

SYNTHESIS OF 3,3'-DIHYDROXY-6-METHYLBIBENZYL, AND ITS OXIDATION*

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The oxidation of phenolic compounds with one-electron oxidizing agents has attracted considerable attention since the successful synthesis of (\pm)-usnic acid by Barton, Deflorin, and Edwards.¹ Yields have varied considerably but were almost quantitative with several oxidizing agents in the case of (\pm)-dehydrogriseofulvin.² It was envisaged that the successful intramolecular *para-para* coupling of 3,3'-dihydroxy-6-methylbibenzyl might offer a new route to some tricyclic diterpene intermediates. Accordingly this compound has been synthesized and some oxidations carried out.

2-Methyl-5-nitrobenzoic acid was prepared from *o*-toluic acid.³ Catalytic reduction gave a high yield of the corresponding amino acid and was more convenient than the reduction with hydrogen sulphide and ammonia.³ This amino acid was converted to 5-hydroxy-2-methylbenzoic acid by the method of Peltier.³ Methyl 5-methoxy-2-methylbenzoate, prepared by methylation with dimethyl sulphate followed by diazomethane, was reduced with lithium aluminium hydride to the corresponding alcohol.⁴ Chlorination with thionyl chloride in pyridine was better than the literature method⁴ and gave 5-methoxy-2-methylbenzyl chloride in 96% yield. Diethyl 5-methoxy-2-methylbenzylphosphonate, prepared in 81% yield by the Michaelis-Arbusov reaction,⁵ gave the expected stilbene (83%) when reacted with *m*-methoxybenzaldehyde. The stilbene (presumably *trans* by analogy with the work of Seus⁶) gave 3,3'-dihydroxy-6-methylbibenzyl directly when treated with hydriodic acid and red phosphorus, both the removal of the methoxyl groups and the reduction of the double bond taking place.

Oxidations were carried out with alkaline potassium ferricyanide, manganese dioxide, lead oxide, silver oxide, ceric sulphate, and ferric chloride, by published methods.^{2,7} Thin-layer chromatography on silica gel indicated complex mixtures of products and it was not possible to separate the components. A similar unsuccessful oxidative study on 5,5-dihydroxy-2,2'-dimethylbibenzyl has appeared recently.⁸

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¹ Barton, D. H. R., Deflorin, A. M., and Edwards, O. E., *J. Chem. Soc.*, 1956, 530.

² Taub, D., Kuo, C. H., Slates, H. L., and Wendler, N. L., *Tetrahedron*, 1963, 19, 1.

³ Peltier, D., *Bull. Soc. Sci. Bretagne*, 1956, 31, 7.

⁴ Stork, G., Wagle, S. S., and Mukharji, P. C., *J. Amer. Chem. Soc.*, 1953, 75, 3197.

⁵ Kosolapoff, G. M., "Organophosphorus Compounds." 1st Ed. p. 121. (John Wiley: New York 1950.)

⁶ Seus, E. J., and Wilson, C. V., *J. Org. Chem.*, 1961, 26, 5243.

⁷ Erdtman, H., *Liebigs Ann.*, 1933, 505, 195.

⁸ Gibson, M. S., and Walthew, J. M., *J. Chem. Soc.*, 1963, 4603.

Experimental

Melting points are uncorrected. Analyses were carried out by the Australian Microanalytical Service, Melbourne.

2-Methyl-5-nitrobenzoic Acid

This was prepared by the method of Peltier.³ Crystallization from ethanol gave needles, m.p. 178–179° (lit.³ 179°).

5-Amino-2-methylbenzoic Acid

2-Methyl-5-nitrobenzoic acid (1.2 g) was hydrogenated with Adams's catalyst (50 mg) under 3 atm pressure for 12 hr. After filtration of the catalyst, the methanol was removed and the product crystallized from water (0.9 g, 90%), m.p. 194–195° (lit.³ 196°).

5-Hydroxy-2-methylbenzoic Acid

This was prepared by the method of Peltier.³ Crystallization from water using animal charcoal gave pale yellow crystals, m.p. 183–185° (lit.³ 185°).

Methyl 5-Methoxy-2-methylbenzoate

Dimethyl sulphate (31 g) was added slowly with cooling and stirring to a solution of 5-hydroxy-2-methylbenzoic acid (20 g) in sodium hydroxide (118 ml, 20%). The reaction mixture was allowed to stand at room temperature for 1 hr and then was refluxed for 2 hr. The mixture was acidified with conc. HCl and extracted with ether (3 × 200 ml). The dried (MgSO₄) ethereal solution was treated with excess diazomethane in ether and allowed to stand overnight. The solvent was removed and the residue chromatographed on silica gel (400 g). Benzene-ether (49 : 1) yielded methyl 5-methoxy-2-methylbenzoate (11 g). Elution with ether gave crude material which was recycled. The ester (17.8 g, 75%) was obtained as a colourless liquid, b.p. 134–136°/20 mm (lit.³ 137°/20 mm).

5-Methoxy-2-methylbenzyl Alcohol

This was prepared by the method of Stork, Wagle, and Mukharji.⁴ The product had b.p. 101–103°/0.5 mm (lit.⁴ 104–106°/0.6 mm).

5-Methoxy-2-methylbenzyl Chloride

Thionyl chloride (9.5 g) was added dropwise with stirring to 5-methoxy-2-methylbenzyl alcohol (12 g) in dry pyridine (6.5 g) and stirring continued for 4 hr at less than 30°. The mixture was poured onto ice, extracted with ether (2 × 25 ml) and the dried (Na₂SO₄) ethereal solution was evaporated. 5-Methoxy-2-methylbenzyl chloride (13 g, 96%) was obtained by distillation, b.p. 105–106°/12 mm, m.p. 44–45° (lit.⁴ 44–45°).

Diethyl 5-Methoxy-2-methylbenzylphosphonate

5-Methoxy-2-methylbenzyl chloride (5.09 g) was heated with triethyl phosphite (5.96 g) at 140–160° for 3 hr.⁵ Fractional distillation of the resulting mixture gave the *phosphonate* (6.5 g, 81%) as a colourless liquid, b.p. 138°/0.3 mm (Found: C, 57.0; H, 7.9; P, 11.2%. Calc. for C₁₃H₂₁O₄P: C, 57.3; H, 7.8; P, 11.4%).

trans-3,3'-Dimethoxy-6-methylstilbene

Diethyl 5-methoxy-2-methylbenzylphosphonate (6.5 g) in dimethylformamide (20 ml) was added to sodium methoxide (1.55 g) under a nitrogen atmosphere. *m*-Methoxybenzaldehyde (3.25 g) in dimethylformamide (20 ml) was added dropwise with stirring at 30–40°. After 20 min water was added to the reaction mixture. The crude product (6.1 g), isolated in the usual way with ether, was chromatographed on silica gel (150 g). Light petroleum (b.p. 40–60°) and ether (85 : 15) eluted *trans*-3,3'-dimethoxy-6-methylstilbene (5.1 g, 83%), m.p. 60–61° (Found: C, 80.3;

H, 7.1%. Calc. for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1%. The n.m.r. spectrum (60 Mc/s in $CDCl_3$) had bands at τ 7.67 (3H; methyl protons); 6.22 (6H; methoxyl protons); and 3.28–2.58 (9H; aromatic and olefinic protons).

3,3'-Dihydroxy-6-methylbibenzyl

Hydriodic acid (55%, 17 ml) was added slowly to *trans*-3,3'-dimethoxy-6-methylstilbene (3.32 g) and red phosphorus (5 g) in refluxing acetic acid (17 ml) and refluxing continued for 2 hr. The mixture was poured onto ice and the crude product isolated with ether. The ether was removed and the product chromatographed on silica gel (70 g). The *bibenzyl* (0.66 g) was eluted with benzene-ether (4 : 1). A mixture (1.85 g), eluted with ether, was retreated as above. Crystallization from benzene gave the *bibenzyl* (1.3 g, 44%), m.p. 127–128° (Found: C, 78.9; H, 6.9%. Calc. for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1%).

The n.m.r. spectrum had bands at 7.82 (3H; methyl protons); 7.2 (4H; methylene protons); 6.0 (2H; hydroxyl protons); and 3.42–2.77 (7H; aromatic protons).

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