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Reduction of Chalcones by Complex Metal Hydrides

II.* 4- and 4′-Methoxychalcone with Lithium Aluminium Hydride-Aluminium Chloride

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Gas chromatography and degradation of products from lithium aluminium hydride-aluminium chloride treatment of 4- and 4′-methoxychalcone (I and II) show that I yields 1-phenyl-3-anisylpropene (III), whereas II gives a 3:2 mixture of III and 3-phenyl-1-anisylpropene. Structures are postulated for the dimers obtained in the reduction.

In part I,[1] the reduction of 2′-hydroxychalcone with a 1:2 mixture of lithium aluminium hydride and aluminium chloride was described. Contrary to an earlier report,[2] the main product was shown to be a mixture of phenolic 1- and 2-propenes with the 2-propene predominating.

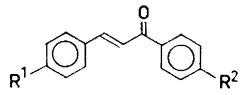
4- and 4′-Methoxychalcone (I and II) are reported [2] to react with the same reagent giving, in addition to nonolefinic, probably polymeric material, selectively anisylpropenes (III and IV, respectively) in which the double bond has migrated with respect to the original chalcone. This behaviour of chalcones, being rather atypical of α,β-unsaturated ketones, has been cited in a recent monograph on reduction.[3] Since such selectivity seemed surprising in view of our result with 2′-hydroxychalcone, the reaction with methoxychalcones was reinvestigated.

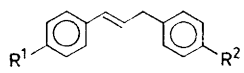
Both the above-mentioned methoxychalcones (I and II) gave on treatment with the 1:2 mixed reagent two major components, with the slower-migrating and faster-migrating pairs (dimers and monomers, respectively) having identical TLC behaviour. The components were isolated by preparative TLC, and the monomers found to have very similar ultraviolet, infrared, and proton magnetic resonance spectra, which were also in accord with a 1,3-diarylpropane structure. To settle the question on the relationship of the double bond with respect to the anisyl ring, samples of these monomers were oxidised with the Lemieux-von Rudloff reagent and with ozone (followed by

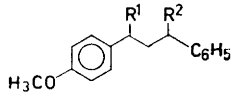
* Part I, see Ref. 1.

triphenylphosphine). The acids were converted to the methyl esters and analysed by VPC, and the aldehydes were converted to the 2,4-dinitrophenylhydrazones and analysed by TLC. In each case the derivatives were compared with authentic samples.

The Lemieux-von Rudloff oxidation gave irreproducible results, and varying proportions of benzoic, phenylacetic, anisic, and *p*-methoxyphenylacetic acid were formed in all cases. Ozonisation was more reproducible and indicated that the monomeric propene from 4-methoxychalcone (I) consisted only of the isomer in which the double bond had migrated (*i.e.*, III), thus supporting the previous observation.[2] On the other hand, the propene from 4′-methoxychalcone (II) gave on ozonisation all of the four possible aldehydes, and indicated that the propene consisted of III and IV at about 3 to 2 ratio. The exact proportions of III and IV were still uncertain after the ozonisation







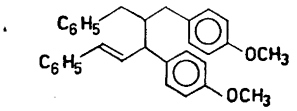
	R^1	R^2		R^1	R^2		R^1	R^2
I	OCH_3	H	III	H	OCH_3	V	H	OH
II	H	OCH_3	IV	OCH_3	H	VI	OH	H

experiments, as there was some scattering in the distribution of products, presumably caused by different rates of oxidation and varying stabilities of the oxidation products. For this reason, the monomeric propene fractions were analysed directly by VPC. For comparison, III and IV were prepared by dehydration of the corresponding saturated alcohols (V and VI). The VPC analysis of the chalcone reduction products shows that no IV is indeed formed from 4-methoxychalcone, and that the monomeric propene fraction from 4′-methoxychalcone consists of 62 % of III and 38 % of IV.

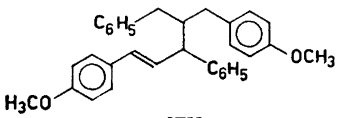
The amounts of *cis*-isomers present in synthetic III and IV as well as in chalcone reduction products were negligible, as was shown by VPC comparison with *cis*-enriched III, prepared by methyllithium treatment [4] of 1-phenyl-3-anisyl-1-propanone tosylhydrazide. The synthetic propenes, as well as those from the chalcones also lacked in their infrared spectrum a band at 675—730 cm^{-1} (out-of-plane δ CH),[5] as well as a complex proton magnetic resonance signal at τ 4.0—4.4, displayed by the *cis*-enriched III.

The dimers from the methoxychalcone reductions had infrared spectra practically identical with each other and with the monomeric propenes, with a prominent band at ν 965 cm^{-1} (*trans*-disubstituted double bond). The proton magnetic resonance spectra displayed, in addition to 20 protons in the aromatic and olefinic region, a broad one-proton signal at τ 6.4 (partly obscured by the six methoxyl protons) and a broad five-proton signal at τ 7.5. The PMR spectrum in benzene solution had a larger chemical shift difference between the methoxyls and the single proton, also establishing the 6:1 ratio. Each dimer gave on ozonolysis varying amounts of benzaldehyde and anisaldehyde in addition to other carbonylic material. Analogously, Lemieux-von Rudloff

oxidation gave benzoic and anisic acid. Since the dimers were evidently mixtures, no further study of their structures was undertaken. However, on the basis of results with other chalcones,[6] the dimer mixtures evidently consist of VII and VIII.

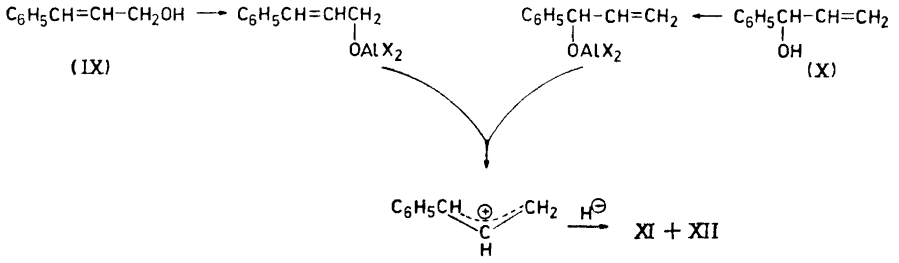


VII

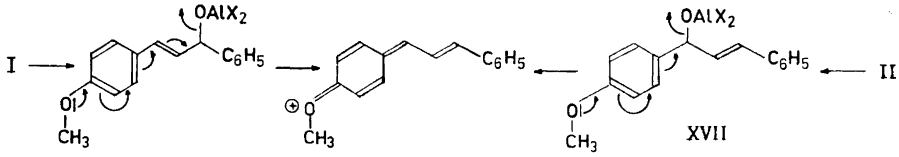


VIII

Cinnamyl alcohol (IX) and 1-phenylallyl alcohol (X) are both known [7] to yield, on treatment with a 1:3 mixture of lithium aluminium hydride and aluminium chloride, a mixture of *trans*-1-phenylpropene (XI) and allylbenzene (XII) at a ratio of about 7 to 3 in addition to other products. This is good evidence for the reaction to proceed *via* an allylic carbonium ion, which accounts for the equilibration.



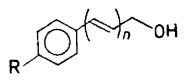
Although this mechanism could account for the products from the reduction of 4′-methoxychalcone (II), it should be noted that both I and II could give the same allylic carbonium ion, which therefore cannot be an intermediate in both reductions.



XVII

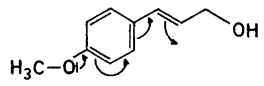
The selective formation of III from 4-methoxychalcone (I) was originally explained in the following way:[2] the chalcone (I) is first reduced to the corresponding saturated alcohol (V) which then undergoes dehydration to III. This was supported [2] by the observed formation of III from V on treatment with aluminium chloride.

However, the reduction rates for the compounds XIV, XV, and XVI are (half time values) 10.6, 44.6 and 753 min, respectively.[10] The effect of



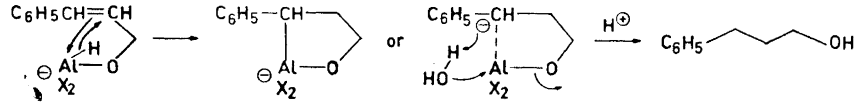
	R	*n*
XIV	H	2
XV	H	1
XVI	OCH_3	1

additional conjugation on the one hand and of electron-donating ring substituent on the other, giving the α-carbon a negative character, are clearly recognisable. It follows from the above results that 4-methoxychalcone should



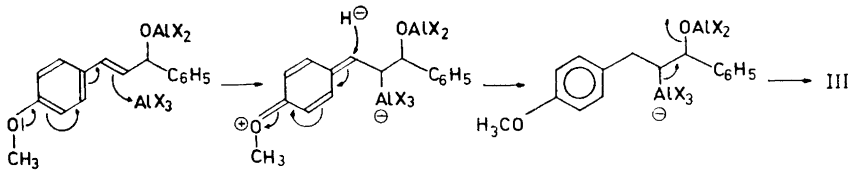
be reduced more slowly to the saturated alcohol than the 4′-isomer. The present results would seem to indicate the opposite to be true, if III is indeed formed from 4-methoxychalcone (I) *via* the saturated alcohol V. Accordingly the saturated-alcohol mechanism does not seem to fit the observed results.

In the lithium aluminium hydride reduction of α,β-unsaturated carbonylic systems to saturated alcohols the initial reaction is assumed to be 1,2- rather than 1,4-.[9] This is supported by results with cinnamic aldehyde, cinnamic alcohol, and allyl alcohol. The second (slower) step involves formation of a carbon-aluminium bond (XIII):[9,10]



XIII

In the present reaction (I→ III) a possibility could be the formation of a carbon-aluminium bond in a sense other than in XIII.



XVIII XIX

This pathway is less favorable to the 4′-methoxychalcone-derived 1,2-reduction product (XVII). The unit XIX (possibly polymeric) should probably contain two aluminium atoms, as the participation of O-bonded aluminium in XVIII would involve formation of a four-membered ring. XIX could subsequently eliminate the chain substituents to give III, or react in the work-up with water to give V.

However, the formation of dimer in addition to III from 4-methoxychalcone would seem to require the allylic carbonium ion mechanism.[6]

EXPERIMENTAL

UV spectra were recorded on a Beckman DK-2 spectrophotometer using ethanol solutions, 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 using CCl_4 solutions, unless otherwise indicated, with TMS as the internal standard. The symbols s, d, t, q, and m denote singlets, doublets, triplets, quartets, and multiplets, respectively. Preparative TLC was performed on silica gel plates (2 mm thickness), made from Merck's $PF_{254+366}$ silica gel. Gas chromatography of the methyl esters was performed with a Perkin-Elmer 452 instrument, equipped with a thermistor detector. Carrier (He) pressure was 1.6 atm. and the column (2 m 4 % SE-30) temperature 128°C. Gas chromatography of the propenes was performed with a Perkin-Elmer 800 instrument equipped with a FI detector. Carrier (N_2) flow rate was 5 ml/min, the split 1:5, injector temperature 250°C and column (support-coated open tubular column, DEGS 50 feet) temperature 205°C.

Petroleum ether refers to the fraction boiling at 40—60°C. All melting points are uncorrected. Elementary analyses were carried out on an F & M CNH Analyzer Model 185.

Reduction of chalcones with $LiAlH_4$—$AlCl_3$. The procedure of Bokadia *et al.*[2] was followed. 40 mmoles of anhydrous $AlCl_3$ was dissolved, with cooling, in 10 ml of anhydrous ether, and 20 mmoles of $LiAlH_4$ was then slowly added, followed by 10 mmoles of the chalcone in 10 ml of ether. The reaction mixture was stirred at room temperature for 2 h, and methyl formate (5 ml), water (5 ml), and dilute H_2SO_4 (20 ml) added. The organic layer was washed with water, dried, evaporated and the residue chromatographed (preparative TLC, elution with cyclohexane:chloroform 1:1). 4-Methoxychalcone gave 0.695 g (31 %) of faster-migrating monomer (*41*) and 0.535 g (24 %) of slower-migrating dimer (*42*); 4′-methoxychalcone, 0.740 g (33 %) of *4′1* and 0.560 g (25 %) of *4′2*, respectively.

Both dimers had λ_{max} 259, 284sh, 293sh, and 307 nm; ν_{max} 1608, 1510, 1247, and 965 cm^{-1}; τ 2.55—3.73 (20 H, m), 6.38 (6 H, s), 6.3—6.5 (1 H, broad), 7.2—7.7 (5 H, broad); τ (C_6H_6 solution) 6.27—6.42 (1 H, broad), 6.58 (6 H, s). (Found: (*42*) C 85.60; H 7.21; (*4′2*) C 85.66; H 7.23) $C_{32}H_{32}O_2$ requires C 85.68; H 7.19).

Oxidation of the reduction products. A. Lemieux-von Rudloff oxidation.[11] The olefins were only slowly attacked by the reagent, as judged by TLC, and the composition of the resulting diazomethane-treated mixture varied with reaction time. VPC analysis indicated that *41* gave mostly benzoic and *p*-methoxyphenylacetic acid in addition to some anisic and phenylacetic acid; *42* gave benzoic and anisic acid. *4′1* gave comparable amounts of all of the four acids, while *4′2* gave benzoic and anisic acid. Retention times (from solvent peak): methyl benzoate 1.66 min, methyl phenylacetate 2.2 min, methyl anisate 6.2 min, and methyl *p*-methoxyphenylacetate 8.0 min.

B. Ozonisation. Samples of olefins were treated with 2 % O_2—O_3 mixture at −77°C in $CHCl_3$—CH_3OH solution, until TLC indicated no starting material left. Excess triphenylphosphine was then added and the stirred solution was allowed to reach room temperature. After 15 h the crude mixture was treated with ethanolic 2,4-dinitrophenylhydrazine, the precipitate collected and analysed by TLC (silica gel $GF_{254+366}$, benzene). *41* gave only benzaldehyde and *p*-methoxyphenylacetaldehyde, while *4′1* gave phenylacetaldehyde and anisaldehyde in addition. The estimated concentrations of the aldehydes corresponded to about 3:2 ratio of III and IV present in *4′1*. *42* and *4′2* gave low yields of benzaldehyde and anisaldehyde.

Gas chromatography of III, IV, 41 and 4′1. Retention times (from solvent peak): III 28.3 min, IV 29.2 min. *41* consisted of pure III, whereas *4′1* contained 62 % of III and 38 % of IV.

1-Phenyl-3-anisyl-1-propanol[8] *(V)*, prepared from 4-methoxychalcone, had ν_{max} 3400, 1610, 1512, 1250, and 1040 cm^{-1}; τ 2.68 (5 H, s, phenyl), 2.90 and 3.21 (4 H, AA′BB′≈AB q, J=8.5 Hz, anisyl), 5.31 (1 H, broad t, J=5.5 Hz, methine), 6.22 (3 H, s, methoxyl), 7.32 (2 H, broad t, J=6.5 Hz, benzylic methylene), 7.76—8.09 (2 H, m, methylene) and 8.03 (1 H, broad s, hydroxyl).

3-Phenyl-1-anisyl-1-propanol [8] *(VI)*, prepared from 4′-methoxychalcone, had ν_{max} 3400, 1610, 1510, 1245, and 1030 cm^{-1}; τ 2.91 (5 H, s, phenyl), 2.90 and 3.30 (4H, AA′BB′≈AB q, J=8.5 Hz, anisyl), 5.55 (1 H, broad t, J= 6.5 Hz, methine), 6.49 (3 H,

s, methoxyl), 6.74 (1 H, broad s, hydroxyl), 7.40 (2 H, broad t, $J=8$ Hz, benzylic methylene), 7.80–8.24 (2 H, m, methylene).

1-Phenyl-3-anisylpropene (III) and 3-phenyl-1-anisylpropene (IV) have been prepared [8] by distillation of V and VI, respectively, with potassium bisulfate. Higher yields (92 % and 94 %, respectively) and pure products were obtained by refluxing V and VI in toluene solution for 14 h in the presence of excess anhydrous oxalic acid, followed by removal of solvent and column chromatography (alumina grade I, petroleum ether). 1-Phenyl-3-anisylpropene (III) had λ_{max} nm (log ε) 254 (4.26), 276sh (3.71), 284 (3.55), and 292 (3.07); ν_{max} 1608, 1505, 1243, and 962 cm^{-1}; 2.72 (5 H, s, phenyl), 2.93 and 3.28 (4 H, AA'BB'≈AB q, $J=8.5$ Hz, anisyl), 3.49–4.16 (2 H, m, olefinic), 6.40 (3 H, s, methoxyl), 6.62 (2 H, broad d, $J=5.5$ Hz, methylene). 3-Phenyl-1-anisylpropene (IV) had λ_{max} nm (log ε) 260 (5.03), 265sh (5.02), 270 (4.98), 295sh (4.16), and 303 (3.92); ν_{max} 1600, 1505, 1245, and 960 cm^{-1}; τ 2.88 (5 H, s, phenyl), 2.85 and 3.36 (4 H, AA'BB'≈AB q, $J=8.5$ Hz, anisyl), 3.53–4.21 (2 H, m, olefinic), 6.36 (3 H, s, methoxyl), 6.59 (2 H, broad d, $J=5.0$ Hz, methylene).

1-Phenyl-3-anisyl-1-propanone [12] *(XVI)*, prepared from 4-methoxychalcone, had τ 2.06–2.29 (2 H, m, benzoyl-2,6-H_2), 2.53–3.44 (7 H, m, aromatic), 6.31 (3 H, s, methoxyl) and 7.00 (4 H, center of symm. A_2B_2-m, methylene).

1-Phenyl-3-anisyl-1-propanone tosylhydrazide (XVII). 1.4 g of the preceding propanone (XVI) was dissolved in methanol (20 ml), and 1.1 g of tosylhydrazide was added. The solution was then refluxed for 18 h, water (5 ml) added and cooled. The precipitate of XVII was recrystallised from aqueous methanol (yield 2.2 g, 92 %). It melted at 140–141°C, and had ν_{max} 3210, 1605, 1592, 1579, 1504, 1333, and 1165 cm^{-1}. (Found: C 67.71; H 6.01; N 6.95). $C_{23}H_{24}N_2O_3S$ requires C 67.63 %, H 5.92 %, N 6.86 %.

cis-*Enriched 1-phenyl-3-anisylpropene (*cis*-enriched III).* Methyllithium (2.2 equiv.) in ether was added, with stirring, to an ethereal solution (35 ml) of 1.9 g of the preceding tosylhydrazide (XVII). The solution was stirred for 2 h, and the residue chromatographed (alumina grade I column, petroleum ether) to give *cis*-enriched III. It had ν_{max} 720 cm^{-1}; τ 3.60–4.15 (m) and 4.15–4.55 (m) (about 2:1 ratio), which indicates about 1:1 ratio of *trans*- and *cis*-III. Shapiro [4] reports 52:48 ratio for the formation of *trans*- and *cis*-1,3-diphenylpropene from 1,3-diphenyl-1-propanone tosylhydrazide. In VPC analysis, two major peaks appeared at a ratio of 55:45 (retention times 28.3 and 19.1 min).

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