I-(3,5,7,3′,4′), *II*-(3,5,7,3′,4′), *III*-(3,5,7,3′,4′) *pentadeca-methoxy*, *III*-4-*hydroxy* (*I*-4, *II*-8, *C-O-C*) (*II*-4,*III*-8 *C-O-C*) *triflavanone*

3,5,7,3′4′-pentamethoxyflavan-4-ol (0·2 g) anhydrous K_2CO_3 (1 g) and dry pyridine (10 ml) was heated slowly to 120° under nitrogen with stirring, then a mixture of 8-iodo-3,5,7,3′,4′-pentamethoxyflavan-4-ol (0·45 g) and Cu_2O (0·5 g) was added. The mixture was stirred for 5 hr at 130° under nitrogen, cooled and extracted with chloroform (Soxhlet). The extract was evaporated to dryness under reduced pressure and the residue was extracted with benzene; the extract was washed with 2% NaOH and 5% aqueous citric acid solution and dried over K_2CO_3. Evaporation left a gum, which was chromatographed on alumina in benzene containing increasing concentration of chloroform. Elution with $CHCl_3$–MeOH (8 : 2) mixture gave trimer as homogeneous amorphous powder (0·3 g), m.p. 208 (*d*).

It was further methylated with DMS/NaOH in acetone to yield homogeneous amorphous powder (0·25 g), m.p. 189° C. It was found to be identical in chromatographic and spectral behaviour with the methyl ether of natural sample.

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SYNTHESIS OF 2′,4′-DIHYDROXY-3′-METHYL-2″,2″-DIMETHYLPYRANO(5″,6″; 5′,6′)CHALCONE

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ABSTRACT

The structure of a new compound, 2′,4′-Dihydroxy-3′-methyl-2″,2″-dimethylpyrano(5″,6″; 5′,6′)chalcone (I) isolated by Crombie *et al.* from Kamala, an extract of *Mallotus phillipinensis* Mull was assigned on the basis of spectral studies. It has now been synthesised starting from C-methyl phloroacetophenone. The latter, on mono-tosylation at 4-position followed by treatment with 2-chloro-2-methyl-but-3-yne/K_2CO_3-acetone gave a propargyl ether (V) and a chromeno ketone (VIII). V on heating with N,N-dimethylaniline gave VIII. VIII on detosylation 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″-dimethylpyranoflavanone (II) besides the main constituents rottlerin and 4-hydroxy rottlerin, have been reported to be isolated by Crombie *et al.*[1] from the study of Kamala, an extract of the fruits of the Asiatic shrub, *Mallotus phillipinensis* Mull (*Euphorbiaceae*). The structure assinged to the flavanone was 5-hydroxy-6-C-methyl-2″,2″-dimethylpyrano(5″,6″; 7,8) flavanone (II) on the basis of spectral studies and has been further confirmed by its synthesis reported by us[2]. The structure assigned to the second compound based on the spectral data is 2′,4′-dihydroxy-3′-C-methyl-2″,2″-dimethylpyrano(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[3,4]. In order to further confirm the structure of C-methyl-2″,2″-dimethylpyranochalcone (I), its synthesis was undertaken.

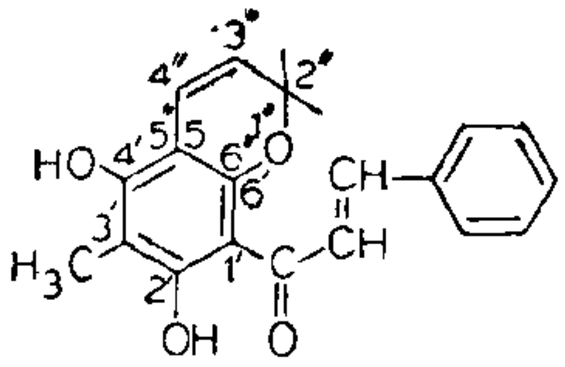
For the synthesis of the pyranochalcone (I), the chromene ring was to be built up at the ketone stage, as the parent 2′,4′,6′-trihydroxy-3′-C-methylchalcone

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-but-3-ene-2-ol[5] was unsuccessful, as the reaction did not proceed appreciably even at 65–70° and stirring for 4 h. The prenylation of C-methyl phloroacetophenone using prenyl bromide and methanolic potash[6] also did not yield appreciable amount of the prenylated compound. So the required chromeno ketone (IV) was then prepared by heating the corresponding *α,α*-dimethyl-propargyl ether (V) in boiling N,N-dimethylaniline.

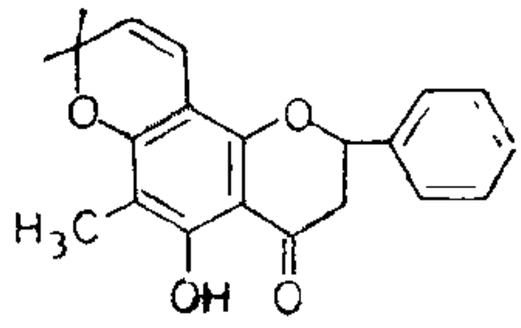
3-C-methyl phloroacetophenone was subjected to tosylation with 1·1 mole of *p*-toluenesulphonyl chloride in dry acetone and ignited potassium carbonate. The product was found to be a mixture of three compounds, *i.e.*, (i) starting material, (ii) 2-hydroxy-3-C-methyl-4, 6-ditosyloxyacetophenone (VI) and (iii) 2,6-dihydroxy-3-C-methyl-4-tosyloxyacetophenone (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[7]. 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[8,9].

2, 6-Dihydroxy-3-C-methyl-4-tosyloxyacetophenone (VII) was treated with 2-chloro-2-methyl-but-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-tosyloxy-6-(*α,α*-dimethyl-propargyloxy) acetophenone (V) and the second compound in minor amount was a chromeno ketone (VIII). The position of the propargyloxy group in (V) is assigned at 6 as this position, *para* to methyl group, is activated[7], while OH at position 2 is sterically hindered. The 6-O-propargyl ether (V) was subjected to cyclisation in boiling N,N-dimethylaniline to give the chromene (VIII).

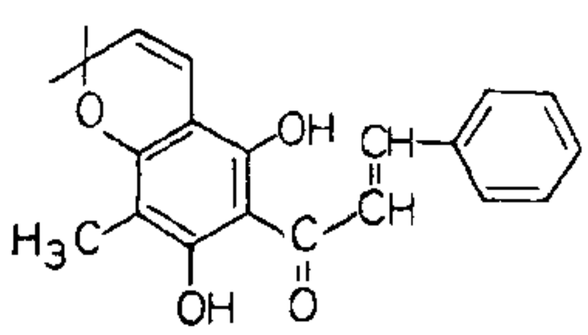
The tosyloxy chromeno ketone (VIII) was detosylated with aq. alcoholic potash and then condensed with benzaldehyde in the cold. The product was purified by passing over a small column of silica gel when a red coloured compound was obtained. It was crystallised from benzene-petroleum ether, m.p. 121–23°.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



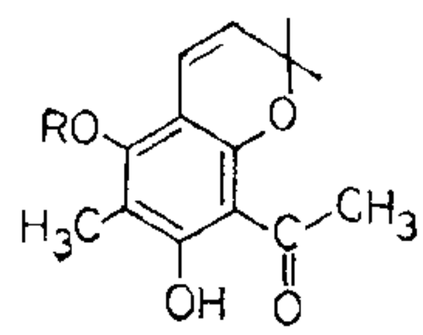
I



II

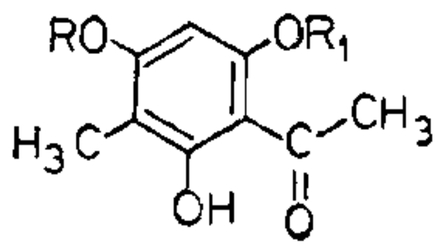


III



IV R=H

VIII R=TS



V R=TS, R_1=PRO

VI R=R_1=TS

VII R=TS R_1=H

TS = TOSYL

PRO=PROPARGYL

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 phloroacetophenone

3-C-Methyl phloroacetophenone (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: $C_{23}H_{22}O_8S_2$ requires: C, 56·3; H, 4·5%.) ν_{max}^{KBr}: 1630 cm^{-1} (carbonyl) and 3000 cm^{-1} broad (chelated OH) NMR ($CDCl_3$, δ), 13·20 (s, 1H, chelated OH); 7·50–8·10 (m, 8H, aromatic protons of tosyl groups); 6·65 (s, 1H, $C_5\underline{H}$), 2·80 (s, 3H, $-COC\underline{H}_3$), 2·50 (s, 6H, 2 × $C\underline{H}_3$–$C_6H_4SO_2$); 2·00 (s, 3H, Ar–$C\underline{H}_3$). This suggested the structure to be 2-hydroxy-3-C-methyl-4, 6-ditosyloxyacetophenone (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; $C_{16}H_{16}O_6S$ requires :

C, 57·2; H, 4·8%.) ν_{max}^{KBr}: 1630 cm^{-1} (C=O) and 3450 cm^{-1} (a chelated OH group). NMR ($CDCl_3$, δ): 13·20 (s, 1H, chelated OH group), 7·30 (s, 1H, C_5-H) 7·60 and 8·20 (2d, 4H, aromatic protons of tosyl group), 2·70 (s, 3H, $-CO-CH_3$), 2·52 (s, 3H, $CH_3-C_6H_4-SO_2-$), 2·10 (s, 3H, CH_3-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; $C_{21}H_{22}O_6S$ requires: C, 62·7; H, 5·5%.) ν_{max}^{KBr}: 1630 cm^{-1} (carbonyl) and 3000 cm^{-1} broad (chelated hydroxyl group). NMR ($CDCl_3$, 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, C_5-H); 2·80 (s, 3H, $-COCH_3$); 2·55 (s, 3H, $CH_3-C_6H_4-SO_2$); 1·95 (s, 4H, $ArCH_3$ and C≡CH) and 1·60 (s, 6H, $(CH_3)_2-$). The above data suggested the structure to be 2-hydroxy-3-C-methyl-4-tosyloxy-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. 109–10°, violet ferric reaction. (Found: C, 63·0; H, 5·5; $C_{21}H_{22}O_6S$ requires: C, 62·7; H, 5·5%.) ν_{maz}^{KBr}: 1629 cm^{-1} (C=O); NMR ($CDCl_3$, 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, CH_3-Ar); 1·5 (s, 6H, $(CH_3)_2$ C). Based on the above data, it is formulated as 2-hydroxy-3-C-methyl-4-tosyloxy-2′, 2′-dimethylpyrano (5′, 6′; 5, 6) acetophenone (VIII).

2-Hydroxy-3-C-methyl-4-tosyloxy-2′,2′-dimethyl-pyrano (5′,6′; 5,6)acetophenone (VIII)

Compound V (250 mg) was taken in distilled N,N-dimethyl aniline (5 ml) and heated on the oil bath at 220–25° for one hour. It was cooled and poured on crushed ice containing some HCl and then extracted with ether. The ethereal 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. 109–10°. 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 to this was added aq. alcoholic KOH (2 ml EtOH + 5 g KOH/3 ml H_2O). 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.[1] m.p. 120–22°), giving a dark brown ferric reaction. (Found: C, 74·9; H, 6·1; $C_{21}H_{20}O_4$ 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 ($CDCl_3$, δ): 1·55 [s, 6H, $(CH_3)_2$ C], 2·00 (s, 3H, CH_3-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).

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