

A convenient synthesis of lonchocarpin and isolonchocarpin

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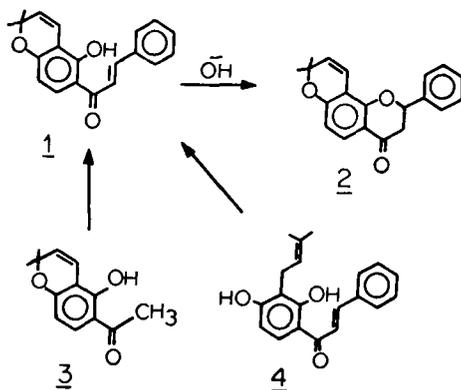
MS received 21 November 1977; revised 7 June 1978

Abstract. 1, 1-Dimethyl propargylation of 7-hydroxyflavanone (5) with 2-chloro-2-methyl-3-butyne in the presence of K_2CO_3 , Me_2CO , KI and DMF yielded a mixture of four compounds. Its 1, 1-dimethyl propargyl ether (6) and the corresponding chalcone (7) resulted in major amounts; their corresponding cyclised products (2 and 1) also formed albeit in smaller amounts. These cyclised products, lonchocarpin (1) and isolonchocarpin (2) were the sole products when the above mixture was heated in *N,N*-dimethylaniline. Lonchocarpin (1) is best synthesized by 1, 1-dimethyl propargylation of 2', 4'-dihydroxychalcone (8) followed by heating in *N,N*-dimethylaniline, because it was noted that in the above two reactions, the flavanone ring tends to open out whereas the chalcone does not cyclise.

Keywords. 7-Hydroxyflavanone; 2',4'-dihydroxychalcone; 1,1-dimethyl propargylation; thermal transformations.

1. Introduction

Lonchocarpin was first isolated from the roots of *Derris sericea* (Baudrenghien *et al* 1953) and assigned its correct structure as 2'-hydroxy-6'',6''-dimethylpyrano-(2'', 3'': 4', 3') chalcone (1) by the same workers (1953). Later, this compound along with the corresponding flavanone called isolonchocarpin (2) was detected in the root bark of the same plant (Nascimento *et al* 1970, 1973). This flavanone (2) had previously been obtained in the laboratory by the isomerisation of natural lonchocarpin (1) with 2% alkali (Baudrenghien *et al* 1949). Lonchocarpin, itself has been synthesized earlier in two ways. One method consists in reacting 2, 2-dimethyl-6-acetyl-5-hydroxychromene (3) by condensation with benzaldehyde in the presence of alkali



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(Nickl 1958; Sharma *et al* 1973). The second method starts with the synthesis of 3-C-prenyl-2',4'-dihydroxychalcone (also called isocordoin, 4), followed by cyclo-dehydrogenation with DDQ (Khanna *et al* 1973; Monache *et al* 1973).

2. Results and discussion

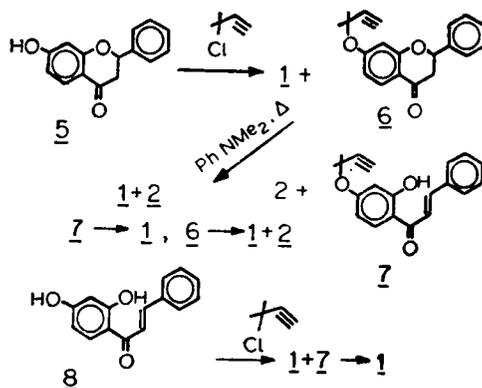
2.1. 1,1-Dimethyl propargylation of 7-hydroxyflavanone

In this paper, an alternative synthesis of isolonchocarpin and lonchocarpin is described. This starts with 7-hydroxyflavanone (5) which when heated with 2-chloro-2-methyl-3-butyne in the presence of potassium carbonate, acetone, potassium iodide and a few drops of *N,N*-dimethylformamide (DMF), gave a mixture of four products separable by column chromatography. These four products are 7-(1,1-dimethyl propargyloxy) flavanone (6) and its corresponding chalcone (7) and their cyclised α -pyrano derivatives (2 and 1). The latter chromenes were found identical in the data reported for naturally occurring isolonchocarpin (2) and lonchocarpin (1). The former 1,1-dimethyl propargyl ethers (6 and 7) were identified on the basis of their ferric reaction, UV and NMR spectra. Thus UV spectra and ferric reaction showed that 6 is flavanone and 7 is a chalcone derivative.

Further NMR spectrum of 7 showed characteristic resonance signals of α - and β -hydrogens at δ 7.51 and 7.70 ppm respectively and of 1, 1-dimethyl propargyloxy group at δ 1.73 ($2XCH_3$) and 2.7 ppm ($C\equiv CH$).

Similarly the NMR spectrum of 6 showed the characteristic hydrogen signals in positions 2 and 3 at δ 5.05–5.37 (m) and 3.10–3.37 (m) respectively and signals of 1,1-dimethyl propargyloxy group at δ 1.65 ($2XCH_3$) and 2.52 ppm ($-C\equiv CH$).

As expected, 6 formed in the largest amount followed by 7, 2 and 1. This experiment indicates that during etherification of 7-hydroxyflavanone, not only the ring opens out but also cyclisation of 1, 1-dimethyl propargyloxy side chain occurs to form the corresponding chromenes.



2.2. Synthesis of lonchocarpin and isolonchocarpin

In order to increase the yields of natural lonchocarpin (1) and isolonchocarpin (2), the crude mixture obtained as above was heated directly in *N,N*-dimethylaniline.

Indeed a mixture of almost equal amounts of lonchocarpin (1) and isolonchocarpin (2) formed. Hence natural lonchocarpin and isolonchocarpin can be prepared in good yields from 7-hydroxyflavanone.

It was further observed that if 1, 1-dimethylpropargyl ether of 2', 4'-dihydroxychalcone (7) is thermally heated, it gave only lonchocarpin. However, 7-(1, 1-dimethylpropargyloxy) flavanone gave both lonchocarpin and isolonchocarpin in almost equal amount. It is therefore clear that under thermal conditions the chalcone does not become flavanone but the reverse happens.

2.3. A more convenient synthesis of lonchocarpin

In order to confirm the observations, 1, 1-dimethyl propargylation of 2', 4'-dihydroxychalcone (8) was carried out, when it was observed that only 2'-hydroxy-4' (1, 1-dimethylpropargyloxy) chalcone (7) and lonchocarpin (1) formed and no corresponding flavanone resulted. Hence the synthesis of lonchocarpin is best achieved by 1, 1-dimethyl propargylation of 2', 4'-dihydroxychalcone (8) followed by heating in *N, N*-dimethylaniline.

3. Experimental

All melting points are uncorrected. Unless otherwise stated, all UV spectra were recorded in MeOH; NMR spectra were measured in CDCl_3 using 80 MHz BS487C spectrometer and TMS as internal standard; the chemical shifts are given in δ values; light petroleum ether used had boiling range 60–80°C; silica gel was used for column chromatography; R_F values are for TLC on silica gel G using C_6H_6 : light petroleum (7:3) for the development of the chromatogram and 1% alcoholic FeCl_3 or 10% aqueous H_2SO_4 for spraying.

3.1. 1,1-Dimethyl propargylation of 7-hydroxyflavanone (5) and formation of 1, 2, 6 and 7

7-Hydroxyflavanone (5, 0.5 g) prepared according to the procedure of Ellison (1927) was dissolved in acetone (25 ml), treated with 2-chloro-2-methyl-3-butyne (0.27 ml), anhydrous potassium carbonate (2 g), potassium iodide (1 g) and a few drops of *N, N*-dimethylformamide and the whole mixture refluxed for 30 hr. Acetone was distilled off and the residue treated with water. The resulting viscous solid was treated with 5% aqueous Na_2CO_3 to dissolve the starting flavanone and the corresponding chalcone. The residue was dried and found to be a mixture of four compounds on TLC. Hence it was subjected to column chromatography. Elution with light petroleum gave three fractions A, B and C and that with light petroleum: benzene (9:1) gave a fraction D.

Fraction A: It crystallized from light petroleum when 2'-hydroxy-6'', 6''-dimethylpyrano-(2'', 3'': 4', 3')-chalcone (or lonchocarpin, 1) formed as yellow crystals (10 mg), mp 108-9° (lit. mp 108°) (Baudrenghien 1953); R_F 0.75, dark brown ferric reaction (Found: C, 78.1; H, 6.1. Calculated for $\text{C}_{20}\text{H}_{18}\text{O}_3$; C, 78.4; H, 5.9%).

λ_{\max} 297, 348 (log ϵ 4.46, 4.50); NMR (CCl_4): 1.47 (s, 6H, 2XCH_3), 5.45 (d, $J_{\text{ortho}}=9\text{ Hz}$, 1H, $\underline{\text{H-5}}$ '), 6.20 (d, $J_{\text{ortho}}=9\text{ Hz}$, 1H, $\underline{\text{H-5}}$ '), 6.70 (d, $J_{\text{ortho}}=9\text{ Hz}$, 1H, $\underline{\text{H-5}}$ '), 7.23-7.40 (m, 5H, C_6H_5), 7.45 (d, $J_{\text{trans}}=15\text{ Hz}$, 1H, $\underline{\text{H-}\alpha}$), 7.58 (d, $J_{\text{ortho}}=9\text{ Hz}$, 1H, $\underline{\text{H-6}}$ ') and 7.62 ppm (d, $J_{\text{trans}}=15\text{ Hz}$, 1H, $\underline{\text{H-}\beta}$).

Fraction B: It crystallized from light petroleum as yellow crystals and yielded 4'-(1, 1-dimethylpropargyloxy)-2'-hydroxychalcone (7, 80 mg), mp 88-9°, R_F 0.69, dark brown ferric reaction (Found: C, 78.2; H, 6.3. $\text{C}_{20}\text{H}_{18}\text{O}_3$ requires C, 78.4; H, 5.9%). λ_{\max} 319, 352 (log ϵ 4.32, 4.34); NMR: 1.73 (s, 6H, X_2CH_3), 2.7 (s, 1H, $\text{C}\equiv\text{CH}$), 6.71 (d, $J_{\text{ortho}}=9\text{ Hz}$, $J_{\text{meta}}=3\text{ Hz}$, 1H, $\underline{\text{H-5}}$ '), 6.90 (d, $J_{\text{meta}}=3\text{ Hz}$, 1H, $\underline{\text{H-3}}$ '), 7.21-7.47 (m, 5H, C_6H_5), 7.51 (d, $J_{\text{trans}}=15\text{ Hz}$, $\underline{\text{H-}\alpha}$), 7.70 (d, $J_{\text{trans}}=15\text{ Hz}$, 1H, $\underline{\text{H-}\beta}$), 7.83 (d, $J_{\text{ortho}}=9\text{ Hz}$, 1H, $\underline{\text{H-6}}$ '), 13.23 ppm (s, 1H, chelated OH).

Fraction C: It crystallized from benzene-light petroleum mixture and afforded 7-(1, 1-dimethyl propargyloxy) flavanone (6) as colourless crystals (100 mg), mp 98-99°; R_F 0.56, negative ferric reaction (Found: C, 78.2; H, 6.4. $\text{C}_{20}\text{H}_{18}\text{O}_3$ requires C, 78.4; H, 5.9%). λ_{\max} 268 (log ϵ 4.27); NMR: 1.65 (d, 6H, 2XCH_3), 2.52 (s, 1H, $\text{C}\equiv\text{CH}$), 3.10-3.37 (m, 2H, $\underline{\text{H-3}}$), 5.05-5.37 (m, 1H, $\underline{\text{H-2}}$), 6.52 (2d, $J_{\text{ortho}}=10\text{ Hz}$, $J_{\text{meta}}=3\text{ Hz}$, 1H, $\underline{\text{H-6}}$), 6.75 (d, $J_{\text{meta}}=3\text{ Hz}$, 1H, $\underline{\text{H-8}}$), 7.00-7.35 (m, 5H, C_6H_5), 7.55 ppm (d, $J_{\text{ortho}}=10\text{ Hz}$, 1H, $\underline{\text{H-5}}$).

Fraction D: It crystallized from benzene-light petroleum mixture and yielded isolonchocarpin (2) as colourless crystals (25 mg); mp 122-24° (lit. mp 123°) (Nascimento *et al* 1973); R_F 0.45; negative ferric reaction (Found: C, 78.4; H, 6.2. Calculated for $\text{C}_{20}\text{H}_{18}\text{O}_3$; C, 78.4; H, 5.9%). λ_{\max} 265 (log ϵ 4.37); NMR: 1.58 (s, 6H, 2XCH_3), 2.77-3.05 (m, 2H, $\underline{\text{H-3}}$), 5.35 (q, 1H, $\underline{\text{H-2}}$), 5.52 (d, $J=10\text{ Hz}$, 1H, $\underline{\text{H-5}}$ '), 6.44 (d, $J_{\text{ortho}}=9\text{ Hz}$, 1H, $\underline{\text{H-6}}$), 6.58 (d, $J=10\text{ Hz}$, 1H, $\underline{\text{H-4}}$ '), 7.15-7.48 (m, 5H, C_6H_5), 7.68 ppm (d, $J_{\text{ortho}}=9\text{ Hz}$, 1H, $\underline{\text{H-5}}$).

3.2. Thermal rearrangement of the above mixture and formation of lonchocarpin (1) and isolonchocarpin (2)

The above mixture (0.1 g) was refluxed in *N,N*-dimethylaniline (10 ml) for 4 hr at 210-20°. The resulting brown liquid was poured into ice-cold dilute hydrochloric acid. The solid was filtered, dried and separated by column chromatography. Elution successively with light petroleum and light petroleum : benzene (9 : 1) gave two fractions *A* and *B*.

Fraction A: It crystallized from light petroleum and gave lonchocarpin (1) as yellow crystals (30 mg); mp and mmp with the sample prepared above 108-9° and identical TLC.

Fraction B: It crystallized from benzene-light petroleum mixture and yielded isolonchocarpin (2) as colourless crystals (35 mg); mp and mmp with the sample prepared above 122-4°; identical TLC, R_F 0.45.

3.3. *Thermal rearrangement of 2'-hydroxy-4' (1,1-dimethylpropargyloxy) chalcone (7) and formation of lonchocarpin (1)*

A solution of the chalcone (7) (0.05g) in *N, N*-dimethylaniline (8 ml) was refluxed for 3 hr at 210-20° and poured on ice-cold dilute HCl. The solid was filtered, dried and crystallized from light petroleum. Lonchocarpin (1) (30 mg) was obtained as yellow crystals; mp and mmp with the sample prepared earlier 108-9° and identical TLC.

3.4. *Thermal rearrangement of 7-(1, 1-dimethyl propargyloxy) flavanone (6) and formation of lonchocarpin (1) and isolonchocarpin (2)*

The flavanone (6) (0.08 g) in *N, N*-dimethylaniline (10 ml) was refluxed for 4 hr. The product was found to be a mixture of two compounds on TLC. On column chromatography, it yielded lonchocarpin (15 mg) and isolonchocarpin (45 mg).

3.5. *1, 1-Dimethyl propargylation of 2',4'-dihydroxychalcone (8) and formation of 1 and 7*

2', 4'-Dihydroxychalcone (8) (0.25 g) was prepared according to the method of Saiyad *et al* (1937) and dissolved in acetone (25 ml). The solution was treated with 2-chloro-2-methyl-3-butyne (0.27 ml), anhydrous potassium carbonate (2 g), potassium iodide (1 g) and a few drops of *N, N*-dimethylformamide and then refluxed for 35 hr. The product on column chromatography yielded two fractions *A* and *B*.

Fraction A: It crystallized from light petroleum to yield lonchocarpin (1) as yellow crystals (30 mg).

Fraction B: It crystallized from light petroleum and afforded 4'-(1,1-dimethyl-propargyloxy)-2'-hydroxychalcone (7) as yellow crystals (85 mg), mp and mmp with the sample described earlier 88-9°, R_F 0.69.

3.6. *Thermal rearrangement of the mixture of 1 and 7 and synthesis of lonchocarpin (1)*

The above mixture (100 mg) when heated in *N, N*-dimethylaniline (6 ml) for 3 hr gave lonchocarpin (1) as the sole product.

Acknowledgements

The authors are grateful to the UGC New Delhi for fellowship to AK and to CSIR (India) for fellowship to RCG.

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