SYNTHESIS OF 2',4'-DIHYDROXY-3'-METHYL-2',2'-DIMETHYLCRYANO(5',6'; 5',6')CHALCONE

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ABSTRACT

The structure of a new compound, 2',4'-Dihydroxy-3'-methyl-2',2'-dimethylpyran0(5',6'; 5',6')chalcone (I) isolated by Crowbne et al. from Kamala, an extract of Mallotus philippinensis Mull was assigned on the basis of spectral studies. It has now been synthesised starting from 3-methyl phloracetophene. The latter, on monooxysilation at 4-position followed by treatment with 2-chloro-2-methylbut-3-yn-2-ynyl/K₂CO₃-acetone gave a propargyl ether (V) and a chromeno ketone (VIII). V on heating with N,N-dimethylamine gave VIII. VIII on deoxygenation followed by condensation with benzaldehyde in aqueous alcoholic KOH gave the chalcone (I).

THERE are only a few examples where the isopentenyl as well as methyl groups are present together in naturally occurring polyphenolic compounds. Two such new compounds, a C-methyl-2',2'-dimethylpyranochalcone (I) and a C-methyl-2',2'-dimethylpyranolflavone (II) besides the main constituents rotterin and 4-hydroxy rottenin, have been reported to be isolated by Crowbne et al. from the study of Kamala, an extract of Mallotus philippinensis Mull (Euphorbiaceae). The structure assigned to the flavanoid was 5-hydroxy-6-C-methyl-2',2'-dimethyl-pyran0(5',6'; 7,8) flavanone (II) on the basis of spectral studies and has been further confirmed by its synthesis reported by us. The structure assigned to the second compound based on the spectral data is 2',4'-dihydroxy-3'-C-methyl-2',2'-dimethylpyran0(5',6'; 5',6') chalcone (I). Differentiation of this compound from its isomeric chalcone (III) was done on the basis of comparison of UV data. In order to further confirm the structure of C-methyl-2',2'-dimethylpyranochalcone (I), its synthesis was undertaken.

For the synthesis of the pyranochalcone (I), the chromone ring was to be built up at the ketone stage, as the parent 2',4',6'-trihydroxy-3'-C-methylchalcone...
is very unstable and could not be prepared. An attempt to synthesise 2,4,6-trihydroxy-3-C-methyl-5-C-prenylacetophenone using 2-methyl-butyrolactone was unsuccessful, as the reaction did not proceed appreciably even at 65–70° and stirring for 4 h. The prenylation of C-methyl chloroacetophenone using prenyl bromide and methanolic potassium carbonate did not yield appreciable amount of the prenylated compound. So the required chromeno ketone (IV) was then prepared by heating the corresponding \(a\)-a-dimethylpropargyl ether (V) in boiling N,N-dimethylformamide.

3-C-methyl chloroacetophenone was subjected to tosylation with 1:1 mole of \(p\)-toluenesulphonyl chloride in dry acetone and ignited potassium carbonate. The product was found to be a mixture of three compounds, i.e., (i) starting material, (ii) 2-hydroxy-3-C-methyl-4,6-ditosyl oxyacetophenone (VI) and (iii) 2,6-dihydroxy-3-C-methyl-4-tosyl oxyacetophenone (VII). In compound (VI) the positions of the two tosyl groups are fixed at 4 and 6, as these are the two reactive positions, one para to carbonyl group and the other para to methyl group. The position of the tosyl group in VII is fixed at position-4 as the hydroxyl group para to the carbonyl group is the most reactive and is the first to undergo alkylation or acylation.

2, 6-Dihydroxy-3-C-methyl-4-tosyl oxyacetophenone (VII) was treated with 2-chloro-2-methylbut-3-yne in dry acetone containing ignited potassium carbonate and a trace of sodium iodide. The product was found to be a mixture of two compounds, besides the starting substance. The mixture of the products was separated by column chromatography over silica gel and the first compound obtained in good yield was identified to be 2-hydroxy-3-C-methyl-4-tosyl oxy-6-(a,a-dimethylpropargyl) acetophenone (V) and the second compound in minor amount was a chromeno ketone (VIII). The position of the propargyl group in (V) is assigned at 6 as this position, para to methyl group, is activated, while OH at position 2 is sterically hindered. The 6-O-propargyl ether (V) was subjected to cyclisation in boiling N,N-dimethylformamide to give the chromene (VIII).

The tosyl oxy chromeno ketone (VIII) was desulphonated withaq. alcoholic potassium and then condensed with benzaldehyde in the cold. The product was purified by passing over a small column of silica gel when a red coloured compound was obtained. It was crystallised from benzene-petroleum ether, m.p. 121–23°. Its spectral data agreed with the reported data for the naturally occurring chalcone (I).

**Experimental**

Recorded melting points are uncorrected. UV, IR and NMR spectra were recorded on Beckman DU-2, Perkin–Elmer model 137 and Varian A–60 Spectrometers, respectively.

**Tosylation of 3-C-methyl chloroacetophenone**

3-C-Methyl chloroacetophenone (5 g) was dissolved in dry acetone (50 ml) and treated with \(p\)-toluenesulphonyl chloride (5.5 g) and freshly ignited potassium carbonate (20 g) and the mixture refluxed on a water bath for 6 hrs with occasional shaking. On working up as usual, the product obtained was found to be a mixture of two compounds, besides the starting material. It was subjected to column chromatography over silica gel.

**Fraction 1**

Elution of the column with petroleum ether-benzene mixture (3:1) gave a compound which crystallised from methanol as colourless needles (2 g), m.p. 138–40°. It gave a violet colour with ferric chloride. (Found: C, 56.6; H, 4.8; \(C_{8}H_{14}O_{2}S_{2}\) requires: C, 56.3; H, 4.5%) \(\lambda_{	ext{max}} \) in cm\(^{-1}\) (carbonyl) and 3000 cm\(^{-1}\) (broad (chelated OH)) NMR (CDCl\(_3\), \(\delta\)), 13.20 (s, 1H, chelated OH); 7.50–8.10 (m, 8H, aromatic protons of tosyl groups); 6.65 (s, 1H, C\(_{8}H\)), 2.80 (s, 3H, –COCH\(_3\)); 2.50 (s, 6H, 2 \times \text{CH}_{2}–\text{C}_{8}H_{4}SO_{2}); 2.00 (s, 3H, Ar–CH\(_3\)).

This suggested the structure to be 2-hydroxy-3-C-methyl-4,6-ditosyl oxyacetophenone (VI).

**Fraction 2**

Further elution of the above column with petroleum ether-benzene mixture (2:3) gave the 2nd compound (VII), crystallised from benzene-petroleum ether as colourless needles (2 g), m.p. 182–84°, giving a violet colour with ferric chloride. (Found: C, 57.3; H, 4.7; \(C_{8}H_{14}O_{2}S\) requires:...
C, 57.2; H, 4.8%; ν_{max}^{KBr}: 1630 cm⁻¹ (C=O) and 3450 cm⁻¹ (a chelated OH group). NMR (CDCl₃, δ): 13.20 (s, 1H, chelated OH group), 7.30 (s, 1H, C₃-H) 7.60 and 8.20 (2d, 4H, aromatic protons of tosyl group), 2.70 (s, 3H, –CO–CH₃), 2.52 (s, 3H, CH₂-C₆H₄SO₃-), 2.10 (s, 3H, CH₃-Ar). This suggested the compound to be 2,6-dihydroxy-3-C-methyl-4-tosyloxyacetophenone (VII).

**Reaction of VII with 2-chloro-2-methyl-but-3-yne**

The mixture of VII (2 g) in dry acetone (60 ml), 2-chloro-2-methyl-but-3-yne (1 g), ignited potassium carbonate (18 g) and dry sodium iodide (1 g) was refluxed on a water bath for 90 h with occasional shaking. On working up as usual and extracting the product with ether, a mixture of two compounds besides the starting substance was obtained. It was then subjected to column chromatography over silica gel.

**Fraction 1:** On elution of the column with petroleum ether a pale yellow solid was obtained. It crystallised from methanol as pale yellow needles (250 mg), m.p. 85-87°, giving bluish violet ferric reaction. (Found: C, 62.9; H, 5.6; C₆H₅SO₃ requires: C, 62.7; H, 5.5%.) ν_{max}^{KBr}: 1630 cm⁻¹ (carbonyl) and 3000 cm⁻¹ (broad (chelated hydroxy group). NMR (CDCl₃, δ): 13.4 (s, 1H, chelated OH); 8.00 and 7.32 (2d, J = 9Hz, 4H, 4 aromatic protons of tosyl group); 7.22 (s, 1H, C₅-H); 2.80 (s, 3H, COCH₃); 2.55 (s, 3H, CH₂-C₆H₄SO₃); 1.92 (s, 4H, ArCH₃ and C≡CH) and 1.60 (s, 6H, (CH₃)₂). The above data suggested the structure to be 2-hydroxy-3-C-methyl-4-tosylxy-6-(α,α-dimethylpropargyloxy) acetophenone (V).

**Fraction 2:** Further elution of the column with petroleum ether gave the second yellow compound, crystallised from methanol as pale yellow crystals (30 mg), m.p. 109-109°, violet ferric reaction. (Found: C, 63.0; H, 5.5; C₆H₅SO₃ requires: C, 62.7; H, 5.5%.) ν_{max}^{KBr}: 1629 cm⁻¹ (C=O); NMR (CDCl₃, δ): 14.0 (s, 1H, chelated OH); 8.00 and 7.40 (2d, J = 9Hz, 4H, 4 protons of tosyl group); 6.50 and 5.50 (2d, J = 10Hz, 2H, chromeno protons), 2.80 (s, 3H, CH₂-Ar); 1.5 (s, 6H, (CH₃)₂). Based on the above data, it is formulated as 2-hydroxy-3-C-methyl-4-tosylxy-2',2'-dimethylpyrano (5', 6'; 5, 6) acetophenone (VII).

**Compound V (250 mg)** was taken in distilled N,N-dimethyl aniline (5 ml) and heated on the oil bath at 220-225° for one hour. It was cooled and poured on crushed ice containing some HCl and then extracted with ether. The ether extract was washed with water, dried over anhydrous sodium sulphate and ether evaporated when a light yellow liquid was obtained. On cooling, the liquid solidified and was crystallised from methanol as pale yellow crystals (180 mg), m.p. 109-109°. It was identical with VIII obtained earlier (co-TLC and co-IR).

2',4'-Dihydroxy-3'-C-methyl-2',2'-dimethylpyrano (5', 6'; 5', 6') chalcone (I)

Compound VIII (200 mg) was taken in ethyl alcohol (5 ml) and this was added aq. alcoholic KOH (2 ml EtOH + 5 g KOH/3 ml H₂O). The solution obtained was warmed for 15 min (in an atmosphere of petroleum ether) on water bath at 70-80° and was then left overnight at room temperature. It was then treated with benzaldehyde (0-05 ml) in ethanol (2 ml) and then kept at room temperature out of contact with air for 4 days. On working up of the reaction mixture in the usual way, a coloured product was obtained. It was subjected to column chromatography over silica gel and on elution with benzene-petroleum ether mixture (3:1) gave a red coloured compound which crystallised from benzene-petroleum ether as red needles (30 mg), m.p. 121-23° (lit. m.p. 120-22°), a dark brown ferric reaction. (Found: C, 74.9; H, 6.1; C₆H₅O requires: C, 74.7; H, 5.9%). λ_{max}^{MeOH}: 345, 285 and 225 nm (log ε 4.32, 4.25, 4.35; ν_{max}^{KBr}: 1630, 3580 and 3000 (broad) cm⁻¹.

NMR (CDCl₃, δ): 1.55 [s, 6H, (CH₃)₂Cl], 2.00 (s, 3H, CH₃-Ar), 5.20, 6.65 (2d, J = 10Hz, 2H, chromeno protons); 7.35-7.55 (m, 5H, side chain aromatic protons); 7.80-8.05 (m, 2H, α, β-protons). The m.p. and the other spectral data agreed with the reported data for the natural sample of 2',4'-dihydroxy-3'-C-methyl-2',2'-dimethylpyrano (5', 6'; 5', 6') chalcone (I).