Synthesis of Piloquinone, a Phenanthrene-9,10-quinone from *Streptromyces pilosus*

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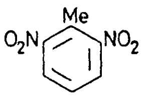
Summary The synthesis of piloquinone, an unusual phenanthrene-9,10-quinone produced by *Streptomyces pilosus*, in twenty steps from 2,6-dinitrotoluene is described.

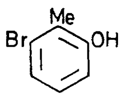
PILOQUINONE (**19**),[1] and its congener 4-hydroxypiloquinone (**20**)[2] are the only[3] known phenanthrene-9,10-quinones produced in nature. We now describe the synthesis of the former metabolite.

2,6-Dinitrotoluene (**1**) was converted by modifications of the method of Noelting[4] into the bromocresol (**2**) (48% overall) which on bromination[5] at 50% conversion in dichloromethane–toluene–isopropylamine at −70 to 20° gave 97% of 3,6-dibromo-2-hydroxytoluene (**3**),[6] m.p. 42—43°. The derived anisole (**4**),† b.p. 85—86° at 0·3 mmHg, on reaction with 1 mol. equiv. of ethereal phenyl-lithium[7] followed by *NN*-dimethylformamide (DMF) gave the bromoaldehyde (**5**)† (79%), m.p. 60—60·5°. The structure of the latter followed from its ready demethylation (96%) with boron trichloride in dichloromethane[8] to give the intramolecularly hydrogen-bonded *o*-hydroxyaldehyde (**6**),† m.p. 42—43°.

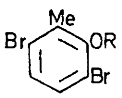
Reaction of *o*-methoxybenzyl chloride[9] with triphenylphosphine in boiling toluene gave the phosphonium salt (**7**)† (92%), m.p. 242—244°. Wittig reaction of the salt (**7**) and the aldehyde (**5**) with lithium methoxide as base gave the stilbene (**8**)† (*ca.* 100%) as a mixture of isomers. With methanol as solvent the *trans*-isomer, m.p. 53—54°, predominated, and with DMF as solvent the *cis*-isomer, m.p. 86—88°, predominated. Treatment of the isomer mixture (**8**) with copper(I) cyanide in boiling DMF (15 h) gave the nitrile (**9**)† (85%) (*trans*-isomer m.p. 131—134°). Hydrolysis of (**9**) with aqueous ethanolic potassium hydroxide gave the acid (**10**) which on methylation gave the ester (**11**)† (*trans*-isomer m.p. 77—78°). U.v. irradiation of (**11**) in cyclohexane in presence of iodine[10] gave the expected phenanthrene (**12**)† (35%), m.p. 166—167°, as well as the phenanthrene (**16**)† (16%), m.p. 81—82°, in which ring closure had occurred by formal loss of methanol.



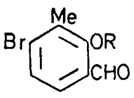
(1)



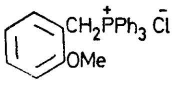
(2)



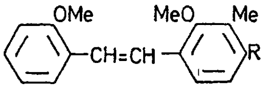
(3) R = H
(4) R = Me



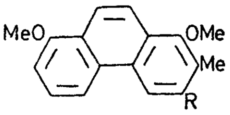
(5) R = Me
(6) R = H



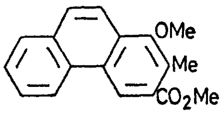
(7)



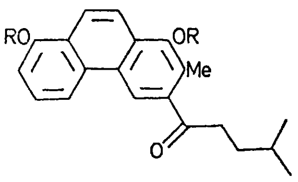
(8) R = Br
(9) R = CN
(10) R = CO_2H
(11) R = CO_2Me



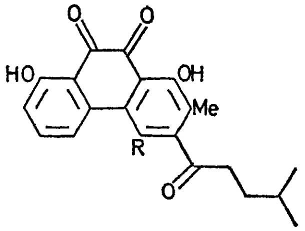
(12) R = CO_2Me
(13) R = CH_2OH
(14) R = CHO
(15) R = $CHOH[CH_2]_2CHMe_2$



(16)



(17) R = Me
(18) R = Ac



(19) R = H
(20) R = OH

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† All new compounds gave satisfactory elemental analyses and their spectroscopic data were in accord with the assigned structures.

Reduction of (**12**) to the alcohol (**13**),† m.p. 155—156°, was accomplished in 99% yield by $LiAlH_4$ in tetrahydrofuran (THF). Manganese dioxide[11] oxidation of the latter gave the aldehyde (**14**)† (92%), m.p. 139—141°, which on reaction with isopentylmagnesium bromide in ether–THF gave the alcohol (**15**) which underwent oxidation with Jones reagent and yielded the ketone (**17**)† (56% overall), m.p. 86—87°. Boron tribromide demethylation[12] of (**17**) followed by acetylation of the crude phenol obtained gave the diacetate (**18**)† (48%), m.p. 159°.

The diacetate (**18**) was oxidised at 70° with chromium trioxide in aqueous acetic acid and the crude product was hydrolysed with aqueous methanolic sodium hydroxide at 20° under nitrogen to afford piloquinone (**19**)† (18%), as brownish red needles, m.p. 176—179°, identical (t.l.c. and mixed m.p.) with the natural product.

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