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The Reduction of 2′-Hydroxychalcone by Complex Metal Hydrides

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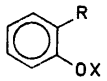
The reduction of 2′-hydroxychalcone by lithium aluminium hydride and aluminium chloride yields 1-(*o*-hydroxyphenyl)-3-phenyl-1- and -2-propene in addition to a small amount of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanone. The treatment of 2-benzyl-2,3-dihydrobenzofuran with sodium in pyridine yields a mixture of the same 1- and 2-propenes. Lithium aluminium hydride reduction of 2′-hydroxychalcone yields 3-flavene and 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanol. Independent syntheses have been devised to confirm the structures of the reduction products.

In an earlier paper [1] we described a ring cleavage of 2,3-dihydrobenzofuran derivatives by sodium in pyridine, which gives substituted *o*-vinylphenols. The reaction product from 2-benzyl-2,3-dihydrobenzofuran could not be identified with certainty, but in analogy with other dihydrobenzofuran cleavages this product was assumed to be 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (I). The same phenol has been described by Bokadia *et al.*,[2] resulting from the reduction of 2′-hydroxychalcone (II) by a 1:2 mixture of lithium aluminium hydride and aluminium chloride. The structure of the reaction product was written by Bokadia *et al.* as I, rather than III (*o*-cinnamylphenol or 1-(*o*-hydroxyphenyl)-3-phenyl-2-propene), based on its ultraviolet spectrum (λ_{max} 254 nm, log ε 4.43), its melting point (67—68°C; reported [3,4] for III: 55—56°C) and its reluctance to undergo a facile cyclisation to flavan on treatment with boiling acid. However, since a recrystallised sample of the 2-propene (III) was found to melt at 67—68°C, and to have λ_{max} 254 nm, log ε 4.27, it seemed to us that the compound obtained by Bokadia *et al.*[2] was in fact 1-(*o*-hydroxyphenyl)-3-phenyl-2-propene (III) rather than the 1-propene isomer (I).

Repetition of the procedure of Bokadia *et al.* by us gives from 2′-hydroxychalcone (II) a mixture of several compounds, from which three major products were isolated by preparative thin layer chromatography: 8 % of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanone (IV), 44 % of 1-(*o*-hydroxyphenyl)-3-phenyl-2-propene (III), and 17 % of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (I), λ_{max} (log ε) 251 nm (4.19) and 303 nm (3.73) (for complete spectrum, see experi-

mental part). Such an ultraviolet absorption pattern is typical of the *o*-vinylphenol chromophore.[1] The structures of the above compounds were confirmed by independent synthesis.



	R	X
I	$-CH=CHCH_2C_6H_5$	H
II	$-COCH=CHC_6H_5$	H
III	$-CH_2CH=CHC_6H_5$	H
IV	$-COCH_2CH_2C_6H_5$	H
V	$-CHOH-CH_2CH_2C_6H_5$	H
VI	$-CHOH-CH_2CH_2C_6H_5$	CH_3
VII	$-COCH_2CH_2C_6H_5$	CH_3
VIII	$-C(=NNHTs)-CH_2CH_2C_6H_5$	H

4- and 4′-Methoxychalcones are reduced [5] by lithium aluminium hydride alone to the saturated alcohols with the hydroxyl oxygen retaining its position. These yield the corresponding olefins [2] when boiled with aluminium chloride in ether. Bokadia *et al.*[2] obtained the same olefins directly on treatment of the same methoxychalcones with lithium aluminium hydride and aluminium chloride, and accordingly considered that the course of the reaction involves reduction to the saturated alcohol followed by dehydration to the olefin, which accounts for the migration of the double bond. Such a sequence is certainly compatible with our isolation of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanone (IV) from the lithium aluminium hydride-aluminium chloride reduction of 2′-hydroxychalcone and the isolation of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanol (V) from the lithium aluminium hydride reduction of the same chalcone. However, the last-mentioned alcohol (V) was found to be quite resistant to the action of aluminium chloride in boiling ether. Furthermore, the formation of 1-(*o*-hydroxyphenyl)-3-phenyl-2-propene (III) as the main product in the mixed reagent reduction of 2′-hydroxychalcone remains unaccounted for, unless isomerisation of an initially formed 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (I) is responsible. Such an isomerisation into the 2-propene (III) does occur, with much decomposition, when the 1-propene (I) is treated with aluminium chloride in boiling ether.

On the other hand, Brewster and Bayer,[6] using a 1:3 mixture of lithium aluminium hydride and aluminium chloride, obtained from benzalacetone 52 % of 1-phenyl-1-butene and 23 % of 1-phenyl-2-butene, and considered the reaction to involve reduction to the allylic alcohol, followed by hydrogenolysis to the carbonium ion. This view was supported by the isolation of a similar mixture from the reaction of either cinnamylalcohol or 1-phenylallylalcohol with the same hydride-chloride mixture. The reduction of cinnamaldehyde to cinnamylalcohol [7] by aluminium hydride (3:1 mixture of lithium aluminium hydride and aluminium chloride in ether) lends further support to the allylic carbonium ion mechanism.

It is possible that in the reduction of 2′-hydroxychalcone by a 1:2 mixture of lithium aluminium hydride and aluminium chloride both the saturated-alcohol and the allylic carbonium ion mechanism operate simultaneously, as the formation of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanone (IV) is difficult to

rationalise by the latter route. 1,4-Reduction of α,β-unsaturated ketones by lithium aluminium hydride is, however, well known in other cases.[11]

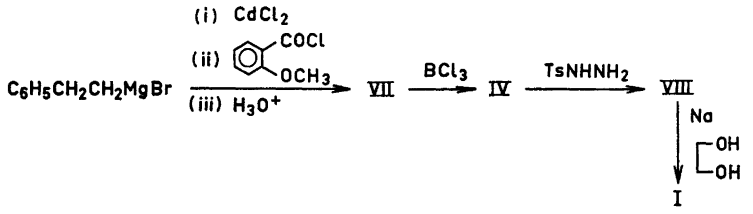
Re-examination by preparative thin layer chromatography of the reaction product from the sodium-pyridine treatment [1] of 2-benzyl-2,3-dihydrobenzofuran gave 32 % and 26 % of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (I) and 1-(*o*-hydroxyphenyl)-3-phenyl-2-propene (III), respectively. This is entirely in accord with the β-elimination mechanism proposed by us [1] in connection with other substituted-2,3-dihydrobenzofuran cleavages, as there are in the 2-benzyl derivative two proton-carrying benzylic carbon atoms β to the oxygen.

SYNTHESIS OF REFERENCE COMPOUNDS

The Wittig reaction with triphenylphenethylidene phosphorane and salicylaldehyde failed to furnish us with a sample of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (I), as did attempted demethylation and dehydration of 1-(*o*-methoxyphenyl)-3-phenyl-1-propanol (VI), prepared from benzylmagnesium bromide and *o*-methoxybenzaldehyde. We next turned our attention to the lithium aluminium hydride reduction of 2'-hydroxychalcone (II), with a view to obtain 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanol (V). This reduction has been studied earlier by Bognár and Rákosi,[8] who reported having obtained only amorphous material. Our experience was that 2'-hydroxychalcone (II) gave on brief treatment with lithium aluminium hydride 31 % of 3-flavene and 39 % of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanol (V), identical with the sodium borohydride reduction product from 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanone (IV). Longer reaction time in the 2'-hydroxychalcone reduction resulted in the disappearance of 3-flavene and the formation of an inseparable mixture of compounds. 3-Flavenes are known to result from sodium borohydride reduction of 2'-hydroxychalcones.[9]

As already mentioned, 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanol (V) was not dehydrated by aluminium chloride in boiling ether. This conversion was smoothly effected by anhydrous oxalic acid in boiling benzene, with 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (I) as the sole product.

Since it was felt that a non-chalconoid route would be desirable for establishing the structures of the various reduction products, the following synthetic scheme was carried out:



It is of interest to note that in the decomposition of the propanone tosylhydrazone (VIII) 1-(*o*-hydroxyphenyl)-3-phenyl-2-propene (III) was formed to the extent of 28 % yield in addition to the expected 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (I) (48 % yield).

EXPERIMENTAL

UV spectra were recorded on a Beckman DK-2 spectrophotometer in ethanol solution, and IR spectra on a Perkin-Elmer 125 spectrophotometer using KBr pellet and liquid film techniques for solids and liquids, respectively. NMR spectra were recorded on a Varian A-60 spectrometer in $CDCl_3$ solution with TMS as the internal standard. The symbols s, d, t, and m denote singlets, duplets, triplets, and multiplets, respectively. Preparative thin layer chromatography was performed on silica plates, prepared from Merck's $PF_{254+366}$ silica gel. Petroleum ether refers to the fraction boiling at 40–60°C. All new compounds gave satisfactory elementary analyses.

1-(o-Hydroxyphenyl)-3-phenyl-2-propene (III, o-cinnamylphenol) was prepared according to Claisen's directions,[3] m.p. 67–68°C (petroleum ether); λ_{max} nm (log ε) 292.5 (3.14), 284sh (3.61), 275sh (3.90), 254 (4.27); ν_{max} 3550–3300, 1585, 1500 cm^{-1}; τ 2.6–3.8 (11 H, m), 5.25 (1 H, s), 6.40–6.53 (2 H, broad d). TLC spots of III assume violet coloration after spraying with dilute H_2SO_4 and warming.

Reduction of 2'-hydroxychalcone with $LiAlH_4$–$AlCl_3$. The procedure of Bokadia *et al.*[2] was followed. The crude product (2.95 g from 4.36 g of 2'-hydroxychalcone) was chromatographed in a silica gel column, eluting first with petroleum ether (400 ml, fraction A) followed by benzene:petroleum ether 2:1 (350 ml, fraction B). Fraction A gave, after preparative TLC (elution with petroleum ether) 0.325 g (8 %) of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanone (IV), m.p. 30°C (lit.[3] m.p. 30–31°C); ν_{max} 3350–3100, 1635, 1610, 1578 cm^{-1}; τ −2.3 (1 H, s), 2.3–3.4 (9 H, m), 6.92 (4 H, m, centre of A_2B_2). Fraction B gave, after preparative TLC (elution 6 times with chloroform:cyclohexane 1:3), 1.81 g (44 %) of faster-running 1-(*o*-hydroxyphenyl)-3-phenyl-2-propene (III) and 0.70 g (17 %) of slower-running 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (I); λ_{max} nm (log ε) 317sh (3.37), 303 (3.73), 295sh (3.69), 283sh (3.53), 263sh (3.99), 251 (4.19); ν_{max} 3520, 3400, 1598, 1580 cm^{-1}; τ 2.7–4.1 (11 H, m), *ca.* 5.0 (1 H, broad), 6.49–6.58 (2 H, broad d). TLC spots of I assume brown coloration after spraying with dilute H_2SO_4 and warming. (Found: C 85.58; H 6.79. Calc. for $C_{15}H_{14}O$: C 85.68; H 6.71.)

Reduction of 2'-hydroxychalcone with $LiAlH_4$. A. A solution of 1.90 g of 2'-hydroxychalcone in 100 ml of anh. ether was added while stirring into a cooled suspension of 0.25 g of $LiAlH_4$ in 50 ml of anh. ether. The stirring was continued for another 15 min, excess $LiAlH_4$ decomposed with methyl formate, 100 ml of 2 N H_2SO_4 added, the ethereal layer washed with water, dried and evaporated. The residue was chromatographed in a silica gel column, eluting first with benzene (fraction A), followed by chloroform (fraction B). Fraction A consisted of 3-flavene (0.55 g, 31 %); λ_{max} nm (log ε) 323sh (3.27), 309 (3.49), 280sh (3.42), 266 (3.63), 250sh (3.62), 223 (4.69); ν_{max} 1625, 1600, 1570 cm^{-1}; τ 2.5–3.5 (9 H, m), 3.65–3.85 (1 H, d of d, J_1 9.5 Hz, J_2 1.5 Hz), 4.27–4.33 (1 H, d of d, J_1 3.5 Hz, J_2 1.5 Hz), 4.41–4.64 (1 H, d of d, J_1 3.5 Hz, J_2 9.5 Hz).* Fraction B gave, after preparative TLC (elution twice with chloroform), 0.79 g (39 %) of oily 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanol (V), which crystallised on standing, m.p. 57–58°C; ν_{max} 3520, 3400–3250, 1600, 1585, 1235, 1025–1050 cm^{-1}; τ *ca.* 1.9 (1 H, broad), 2.8–3.35 (9 H, complex), 5.32 (1 H, centre of broad t, J 6 Hz), 7.20–7.53 (2 H, m), 7.75–8.17 (2 H, m). (Found: C 79.11; H 7.00. Calc. for $C_{15}H_{16}O_2$: C 78.92; H 7.06.)

B. The reaction was conducted as described above under A, except for stirring the reaction mixture at room temperature for 15 h. After this period no 3-flavene was present judging by TLC (lack of formation of an intense yellow colour on spraying with dilute H_2SO_4). In the slower-running portion a large number of products was present.

Treatment of 1-(o-hydroxyphenyl)-3-phenyl-1-propene (I) with $AlCl_3$. 0.37 g of the 1-propene (I) was dissolved in 15 ml of ether and 0.15 g of anh. $AlCl_3$ added at room temperature. After 5 h dilute H_2SO_4 was added while cooling, and examination of the ethereal layer by TLC (silica gel, chloroform:cyclohexane 1:1) indicated that several compounds were present, including a slow-running material near the origin, starting material, and the 2-propene (III).

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* Marathe *et al.*[10] have measured the NMR spectrum of 3-flavene. However, they merely state "NMR spectrum showed the presence of the three non-aromatic hydrogen atoms of a −CH=CH−CH− group" without giving chemical shift values or coupling constants.

Ring cleavage of 2-benzyl-2,3-dihydrobenzofuran. In the treatment of the furan with sodium in pyridine the procedure described earlier [1] was followed. Preparative TLC, as described above under the $LiAlH_4-AlCl_3$ reduction of 2'-hydroxychalcone, gave from 0.91 g of starting material 0.29 g (32 %) and 0.24 g (26 %) of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (I) and 1-(*o*-hydroxyphenyl)-3-phenyl-2-propene (III), respectively.

1-(o-Methoxyphenyl)-3-phenyl-1-propanone (VII). Into a suspension of diphenethylcadmium in benzene (from 16.25 g of phenethyl bromide) was added a solution of 12 g of *o*-methoxybenzoyl chloride in 50 ml of benzene. The mixture was refluxed for 5 h, ice and dilute H_2SO_4 added, the organic layer washed with dilute Na_2CO_3, dried, and the solvent removed. Chromatography in a silica gel column (elution with benzene) gave 14 g of 1-(*o*-methoxyphenyl)-3-phenyl-1-propanone (VII), ν_{max} 1670, 1593, 1575 cm^{-1}; τ 2.25—3.3 (9 H, m), 6.33 (3 H, s), 6.90 (4 H, m, centre of A_2B_2). (Found: C 80.11; H 6.71. Calc. for $C_{16}H_{16}O_2$: C 79.97; H 6.71.)

1-(o-Hydroxyphenyl)-3-phenyl-1-propanone (IV). 6.5 g of BCl_3 was added to a cooled and stirred solution of 12.2 g of the preceding propanone (VII) in 50 ml of chloroform. The solution was stirred at room temperature for 30 min, poured on ice, washed with dilute H_2SO_4 and water and the organic layer evaporated after drying. Silica gel column chromatography (elution with chloroform) gave 10.5 g (91 %) of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanone (IV), identical with the ketone obtained from the $LiAlH_4-AlCl_3$ reduction of 2'-hydroxychalcone.

1-(o-Hydroxyphenyl)-3-phenyl-1-propanol (V). 2.10 g of the preceding propanone (IV) was dissolved in 25 ml of methanol, and 0.53 g of $NaBH_4$ added during 10 min to the stirred solution. Stirring was continued for 15 min, water (10 ml) and conc. aqueous NH_4Cl (2 ml) added, the ethereal layer washed with water, dried, and the solvent removed. Silica gel column chromatography (elution with chloroform) gave 1.67 g (79 %) of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propanol (V), identical with the alcohol obtained from $LiAlH_4$ reduction of 2'-hydroxychalcone.

1-(o-Hydroxyphenyl)-3-phenyl-1-propanone tosylhydrazide (VIII). 6.10 g of the preceding propanone (IV) was dissolved in 50 ml of ethanol, 5.00 g of tosylhydrazide added and the solution refluxed for 16 h. The yellow crystalline tosylhydrazone (VIII) was filtered from the hot solution and washed with hot ethanol; the compound (10.10 g, 95 %) melted at 231°C and had ν_{max} 3500—2500, 1600, 1580, 1550, 1330 cm^{-1}. (Found: C 70.05; H 5.54; N 7.11. Calc. for $C_{22}H_{22}N_2SO_3$: C 66.99; H 5.62; N 7.10.)

1-(o-Hydroxyphenyl)-3-phenyl-1-propene (I). A. 1 g of sodium was added to 50 ml of ethylene glycol. After the reaction had subsided, 9.4 g of the preceding hydrazone (VIII) was added. The solution was refluxed for 40 min, cooled, poured on ice, acidified, and extracted with ether. Removal of solvent from the dried ethereal solution and preparative TLC (elution 6 times with chloroform:cyclohexane 1:3) gave 1.40 g (28 %) of 1-(*o*-hydroxyphenyl)-3-phenyl-2-propene (III) and 2.21 g (48 %) of 1-(*o*-hydroxyphenyl)-3-phenyl-1-propene (I), identical with the phenol obtained from the $LiAlH_4-AlCl_3$ reduction of 2'-hydroxychalcone.

B. 1.28 g of the alcohol (V) was dissolved in 20 ml of benzene, 1.5 g of anh. oxalic acid added, the mixture refluxed for 15 h, cooled, and filtered. Evaporation of the filtrate and silica gel column chromatography (elution with benzene:petroleum ether 1:1) gave 1.02 g (86 %) of the 1-propene (I), identical with the phenol obtained from the $LiAlH_4-AlCl_3$ reduction of 2'-hydroxychalcone.

C. Treatment of 1-(o-hydroxyphenyl)-3-phenyl-1-propanol (V) with $AlCl_3$. 0.29 g of the alcohol (V) was dissolved in 15 ml of anh. ether and 0.15 g of anh. $AlCl_3$ added. From the solution, kept at room temperature, samples were taken after 3 h and 15 h, and after refluxing for 6 h. Dilute H_2SO_4 was added to the samples and the ethereal layers examined by TLC (silica gel, chloroform:cyclohexane 1:1). Only slow-running material was visible on the plates; no spots corresponding to either of the olefinic phenols (I or III) could be observed.

D. Triphenylphenethylidene phosphorane and salicylaldehyde. 1.3 g of triphenylphosphine and 0.92 of phenethyl bromide were refluxed in xylene for 15 h, the precipitate washed with benzene and dried. Sodium ethoxide (from 0.16 g of Na in 100 ml of ethanol) was then added while stirring, followed after 5 min by 0.61 g of salicylaldehyde. No reaction was observed (TLC, silica gel, benzene) after 16 h at room temperature or after refluxing for 6 h.

E. 1-(o-Methoxyphenyl)-3-phenyl-1-propanol (VI). The propanol (V), prepared in 42 % yield from *o*-methoxybenzaldehyde and phenethyl bromide *via* the Grignard compound, had ν_{max} 3550, 3400, 1597, 1585, 1050 cm^{-1}; τ 2.7—3.45 (9 H, m), 5.17 (1 H, centre of broad t, J 6 Hz), 6.38 (3 H, s), 7.18—7.38 (2 H, m), 7.48 (1 H, broad),7.90—8.29 (2 H, m). Treatment of this propanol in acetic acid solution with a few drops of 48 % HBr at R.T. gave rise to a complex mixture (TLC, silica gel, chloroform:cyclohexane 1:1), which was not investigated further.

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