted into the acid chloride by treatment with thionyl chloride. The acid chloride was dissolved in tetrachloroethane (10 ml) and this solution was added to a stirred mixture of aluminium chloride (9 g), anisole (4 g) and tetrachloroethane (20 ml) kept below 0°. Stirring was continued for two hours, then the mixture was allowed to warm up to room temperature, and poured onto ice. The organic layer was separated, and the aqueous layer was extracted with tetrachloroethane. From the combined tetrachloroethane solutions, the solvent and excess of anisole were removed by steam distillation, and the remaining oil which solidified was recrystallised from methanol giving methyl 13-*p*-methoxyphenyl-13-ketotridecanoate (10.9 g, 92 %), m. p. 66–67°. (Found: C, 72.4, H, 9.4; C₂₁H₃₂O₄ requires C, 72.4, H, 9.3 %).

The above ester (0.5 g) was saponified by boiling with methanolic sodium hydroxide for three hours. The sodium salt, which crystallised on cooling was collected and dissolved in a small amount of acetic acid, and dilute sulphuric acid was added. The free acid which precipitated was collected and recrystallised, first from acetic acid and then from benzene-light petroleum, m. p. 93–94°. (Found: C, 71.9, H, 9.2; C₂₀H₃₀O₄ requires C, 71.8, H, 9.0 %).

13-p-Methoxyphenyltridecanoic acid. I. Methyl 13-*p*-methoxyphenyl-13-ketotridecanoate (5.8 g) was boiled with amalgamated zinc (30 g) hydrochloric acid (2 : 1, 90 ml) and toluene (30 ml). Conc. hydrochloric acid was added from time to time, and an additional amount of amalgamated zinc (15 g) was added after 48 hours. After the mixture had been boiled for 72 hours, unreacted zinc was filtered off and washed with ether. The combined ether and toluene layer was separated and the solvents removed by steam distillation. The remaining oil was saponified by boiling for three hours with methanolic sodium hydroxide. Dimethyl sulphate (1 ml) was added and boiling was continued for another hour. The methanol was distilled off, the sodium salt of 13-*p*-methoxyphenyltridecanoic acid which separated on cooling was collected and converted into the free acid (4.5 g; 87 %) which was recrystallised from light petroleum, m. p. 71–72.5°. (Found: C, 75.0, H, 10.3; C₂₀H₃₂O₃ requires C, 75.0, H, 10.1 %).

II. 13-*p*-Methoxyphenyl-13-ketotridecanoic acid (1.7 g) was added to a solution of sodium (1.7 g) in glycol (50 ml) and, after the addition of hydrazine hydrate (2.5 g), the mixture was heated at 175° for 30 hours. The cooled solution was poured into water and acidified, the precipitated acid was taken up in ether, and the ether was removed and the residue was recrystallised from light petroleum, m. p. 70–72°, undepressed in admixture with the acid prepared by the alternative route.

13-p-Hydroxyphenyltridecanoic acid. 13-*p*-Methoxyphenyltridecanoic acid (1.4 g) was dissolved in acetic acid (6 ml), hydrobromic acid (50 %; 2 ml) was added, and the mixture was boiled for five hours. On cooling the 13-*p*-hydroxyphenyltridecanoic acid crystallised out and was filtered off. By the addition of water to the mother liquor a further amount of the acid can be obtained. Recrystallised from benzene it has m. p. 94–96°. (Found: C, 74.3, H, 10.2; C₁₉H₃₀O₃ requires C, 74.5, H, 9.9 %).

Methyl 13-*p*-hydroxyphenyltridecanoate was prepared by esterification of the acid with methanol and sulphuric acid. After recrystallisation from light petroleum and vacuum distillation it has m. p. 71–72°. (Found: C, 75.0, H, 10.2; C₂₀H₃₂O₃ requires C, 75.0, H, 10.1 %).

15-p-Methoxyphenyl-13-ketopentadecanoic acid. A Grignard solution was made from 2-*p*-methoxyphenylethyl bromide⁴ (9.8 g) and magnesium (1.1 g). Finely powdered cadmium chloride (4.3 g) was added with efficient stirring, and the mixture was boiled for one hour. The ether was then distilled off with the simultaneous addition of benzene. The acid chloride of monomethyl brassylate, prepared from monomethyl brassylate (7.5 g) and thionyl chloride was then added dropwise. The mixture was boiled for 15 minutes, set aside overnight, then poured into very dilute hydrochloric acid. The benzene layer was separated and washed with water, and the benzene was removed by steam distillation. The remaining oil was taken up in ether, and the ether solution was washed with sodium carbonate and evaporated. The oil obtained was saponified by boiling with methanolic sodium hydroxide. On cooling, the sodium salt of 15-*p*-methoxyphenyl-13-ketopentadecanoic acid crystallised out and was filtered off and washed with methanol and ether. It was decomposed with sulphuric acid, and the acid was taken up in ether. Removal of the ether and recrystallisation from dilute acetic acid gave 15-*p*-methoxyphenyl-13-ketopentadecanoic acid, m.p. 88–89° (4.9 g, 47 %). (Found: C, 73.1, H, 9.5; C₂₂H₃₂O₄ requires C, 72.9, H, 9.4 %).

15-p-Methoxyphenylpentadecanoic acid. 15-*p*-Methoxyphenyl-13-ketopentadecanoic acid (2 g) was boiled with amalgamated zinc (5 g), hydrochloric acid (2 : 1, 30 ml) and toluene (10 ml) for 48 hours. Unreacted zinc was filtered off and the toluene was removed by steam distillation. The remaining oil (1.7 g), which solidified upon cooling, was recrystallised from acetic acid giving a product, m. p. 77–78° which was still somewhat impure. (Found: C, 75.4, H, 10.4; C₂₂H₃₀O₃ requires C, 75.8, H, 10.4 %).

15-p-Hydroxyphenylpentadecanoic acid Crude 15-*p*-methoxyphenylpentadecanoic acid (1 g) was added to hydrobromic acid (50 %, 2 ml) and acetic acid was added until a clear solution was obtained. The mixture was boiled for one hour. On cooling a small amount of 15-*p*-hydroxyphenylpentadecanoic acid crystallised out and water was added to precipitate the remainder of the acid, which was collected and recrystallised from dilute acetic acid, benzene and dilute alcohol. It was then dissolved in ether and benzene and chromatographed on aluminium oxide. Elution with ether removed crystalline material which was not further investigated, and further elution with ether containing a few drops of acetic acid gave 15-*p*-hydroxyphenylpentadecanoic acid, which after recrystallisation from dilute alcohol had m. p. 99–100° (Found: C, 75.4, H, 10.3; C₂₁H₃₄O₃ requires C, 75.4, H, 10.3 %).

SUMMARY

The synthesis of 13-*p*-hydroxyphenyltridecanoic acid and 15-*p*-hydroxyphenylpentadecanoic acid are described.

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