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THE SYNTHESIS OF RUSCODIBENZOFURAN

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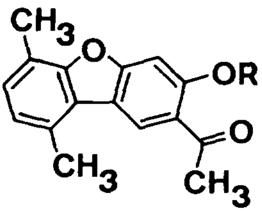
A phenolic compound, ruscodibenzofuran (1) has recently been isolated by Schiff and coworkers from the root of *Ruscus aculeatus* L. (Liliaceae), a plant of some pharmacological interest.[1]

Compound 3, an isomer of ruscodibenzofuran methyl ether (2), was synthesised by Schiff *et al.* through a mixed Ullmann coupling of 2,4-dimethyl-6-iodoanisole with 4-iodoresorcinol dimethyl ether, followed by reflux with hydrobromic acid to give, after methylation, 2,4-dimethyl-7-methoxydibenzofuran, which when acylated with acetyl chloride furnished compound 3.[1] The same approach was, however, not successful when applied to the synthesis of ruscodibenzofuran itself.[1]

We have synthesised ruscodibenzofuran (1) using an alternative route for obtaining the key intermediate, the methoxydibenzofuran 4. One of us has shown that the acid-catalysed



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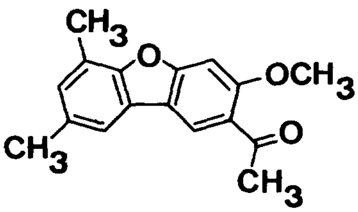

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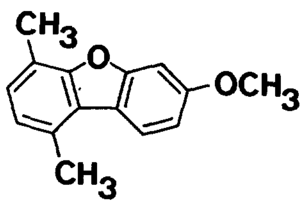

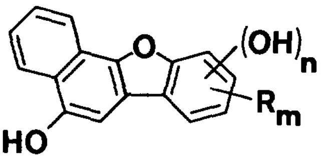

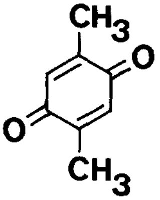

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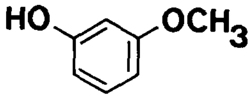

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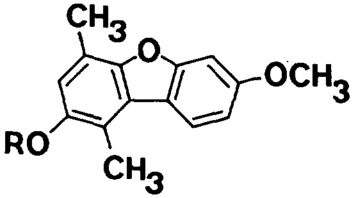
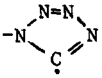


8: R = H

9: R = $COCH_3$

10: R = (C_6H_5)-

reactions of α-naphthoquinone with various phenols give good yields of polyhydroxybenzonaphthofurans of type 5.[2]

It seemed likely that the same reaction might be used in the benzoquinone series. Thus, if *p*-xyloquinone (6) were reacted with 3-methoxyphenol (7) the hydroxydibenzofuran 8 might be obtained. Removal of the hydroxyl group should then give compound 4, which on acylation followed by hydrolysis should lead to ruscodibenzofuran (1).

When treated with a catalytic amount of sulfuric acid in refluxing (2 h) acetic acid, a mixture of *p*-xyloquinone (6) and 3-methoxyphenol (7) gave a phenolic product. This was acetylated (acetic anhydride/pyridine) and subjected to column chromatography (silica gel/methylene chloride). 2-Acetoxy-1,4-dimethyl-7-methoxydibenzofuran (9) was eluted first (22%), m.p. 137-138 °C.[3] ^1H NMR (60 MHz, $CDCl_3$): δ 2.33 (3H, s, $-COCH_3$), 2.47 (6H, m, 2 $ArCH_3$), 3.85 (3H, s, $-OCH_3$), 6.91 (1H, broad s, H_3) 6.97 (1H, d of d, H_8, J = 2.2 and 8.2 Hz), 7.10 (1H, d, H_6, J = 2.2 Hz), 7.79 (1H, d, J = 8.2 Hz) ppm. Irradiation at δ 2.47 ppm gave a sharp singlet at δ 6.91 ppm.

The acetate 9 was hydrolysed (methanol/trace sulfuric acid, reflux 2 h) to give the phenol 8 in quantitative yield, m.p. 169-170 °C.[3]

There are several methods described in the literature for replacing phenolic hydroxyl groups with hydrogen.[4-8] We found the method of Musliner and Gates[5] suitable for our purpose. The phenol 8 was reacted with an equimolar amount of 5-chloro-1-phenyltetrazole in the presence of potassium carbonate in dimethyl formamide (72 h, 110 °C). This gave the phenyltetrazolyl ether 10 (72%), m.p. 188-189 °C.[3] MS 70 eV, [*m/e* (rel. int.)]: 386(32, M$^{+\cdot}$), 316(41), 242(54), 241(100), 117(56), 46(27), 45(56). More conveniently, the phenyltetrazolyl ether 10 was obtained (although in a slightly lower yield: 63%) when one mol of tetra-*n*-butylammonium hydrogen sulfate and 2 mol of sodium hydroxide in water was stirred with one mol of each of the phenol 8 and 5-chloro-1-phenyltetrazole in methylene chloride at room temperature for 2 h.

The phenyltetrazolyl ether 10 was hydrogenated at 4 atm in ethyl acetate over palladium on charcoal. This gave the methoxydibenzofuran 4 (80%), m.p. 69-70 °C.[3] ^{1}H NMR (200 MHz, CDCl$_3$): δ 2.54 (3H, broad s, ArCH_3), 2.71 (3H, broad s, ArCH_3), 3.90 (3H, s, -OCH_3), 6.94 (1H, d of d, H_8, J = 2.4 and 8.5 Hz), 6.98 (1H, broad d, H_2 or H_3, J = 7.7 Hz), 7.07 (1H, broad d, H_3 or H_2, J = 7.7 Hz), 7.13 (1H, d, H_6, J = 2.4 Hz), 7.86 (1H, d, H_9, J = 8.5 Hz) ppm. Irradiation at δ 2.54 ppm gave a sharp doublet at δ 7.07 ppm and changed the broad doublet at δ 6.98 ppm into a pair of quartets (J = 0.7 Hz for the quartet, which is due to coupling with the ArCH_3 protons giving rise to the signal at δ 2.71 ppm). Similarly irradiation at δ 2.71 ppm gave a sharp doublet at δ 6.98 ppm and a pair of quartets (J = 0.7 Hz) at δ 7.07 ppm. Irradiation at δ 7.86 ppm gave a doublet at δ 6.94 ppm (J = 2.4 Hz). These decoupling experiments confirm the structure of compound 4.

When an equimolar amount of acetyl chloride was added to the methoxydibenzofuran 4 and aluminium chloride in methylene chloride at 0 °C over 30 min a 60% yield of ruscodibenzofuran methyl ether (2) was obtained (m.p. 155-156 °C; lit.[1] m.p. 155 °C). A small amount of ruscodibenzofuran (1) was also isolated. Obviously slow demethylation of the initial product 2 takes place at 0 °C. If the reaction mixture is allowed to stand at 25 °C for 6 h after completion of the acylation reaction at 0 °C as above, the sole product isolated is ruscodibenzofuran (1) (67%) which crystallised as faintly greenish plates from ethanol, m.p. 171-172 °C (lit.[1] m.p. 168 °C). The synthetic material was identical in all respects with the natural ruscodibenzofuran (mixed m.p., IR, MS, 60 MHz NMR). Its structure has been established by Schiff *et al.* by X-ray crystallography.[1] The well resolved 200 MHz ^{1}H NMR (CDCl$_3$) was consistent with the structure: 2.53 (3H, broad s, ArCH_3), 2.73 (3H, broad s, ArCH_3), 2.76 (3H, s, -COCH_3), 7.03 (1H, broad d, H_2 or H_3, J = 7.4 Hz), 7.09 (1H, s, H_6 or H_9), 7.12 (1H, broad d, H_3 or H_2, J =

7.4 Hz), 8.29 (1H, s, H_9 or H_6), 12.78 (1H, s, -O*H* *ortho* to $ArCOCH_3$) ppm. Irradiation at δ 2.53 and δ 2.73 ppm gave sharp doublets at δ 7.12 and δ 7.03 ppm respectively.

p-Xyloquinone (6) has two reactive positions and can therefore give side products resulting from the addition of two mol of phenol (*cf.* ref. 2.). The starting methoxyphenol also has two reactive positions. It is therefore not surprising, that the yield in the first step of this synthetic scheme is rather low. It may, however, still be of some practical value since simple, commercially available starting materials are used.

In an attempt to improve the yield by blocking one of the positions in the quinone, the trisubstituted 2-chloro-3,6-dimethylquinone was reacted with methoxyphenol as above. The desired dibenzofuran could, however, not be isolated from the product. Apparently the chlorine substituent has a profound influence on the course of the reaction.

We are presently investigating the scope of the reaction of benzoquinones and polyhydric phenols.

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