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A STUDY OF THE CLAISEN REARRANGEMENT OF 7-CINNAMYLOXY BENZO-γ-PYRONES

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Abstract—The Claisen rearrangement of 7-O-cinnamyl noreugenin (**2**) yields 4',5' - dihydro - 5 - hydroxy - 2,4' - dimethyl - 5' - phenyl - furo (2',3': 7,8) chromone (**6**) as established by its NMR spectrum, whereas that of 7-cinnamyloxyflavone (**10a**) and 5 - hydroxy - 7 - cinnamyloxy - 2 - methylisoflavone (**10b**) afford the corresponding furo derivatives (**12a** and **12b** respectively). All these rearrangements are symmetry-allowed but are accompanied by further reactions of thermal cyclisation via 3-membered cyclic intermediate (**5**) and/or dehydrogenation.

The natural occurrence of simple cinnamyl phenols (also called benzyl styrenes),[1] 3,3 - diphenyl - 1 - propenes[2] and related neoflavonoids[2] such as dalbergiquinols, dalbergiquinones, 2,3 - dihydro - 2 - phenyl - 3 - methyl benzofurans and quinomethides[3,4] prompted us to study the Claisen rearrangement of cinnamyl ethers of typical benzo - γ - pyrones so that it could be a method alternative to the direct cinnamylation method[5] for the preparation of such cinnamylated derivatives. In the course of this study, some products have been obtained which contain further variants of the cinnamyl unit.

The Claisen rearrangement of 7-cinnamyl ethers of noreugenin,[6] (**1**), 7-hydroxyflavone[7] (**9a**) and 5,7 - dihydroxy - 2 - methyl - isoflavone[8] (**9b**) has now been studied. These cinnamyl ethers were prepared by the reaction of the corresponding hydroxy compound with one mole of cinnamyl bromide in the presence of potassium carbonate and acetone and their identity has been established by their NMR spectra. Thus there are resonance signals of a methylenoxy group at δ *ca.* 4·70 as a doublet (J 5·5 Hz), two olefinic protons of the cinnamyl residue as a multiplet centered at δ *ca.* 6·45 and a phenyl group at δ *ca.* 7·35 besides those shown by the starting molecule (Experimental).

The Claisen rearrangement of 7 - O - *cinnamyl noreugenin*[9] (**2**). 5 - Hydroxy - 7 - cinnamyloxy - 2 - methylchromone (**2**) when heated *in vacuo* at 240–60° for 5 hr, gave a mixture of products among which only one crystalline product (A) could be isolated by purification through column chromatography. This product shows positive ferric reaction and is insoluble in aqueous sodium carbonate. Its elemental analysis showed it to be isomeric with the starting molecule. Since its complete acetylation and methylation gave only a monoacetate (NMR: δ 2·29, s, 3H, $OCOCH_3$) and a monomethyl ether (NMR: δ 3·95, s, 3H, OCH_3) respectively, 7-hydroxyl is obviously engaged. NMR spectra of the product A, its acetate and methyl ether indicated further the presence of a condensed 2 - phenyl - 3 - methyl - 2,3 - dihydrofuro unit besides one aromatic proton, one Me group in the 2 position and one olefinic hydrogen in the 3 position. Thus there are resonance signals of two protons as two doublets (J 7 Hz) at δ *ca.* 3·65 and 5·35 and a phenyl group as a singlet at δ *ca.* 7·40. The orientation of the dihydrofuro ring is established as an angular one because the signal of an aromatic proton at δ 6·32 in the hydroxy compound (A) and δ 6·38 in its methyl ether undergo a downfield shift to δ 6·62 in the acetate. Hence the structure of the Claisen rearrangement product (A) is 4',5' - dihydro - 5 - hydroxy -, 2,4' - dimethyl - 5' - phenyl - furo(2',3': 7,8)chromone (**6**) and consequently its acetate is **7** and its methyl ether **8**. The stereochemistry of the dihydrofuro moiety could not be decided on the basis of vicinal coupling constants of two olefinic protons which is shown to be almost the same for both the *cis*- and *trans*-isomers.[10]

The formation of the product (**6**) can be explained as follows: In the first step normal Claisen rearrangement product namely 5,7 - dihydroxy - 2 - methyl - 8 - (1 - phenylallyl) - chromone (**4**) is formed which undergoes further thermal rearrangement via the cyclic intermediate (**5**) to give the final product (**6**).

The Claisen rearrangement of 7-*cinnamyloxyflavone* (**10a**). 7-Cinnamyloxyflavone (**10a**) when heated *in vacuo* at 280–300° for 6 hr, also gave one crystalline product purified by column chromatography. As it formed neither acetate nor methyl ether, the OH group was considered to be blocked. Its NMR spectrum suggests that it has a condensed methyl and phenyl substituted furano unit and this unit is angularly orientated. Thus it shows resonance signals of Me group attached to an ethylenic bond at δ 2·46 (s, 3H), one phenyl group at δ 7·14 as a singlet, one proton in the 3 position as a singlet at δ 6·41, one *ortho*-coupled aromatic proton in the 5 position as a doublet at δ 7·74 (J 9 Hz) and one phenyl group and one aromatic proton in the 6 position as a multiplet centered at δ 6·88. The product A could therefore be either 4'' - methyl - 5'' - phenyl - (**12a**) or 4'' - phenyl - 5'' - methyl - (**13a**) furo - (2'',3'':7,8)flavone. The former (**12a**) is more likely than the latter (**13a**) in analogy with the product obtained in the Claisen rearrangement product of 5 - hydroxy - 7 - cinnamyloxy - 2 - methylchromone (**2**). The mechanism of the formation of the product (**12a**) can be explained in the same way through dihydrofuro derivative (**11a**) as given above in the latter case. The final dehydrogenation step seems to be facile in this case.

The Claisen rearrangement of 5 - *hydroxy* - 7 - *cinnamyloxy* - 2 - *methyl* - *isoflavone* (**10b**). The Claisen rearrangement product of the cinnamyl ether (**10b**) shows ferric reaction and is insoluble in sodium carbonate solution. Hence 5-OH is free and 7-OH is blocked. The complete methylation with Me_2SO_4 in the presence of K_2CO_3 and acetone yielded only a monomethyl ether (NMR: δ 4·00 s, 3H, OCH_3) showing negative ferric

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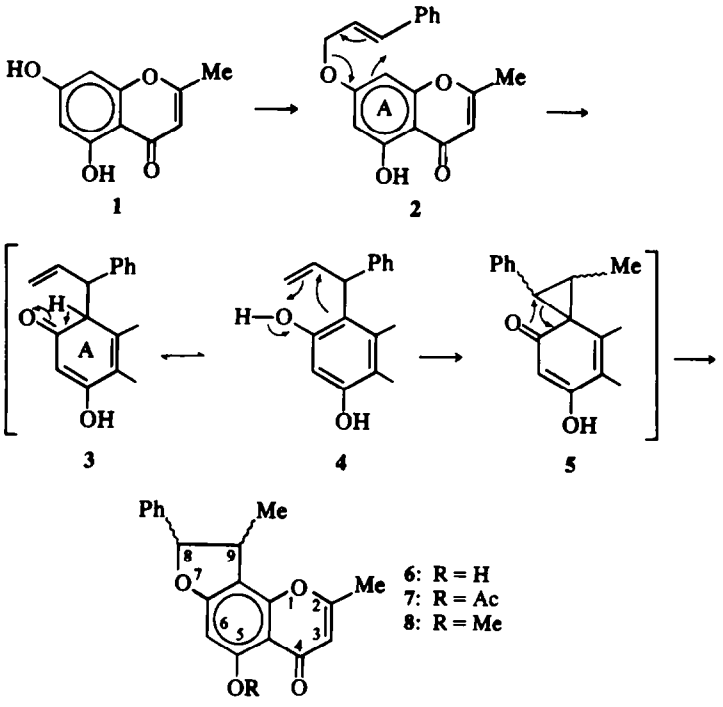
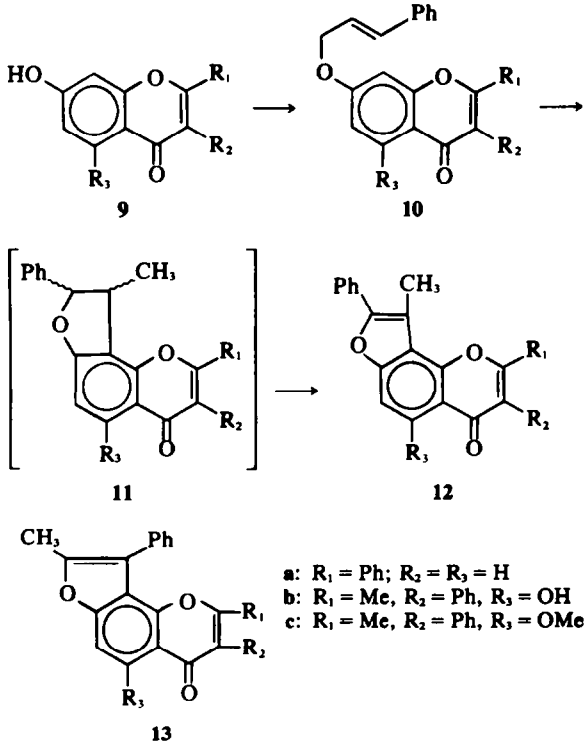


reaction. The NMR spectrum of the compound also shows the presence of a condensed methyl and phenyl substituted furano unit. Thus it shows resonance signals of a Me group attached to an ethylenic bond at δ 2·49, a singlet of a Me group in the 2 position at δ 2·09, a singlet of an aromatic proton in the 6-position at δ 6·92 and a multiplet of two phenyls centered at δ 7·50. Thus the structure of the product could be either 2,4″-dimethyl-5″-phenyl (**12b**) or 2,5″ - dimethyl - 4″ - phenyl - (**13b**)furo (2″,3″:7,8)isoflavone analogous to the above experiment.

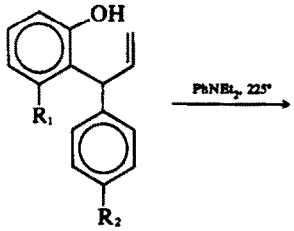
DISCUSSION

From the above experiments, it may be concluded that the Claisen rearrangement of 7 - cinnamyloxybenzo - γ - pyrone derivatives takes place in the normal way, but the rearrangement products undergo cyclisation presumably via cyclopropane intermediates to give dihydrofurano derivatives. In the case of chromone (**2**) the dihydrofurano derivative is stable but in other cases it undergoes further dehydrogenation to give furo derivatives. Earlier in literature, the Claisen rearrangement of



cinnamyl ethers of simple phenols like resorcinol and pyrogallol derivatives was found to give only acylic normal products, viz. cinnamyl phenols and *o* - (1 - phenylallyl)phenols.[11] But tocyl cinnamyl ether[12] was found to give two isomeric *ortho* cinnamyl phenols which are symmetry-forbidden. The formation of these dihydro and furo products in the present experiments is interesting, because two natural products obtusafuran[13] and melanoxin[14] have such a condensed dihydrofuro system.

After writing this paper, we came across the paper of Schmid *et al.*[15] in which 2 - (1' - arylallyl)phenols (**14**) formed by the thermal Claisen rearrangement of 3' - (aryl substituted) - allyl phenyl ethers in $PhNEt_2$ at 182°, are reported to lead predominantly to trans - 2 - aryl - 3 - methyl coumarans (**15**) when heated in $PhNEt_2$ at 225°. This supports our observations.



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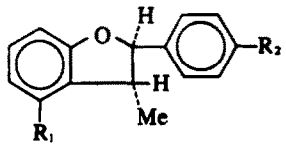

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R_1 and R_2 are H, OMe or Me

EXPERIMENTAL

Unless otherwise stated, m.ps are uncorrected: IR spectra were measured on a Perkin-Elmer infracord machine using KBr disc; NMR spectra were recorded on a 60 MHz spectrophotometer in $CDCl_3$ using Me_4Si as an internal standard and chemical shifts are expressed in δ values; light petroleum had boiling range 60–80°, silica gel was used for column chromatography and TLC; solvent systems for TLC are: (A) EtOAc:benzene (1:19), (B) EtOAc:benzene (1:9), (C) EtOAc:benzene (1:4), (D) MeOH:benzene (1:4); R_f values are those taken on TLC.

5 - *Hydroxy* - 7 - *cinnamyloxy* - 2 - *methylchromone* (**2**). To a soln of **1**[6](3 g) in dry acetone (150 ml) was added cinnamyl bromide (4·2 ml) and anhyd K_2CO_3 (15 g) and the mixture was refluxed on a water bath for 10 hr. The solvent was removed under reduced pressure and the residue treated with water. The solid was collected, dried and crystallised from benzene–light petroleum mixture when **2** was obtained as pale yellow crystals (1·4 g); m.p. 121–22°; violet ferric reaction; R_f 0·54 (Solvent B); NMR: 2·35 (s, 3H, olefinic CH_3 in the 2 position), 4·75 (d, J 5·5 Hz, 2H, –O–CH_2), 6·00 (s, 1H, olefinic H in the position 3), 6·36 (s, 1H, aromatic H in the position 6), 6·36–6·58 (m, 2H, Ar–CH=CH–), 6·65 (d, J 1 Hz, 1H, aromatic H in the position 8) and 7·35 ppm (d, J 1·5 Hz, 5H, C_6H_5) (Found: C, 73·7; H, 5·2. $C_{19}H_{16}O_4$ requires: C, 74·0; H, 5·2%).

The Claisen rearrangement of 5 - *hydroxy* 7 - *cinnamyloxy* - 2 - *methylchromone*

Formation of 4',5' - *dihydro* - 5 - *hydroxy* - 2,4' - *dimethyl* - 5 - *phenylfuro* (2',3': 7,8) *chromone*, (**6**). Compound **2** (1 g) was heated *in vacuo* at 240–60° for 5 hr. The product was examined by TLC (solvent B) which showed only one major compound. It was purified by column chromatography. Elution with benzene–light petroleum (1:1) gave a fraction which crystallised from benzene–light petroleum mixture and gave **6** as light-yellow needles (250 mg), m.p. 161–62°; green ferric reaction; R_f 0·55 (solvent B); ν_{max} 1660 and 1620 cm^{-1} (C=C–C=O–); NMR: 1·57 (d, J 7 Hz, 3H, aliphatic CH_3 in the 4'-position), 2·35 (s, 3H, olefinic CH_3 in the 2 position), 3·62 (m, 1H, ArCH in the 4' position), 5·32 (d, J 7 Hz, 1H, O–CH in the 5' position), 6·00 (s, 1H, olefinic H in the position 3), 6·32 (s, 1H, aromatic H in the position 6) and 7·38 ppm (s, 5H, C_6H_5) (Found: C, 73·8; H, 5·0. $C_{19}H_{16}O_4$ requires: C, 74·0 and H 5·2%).

The diacetate prepared by the Ac_2O–NaOAc method crystallised from benzene–light petroleum mixture as colourless prisms; m.p. 135–36°; R_f 0·35 (solvent C); NMR: 1·60 (d, J 7 Hz, 3H, aliphatic CH_3 in 4' position), 2·29 (s, 3H, $OCOCH_3$) 2·42 (s, 3H, olefinic CH_3, in the 2 position), 3·74 (m, 1H, ArCH in the 4' position), 5·42 (d, J 7 Hz, 1H O–CH in the 5' position), 6·00 (s, 1H, olefinic H in the 3 position), 6·62 (s, 1H, aromatic H in the position 6), and 7·42 ppm (s, 5H, C_6H_5) (Found: C, 71·9; H, 5·4. $C_{21}H_{18}O_5$ requires: C, 72·0; H 5·1%).

4',5' - *Dihydro* - 5 - *methoxy* - 2,4' - *dimethyl* - 5' - *phenylfuro* (2',3': 7,8) - *chromone* (**8**). Compound **6** (100 mg) was refluxed with Me_2SO_4 (0·035 ml), anhyd acetone (30 ml) and ignited K_2CO_3 (500 mg) until negative ferric reaction was obtained (15 hr). Acetone was removed under reduced pressure and water added to the residue. The solid was collected and crystallized from benzene–light petroleum mixture when **8** was obtained as colourless needles (80 mg); m.p. 156–57°; R_f 0·60 (solvent D); negative ferric reaction; NMR: 1·56 (d, J 7 Hz, 3H, aliphatic CH_3 in 4' position), 2·24 (s, 3H, olefinic CH_3 in 2 position), 3·62 (m, 1H, Ar–CH in 4' position), 3·95 (s, 3H, aromatic OCH_3), 5·32 (d, J 7 Hz, 1H, –O–CH in 5' position), 5·96 (s, 1H, olefinic H in 3 position), 6·39 (s, 1H, aromatic H in position 6) and 7·32 ppm (s, 5H, C_6H_5–) (Found: C, 74·3; H, 5·2. $C_{20}H_{18}O_4$ requires: C, 74·5; H 5·5%).

7-*Cinnamyloxyflavone* (**10a**). An acetone soln of 7-hydroxyflavone[7] (**9a**) (3 g) was refluxed with cinnamyl bromide (2·5 ml) in the presence of anhyd K_2CO_3 for 10 hr. The product was crystallized from benzene when 7-cinnamyloxyflavone (**10a**) was obtained as colourless crystals (1·6 g); m.p. 182–83°; R_f 0·30 (solvent B); NMR: 4·69 (d, J 5 Hz, 2H, O–CH_2–), 6·25–6·55 (m, 2H, Ar–CH=CH–), 6·65 (s, 1H, olefinic hydrogen in the position 3), 6·84–7·01 (m, 2H, aromatic H in the 6 and 8 positions), 7·28 (s, 5H, C_6H_5–), 7·34–7·45 (m, 3H, aromatic H in the 3',4' and 5' positions), 7·70–7·88 (m, 2H, aromatic H in the 2' and 6' positions) and 8·08 ppm (d, J 10 Hz, aromatic H in the 5 position) (Found: C, 81·4; H, 5·4. $C_{24}H_{18}O_3$ requires: C, 81·3; H, 5·1%).

The Claisen rearrangement of 7-*cinnamyloxyflavone* (**10a**)

Formation of 4" - *methyl* - 5" - *phenyl* (**12a**) *or* 4" - *phenyl* 5" - *methyl* (**13a**) *furo* (2",3": 7,8)*flavone*. 7 - Cinnamyloxyflavone was heated *in vacuo* at 280–300° for 6 hr. The product on examination with TLC (solvent B) appeared to be mixture but containing only one major compound. It was therefore purified by column chromatography. Elution with benzene–light petroleum (1:1) gave a fraction which crystallised from EtOAc–light petroleum mixture giving **12a** or **13a** flavone as colourless needles (225 mg); m.p. 219–20°; R_f 0·37 (solvent B); ν_{max} 1640 cm^{-1} (C=O); NMR: 2·46 (s, 3H, olefinic CH_3 in the 4' position), 6·41 (s, 1H, olefinic H in the 3 position), 7·14 (s, 5H, C_6H_5), 6·88–7·14 (m, 6H, aromatic H in the 6 position and of C_6H_5) and 7·74 ppm (d, J 9 Hz, 1H, aromatic H in the 5 position) (Found: C, 81·7; H, 4·8. $C_{24}H_{16}O_3$ requires: C, 81·8: H, 4·5%).

5 - *Hydroxy* - 7 - *cinnamyloxy* - 2 - *methylisoflavone* (**10b**). Compound **9b**[8] (3 g) was heated with cinnamyl bromide (2·2 ml) in the presence of anhyd K_2CO_3 (15 g) and anhyd acetone for 10 hr. The product was crystallised from benzene–light petroleum mixture when **10b** was obtained as colourless needles (1·3 g), m.p. 163–64°; R_f 0·71 (Solvent A); violet ferric reaction; NMR: 2·24 (s, 3H, olefinic CH_3 in the 2 position), 4·75 (d, J 5 Hz, 2H, O–CH_2), 6·40–6·58 (m, 2H, Ar–CH=CH–), 6·68 (s, 1H, aromatic H in the position 8) 6·94 (s, 1H, aromatic H in the position 6) and

7·26–7·51 ppm (m, 10H, 2 $C_6\underline{H}_5$) (Found: C, 77·8; H, 5·2. $C_{25}H_{20}O_4$ requires: C: 78·1; H, 5·2%).

The Claisen rearrangement of 5 - *hydroxy* - 7 - *cinnamyloxy* - 2 - *methyl* - *isoflavone* (**10b**)

Formation of 2,4″ - *dimethyl* - 5″ - *phenyl* (**12b**) *or* 2,5″ - *dimethyl* - 4″ - *phenyl* - (**13b**)*furo* (2″,3″: 7,8)*isoflavone.* Compound **10b** (1 g) was heated *in vacuo* at 280–300° for 6 hr. The product was purified by column chromatography. Elution with benzene–light petroleum mixture (4:6) gave a fraction which crystallized from benzene–light petroleum mixture to give (**12b**) or (**13b**) as pale yellow crystals (150 mg); m.p. 204–5°; R_f 0·62 (solvent A); green ferric reaction; ν_{max} 1660, 1620 cm^{-1} (>C=C–C=O); NMR: 2·49 (s, 3H, olefinic $C\underline{H}_3$ in the 4″ position), 2·09 (s, 3H, olefinic $C\underline{H}_3$ in the 2 position), 6·92 (s, 1H, aromatic H in the position 6) and 7·39–7·52 ppm (m, 10H, 2$C_6\underline{H}_5$–) (Found: C, 78·1; H, 5·0. $C_{25}H_{18}O_4$ requires: C, 78·5; H, 4·7%).

Methylation of the product (**12b** *or* **13b**). The above product **12b** or **13b** (100 mg) was refluxed with Me_2SO_4 (0·032 ml) in the presence of anhyd K_2CO_3 (0·5 g) and acetone (40 ml) until ferric reaction was negative (12 hr). The product was crystallised from MeOH when the methyl ether (**12c** or **13c**) was obtained as colourless needles (85 mg); m.p. 189–90°; R_f 0·62 (solvent D); negative ferric reaction; ν_{max} 1660, 1650 cm^{-1} (C=O); NMR: 2·49 (s, 3H, olefinic $C\underline{H}_3$ in 4″ position), 1·96 (s, 3H, olefinic CH_3 in the 2 position), 4·00 (s, 3H, $OC\underline{H}_3$), 6·98 (s, 1H, aromatic H in the 6 position), 7·30–7·51 ppm (m, 10H, 2$C_6\underline{H}_5$–) (Found: C, 78·4; H, 5·8. $C_{26}H_{20}O_4$ requires: C, 78·4; H, 5·5%).

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