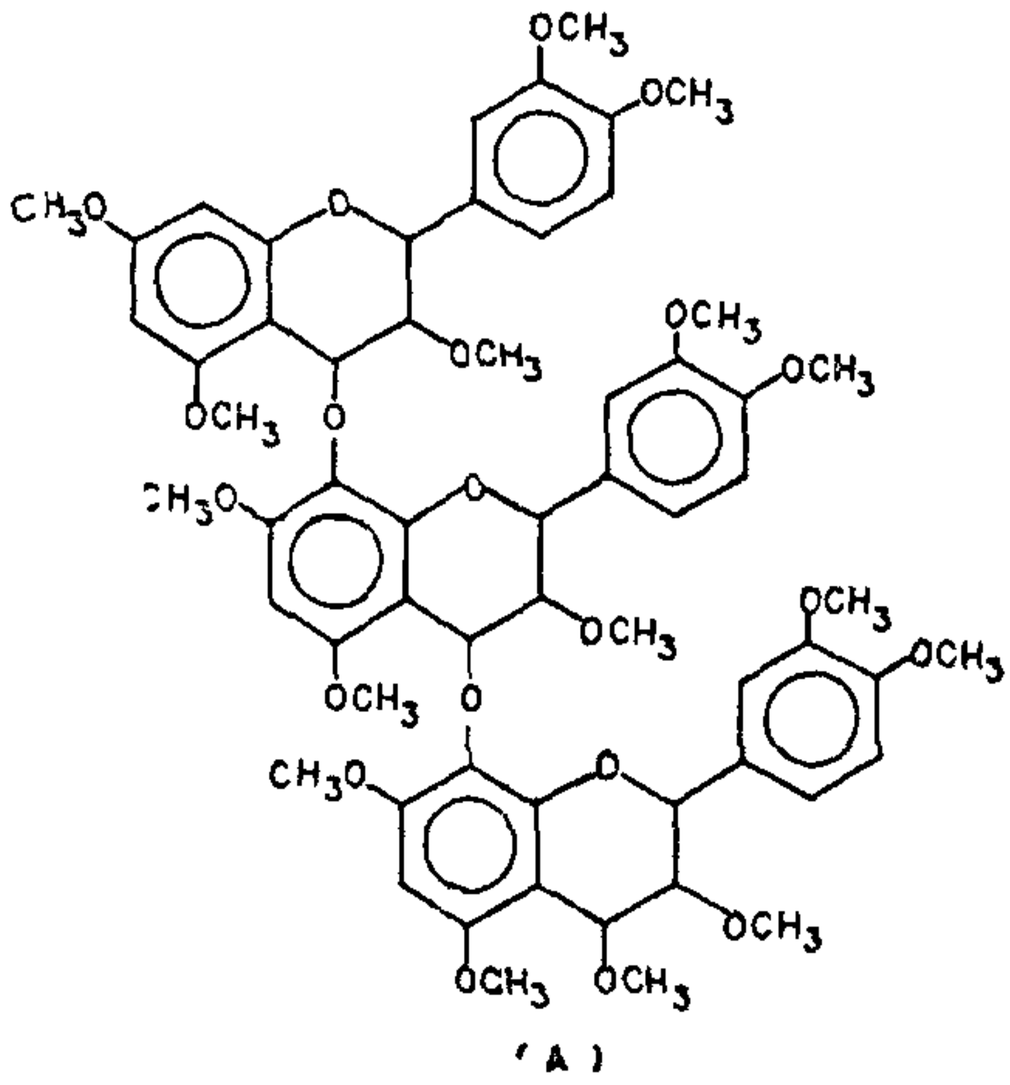
SYNTHESIS OF PROANTHOCYANIDIN; A NEW LEUCOCYANIDIN TRIMER (4–8, C-O-C)

SUDHIR AGRAWAL, A. KUMAR AND (MRS.) K. MISRA
Chemistry Department, Allahabad University, Allahabad 211 002, *India*

ABSTRACT

In our earlier communication[1] we have reported the isolation and characterisation of a new proanthocyanidin(A), which is a leucocyanidin trimer, the three C_{15} units being linked through 4—8, C–O–C linkages and the terminal unit having a free diol group. We now report the synthesis of the methyl ether (B) of the same, which unequivocally confirms the proposed structure.

THE synthesis of the methyl ether of the title compound (A) involves the condensation of 3,5,7,3′,4′-pentamethoxy flavan-4-ol (XI) and 8-iodo-3,5,7,3′,4′-pentamethoxyflavan-4-ol (XII) under the conditions of modified Ullman reaction[2]. The product was a mixture of 4—8 C–O–C linked oligomers which were subsequently separated by column chromatography.



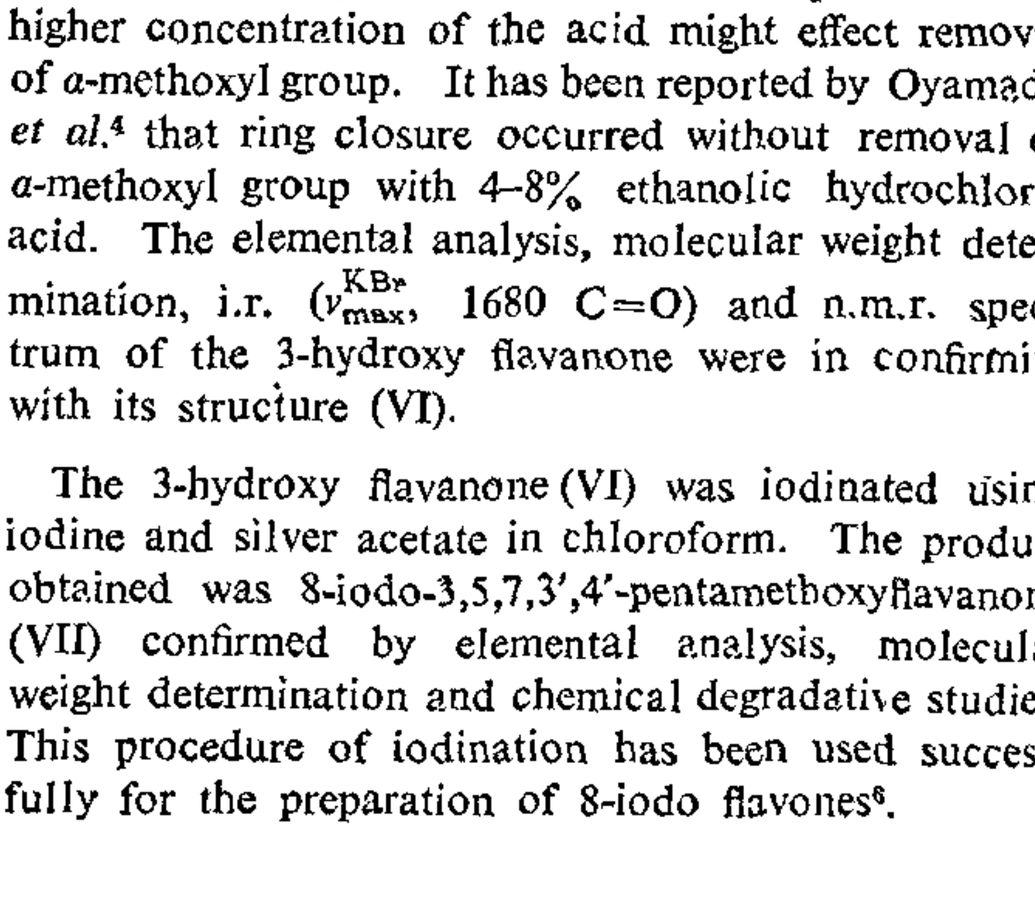
(A)

(A) R = H
(B) R = CH_3

The 8-iodo-3,5,7,3′,4′-pentamethoxyflavan-4-ol (XII) has been prepared by the sodium borohydride reduction of 8-iodo-3,5,7,3′,4′-pentamethoxyflavanone (VII) which in turn was obtained by the iodination of 3,5,7,3′,4′-pentamethoxyflavanone (VI). The flavanone was obtained from 2′-hydroxy- *a*,3,4,4′,6′-pentamethoxy chalcone[3] (II) by a method due to Oyamada *et al.*[4]. The chalcone was prepared by the condensation of 2-hydroxy-*o*,4,6-trimethoxyacetophenone[5] (I) and veratraldehyde.

The 3-hydroxy flavanone (VI) was prepared by refluxing the chalcone (II) with 3% ethanolic hydrochloric acid. Though the conversion of chalcone to 3-hydroxy flavanone was not complete, the mixture was readily separated with cold dilute sodium hydroxide, which dissolves the chalcone. It may be mentioned here that the concentration of the acid used for cyclisation of chalcone to 3-hydroxy flavanone is important since higher concentration of the acid might effect removal of *a*-methoxyl group. It has been reported by Oyamada *et al.*[4] that ring closure occurred without removal of *a*-methoxyl group with 4–8% ethanolic hydrochloric acid. The elemental analysis, molecular weight determination, i.r. (ν_{max}^{KBr}, 1680 C=O) and n.m.r. spectrum of the 3-hydroxy flavanone were in confirmity with its structure (VI).

The 3-hydroxy flavanone (VI) was iodinated using iodine and silver acetate in chloroform. The product obtained was 8-iodo-3,5,7,3′,4′-pentamethoxyflavanone (VII) confirmed by elemental analysis, molecular weight determination and chemical degradative studies. This procedure of iodination has been used successfully for the preparation of 8-iodo flavones[6].



(A)

In order to ascertain that iodine atom has entered exclusively at 8-position the following set of experiments were carried out. 8-Iodo-3,5,7,3′,4′-pentamethoxy flavanone on treatment with Ac_2O and AcONa

yielded the corresponding iodo chalcone (V) the structure of which was established by synthesising it from the corresponding iodoacetophenone derivative (III) and veratraldehyde by condensing the two in presence of aqueous ethanolic KOH.

The 2-hydroxy-3-iodo- ω,4,6-trimethoxy acetophenone (III) was obtained by iodination of (I) with iodine and iodic acid mixture[7]. Nakazawa[8] used this reagent for iodination of 2-hydroxyacetophenones and reported the formation of 3-iodoproducts The synthetic sample of the chalcone was identical with the one obtained by degradation of flavanone (VII) in all respects.

After ascertaining the position of iodine in (VII) it was reduced with sodium borohydride[9] when the 8-iodo-3,5,7,3′,4′-pentamethoxyflavan-4-ol (XII) was obtained. (VI) was also reduced by the same procedure which yielded (XI). I.R. spectrum of both (XI) and (XII) showed absorption peak at 3550 cm^{-1} and no peak at 1680 cm^{-1} indicating thereby that the C=O group is reduced completely to –CHOH. On treatment with boiling ethanolic hydrochloric acid, it gave pink coloured solution which responded to all the colour reactions of 3-hydroxy anthocyanidins[5].

The condensation of the two C_{15} units was carried out under the conditions of modified Ullman reaction[2,10]. The mixture of (XI) and anhydrous K_2CO_3 was heated in pyridine, then a mixture of (XII) and Cu_2O was added. The condensation gave a mixture of 4–8 C-O-C linked products. These were separated by column chromatography using alumina. Elution with a mixture of $CHCl_3$–MeOH (8 : 2) yielded a homogeneous amorphous powder.

It was methylated with DMS/NaOH in acetone. The synthetic sample of the trimer was identical with the methyl ether of natural sample in its λ_{max} and chromatographic behaviour, Rf values were identical in paper and thin layer chromatography. On acid hydrolysis both yielded the same anthocyanidins. The slight difference in m.p.s of the two may be accounted for by the difference in their stereochemistry.

Experimental

All the reaction products were routinely checked by i.r., n.m.r. and elemental analysis, i.r. spectra were recorded on Perkin Elmer in KBr, frequencies are expressed in cm^{-1}, n.m.r. spectra were recorded with a varian A–60 spectrometer and TMS as internal standard. The homogeneity of the compounds was checked by TLC on Silica gel 'G' plates. M.Ps. were determined on electrically heated block and are uncorrected.

2-Hydroxy-ω,4,6-trimethoxy acetophenone[5] (I), 2′-hydroxy- α,3,4,4′,6′-pentamethoxy chalcone[3] (II) and 3,5,7,3′,4′-pentamethoxyflavanone[11] (VI) were prepared by literature procedure.

8-Iodo-3,5,7,3′,4′-pentamethoxyflavanone (VII)

A solution of iodine (1·9 g) in $CHCl_3$ (40 ml) was added with stirring under reflux to a mixture of 3,5,7,3′,4′-pentamethoxy flavanone (VI) (1·8 g), CH_3COOAg (4 g) and$CHCl_3$ (48 ml) and refluxing was continued until iodine colour disappeared. Addition of light petroleum to the filtered solution precipitated 8-iodo-3,5,7,3′,4′-pentamethoxyflavanone (VII) which crystallised from chloroform petroleum mixture (1·4 g) m.p. 204–205° : ν_{max}^{KBr} (cm^{-1}) : 500 (C–I), 1680 (C=O) (Found C, 47·4; H, 4·7; I, 25·0 $C_{20}H_{21}O_7$ I requires C, 47·9; H, 4·59 ; I, 25·14%).

8-Iodo-3,5,7,3′,4′-pentamethoxyflavanone (0·1 g) was treated with acetic anhydride (5 ml) and sodium acetate (0·2 g) for 8 hr and the filtered solution was poured on ice. Deacetylation of the precipitated product gave 2′-hydroxy-3′-iodo- α,4′,6′,3,4-pentamethoxychalcone (V) by aqueous ethanolic potassium hydroxide, crystallised from benzene as orange needles m.p. 192-193° gave green colour with ferric chloride.

An authentic sample was prepared by the condensation (standard procedure) of 2-hydroxy-3-iodo-ω,4,6-trimethoxyacetophenone[7] (III) with veratraldehyde.

8-Iodo-3,5,7,3′,4′-pentamethoxyflavan-4-ol (XII)

Sodium borohydride (0·8 g) was added slowly to a solution of 8–iodo 3,5,7,3′4′-pentamethoxyflavanone (VII) (1 g) in warm isopropanol (60 ml) and after one hour the mixture was diluted with water and extracted with ether (2 × 100 ml). The ether extracts were washed with saturated aqueous sodium hydrogen carbonate, and evaporation of the dried (K_2CO_3) solution left a pale yellow oil which was dissolved in methanol. 8–Iodo 3,5,7,3′,4′-pentamethoxyflavan-4-ol (XII) crystallised in needles (0 6 g), m.p. 168–69° (Found C, 47·7; H, 4·7; I, 24·7. $C_{20}H_{23}O_7$ I requires C, 47·9; H, 4·5; I, 25·1%); ν_{max}^{KBr} 3550 cm^{-1}; NMR ($CDCl_3$): τ 6·59 (S, 3H, 3–OCH_3), 6·24, 6·14, 6·11, 6·09 (each S, 12H, -OCH_3), 6·24, 5·03, 4·75 (each m, 3H, 3–H, 2–H and 4–H resp., $J_{2,3}$ 9·7 ; $J_{3,4}$ 6·6 Hz), 3·81 (S, IH, 6–H), 3·25–2·82 (m, 3H, B-ring).

3,5,7,3′,4′-pentamethoxyflavan-4-ol (XI)

The 3,5,7,3′4′-pentamethoxyflavanone (VI) (0·7 g) was reduced to 3,5,7,3′4′-pentamethoxyflavan-4-ol (XI) with sodium borohydride (0·4 g) in isopropanol (50 ml) by the same procedure as described above. 3,5,7,3′4′-pentamethoxyflavan-4-ol (XI) was crystallised from methanol as needles (0·25g), m.p. 154–155°. (lit 155°) Found C, 63·7 ; H, 6·3. $C_{20}H_{24}O_7$ requires C, 63·8 ; H, 6·4%), ν_{max}^{KBr} 3550 cm^{-1} ; NMR ($CDCl_3$) ; τ3·87, 3·81 (d, 2H, 6–H and 8–H resp. ; $J_{6,8}$ 2·3Hz) other signals are same as in (XII).

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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1. Agrawal, Sudhir and Misra, K., *Curr. Sci.*, 1979, **48** (4), 141.
2. Krishnan, S. K., Murti, V. V. S. and Seshadri, T. R., *Ibid.*, 1966, **35**, 64.
3. Kimura, Y., *J. Pharm. Soc. Japan*, 1938, **58**, 415 (*Chem. Abst.*, 1938, **32**, 6649).
4. Oyamada, T. and Baba, H., *Bull. Chem. Soc. Japan*, 1966, **39**, 507.
5. Robinson, R. and Venkataraman, K., *J. Chem. Soc.*, 1929, p. 63.
6. Chen, F. C., Chang, G. T. and Chen, T. S., *J. Org. Chem.*, 1962, **27**, 85.
7. Keogh, E. J., Philbin, M. *et al.*, *J. Chem. Soc.*, 1963, **21**, 5271.
8. Nakazawa, *Chem. and Pharm. Bull.* (*Japan*), 1962, **10**, 1032.
9. Clark-Lewis, J. W., Jenison, R. W. and Nair, V., *Aust. J. Chem.*, 1968, **21**, 3015.
10. Inubushi, Y., Masaki, Y., Matsumoto, S. and Takami, F., *J. Chem. Soc.*, 1969, p. 1547.
11. Tominaga, T., *J. Pharm. Soc. Japan*, 1960, **80**, 1202 (*Chem. Abst.*, 1961, **55**, 357 *d*).

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

V. P. MANCHANDA, R. B. GUPTA AND R. N. KHANNA
Department of Chemistry, University of Delhi, Delhi 110 007

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