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THE STRUCTURE AND SYNTHESIS OF PONGACHROMENE, A NEW COMPONENT OF *PONGAMIA GLABRA*

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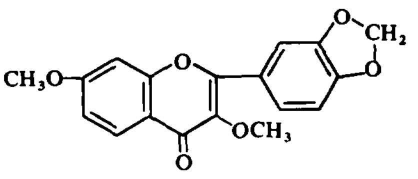
Abstract—Reinvestigation of the stem-bark of *Pongamia glabra*, has given besides the known flavones kanugin and desmethoxy kanugin, a new chromenoflavone pongachromene whose structure has been arrived at as shown in III from spectral and degradative experiments. It has also been confirmed by synthesis.

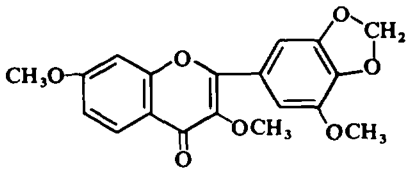
Pongamia glabra, one of the commonest trees of India, has been extensively studied. Thus the seeds contain,[1a,b] four angular furanoflavones karanjin, pongapin, kanjone and pongaglabrone and the diketone pongamol, while the roots[2] and stem-bark[3] contain two flavonols of rare type, e.g. kanugin and desmethoxykanugin. The flowers[4] on the other hand yield kaempferol and γ-sitosterol.

A reinvestigation of the fresh stem-bark of this plant gave, from petroleum ether and acetone extract, besides the known compounds kanugin (I) and desmethoxykanugin (II), a new chromenoflavone to which we give the trivial name pongachromene. It is a pale yellow crystalline compound, m.p. 195–196°, and is very close to desmethoxykanugin in its solubility and adsorption characteristics and hence is separable from the latter only after elaborate chromatography. Its molecular formula is $C_{22}H_{18}O_6$ and it contains one OMe group (Zeisel determination and NMR). Its IR spectra has no absorption in the OH region and its UV spectrum is unchanged on the addition of base. As the compound gives no ferric reaction, alcoholic, enolic or phenolic OH groups are absent. The presence of a methylenedioxy group is indicated by the pronounced green coloration which it gives with concentrated sulphuric acid and ethanolic gallic acid[5] and this is supported by the IR and NMR spectrum (*vide infra*). Pongachromene gives the colour reaction characteristic of 3-substituted flavonoids resembling kanugin (I) and desmethoxykanugin (II) with which it occurs. On the basis that pongachromene is a normal flavonoid (C_{15}) substituted with a methoxyl (C_1) and a methylenedioxy group (C_1), the remaining five C atoms should form part of an isoprenoid C_5-residue. The nature of the C_5 unit is indicated by its IR and NMR spectra. The former had doublets at 1375 and 1360 cm^{-1} for *gem*-dimethyl groups and bands at 770, 720 and 694 cm^{-1} for a *cis* double bond of a 2,2-dimethylchromene system.[6] The latter three bands are absent in the spectrum of dihydropongachromene obtained by catalytic hydrogenation, confirming that they belong to a *cis* double bond. A weak but very characteristic band at 899 cm^{-1} further supports the presence of 2,2-dimethylchromene group.[7] Pongachromene shows a CO band at 1640 cm^{-1} as do flavones and at 1040 and 940 cm^{-1} due to methoxyl and methylenedioxy groups.[8]

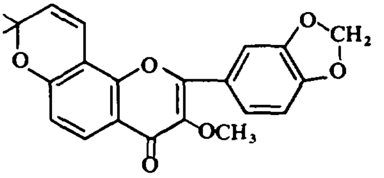
The NMR spectrum of the compound confirms the presence of groups mentioned. The high field singlet (δ 1·45) equivalent to six protons is highly characteristic of a *gem*-dimethyl group adjacent to an oxygen function. The doublets (δ 5·68 and 6·8; $J = 10$ c/s) each equivalent to one proton can be assigned to the *cis* olefinic protons of the dimethylchromene system. The singlet (δ 3·85) equivalent to three protons is due to one OMe group and a second singlet (δ 6·00) equivalent to two protons confirms the presence of one methylenedioxy group. Thus the pongachromene is a 3-substituted flavone with a methoxy, a methylenedioxy and a 2,2-dimethylchromene residue and taking into account its co-occurrence with kanugin and desmethoxykanugin, either structure III or IV may be proposed.



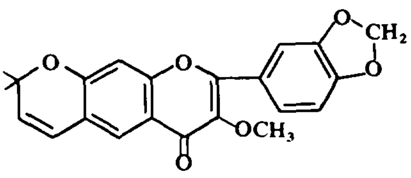
I



II

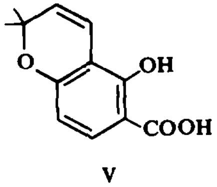


III



IV

Unequivocal proof in favour of III comes from direct alkaline hydrolysis of pongachromene. The reaction gives a complex mixture of several products which is characteristic if ring A of flavanoind is involved in 2,2-dimethylchromene system.[9a, b] It is possible however, to isolate from the acidic fraction of the hydrolysate β-tubaic acid (V) as its methyl ester. In addition, piperonylic acid is a minor product in this mixture. Structure III is the only one compatible with these observations.



V

The NMR spectrum of pongachromene is in full agreement with structure III. In addition to the assignments mentioned, the doublet at the lowest field (δ 7·94; $J_{5,6} = 9$ c/s) equivalent to one proton is due to $H_{(5)}$ and its paramagnetic shift is due to the flavone CO group. The signals of the protons $H_{(6')}$ and $H_{(2')}$ (δ 7·55 and δ 7·69) are also shifted downfield from the usual aromatic region by their neighbouring oxygen functions. The complex multiplet centered at δ 6·82 equivalent to two protons must be due to $H_{(6)}$ and $H_{(5')}$. The doublet due to $H_{(4'')}$ of the chromene system (δ 6·8) is actually superimposed on this multiplet but it is easy to distinguish as it is actually a double doublet with a further very small splitting constant of about 1 c/s. The larger splitting constant ($J_{3'',4''}$ = 10 c/s) is due to its coupling with neighbouring $H_{(3'')}$ and the further small splitting of each peak of this doublet is due to its weak coupling with the aromatic proton $H_{(6)}$ ($J_{4'',6}$ = 1 c/s) of ring A (see III). This characteristic splitting of a sp_2 benzylic proton by inter-ring long range weak coupling has been observed earlier in 2,2-dimethylchromenes[10] and in benzofurans.[11] Finally, the signals due to $H_{(3'')}$ appear as a doublet (δ 5·68, $J_{3'',4''}$ = 10 c/s) as expected.

Synthesis of pongachromene (III). The simplest method would be to build the chromene ring from 7-hydroxy-3-methoxy-3',4'-methylenedioxyflavone (VI) by Nickl's procedure.[12] However the condensation of the hydroxyflavone (VI) with 2-methyl-but-3-yn-2-ol in the presence of basic zinc chloride gave a mixture from which only very small amounts of a neutral product could be isolated. The presence of pongachromene in this mixture could be shown by TLC but its isolation was impractical. In an alternative approach, ω-methoxyresacetophenone on condensation with the same acetylenic carbinol, gave two chromeno ketones. These were isomeric and each gave a positive ferric reaction; hence their structures should be VII and VIII. It is possible to distinguish between them by NMR spectra. The ketone with higher R_f (0·7) shows two doublets (δ 6·18 and δ 7·55; $J_{7,8}$ = 9 c/s) due to $H_{(8)}$ and $H_{(7)}$ respectively (ortho coupling) consistent with structure VII. In addition, as mentioned, $H_{(8)}$ is further weakly coupled to $H_{(4)}$ of the chromene ring showing therefore, a double doublet with a second very small splitting constant of approximately 1 c/s.

In contrast, the isomeric ketone with lower R_f (0·6) gives signals due to $H_{(5)}$ (see VIII) as a singlet (δ 7·38) and $H_{(8)}$ as a doublet (δ 6·24) with only a small splitting constant (J = 1 c/s) as it is coupled weakly to $H_{(4)}$ of the chromene ring. The absence of coupling between the aromatic protons $H_{(5)}$ and $H_{(8)}$ in this spectrum clearly points to the linear structure (VIII) for this ketone.

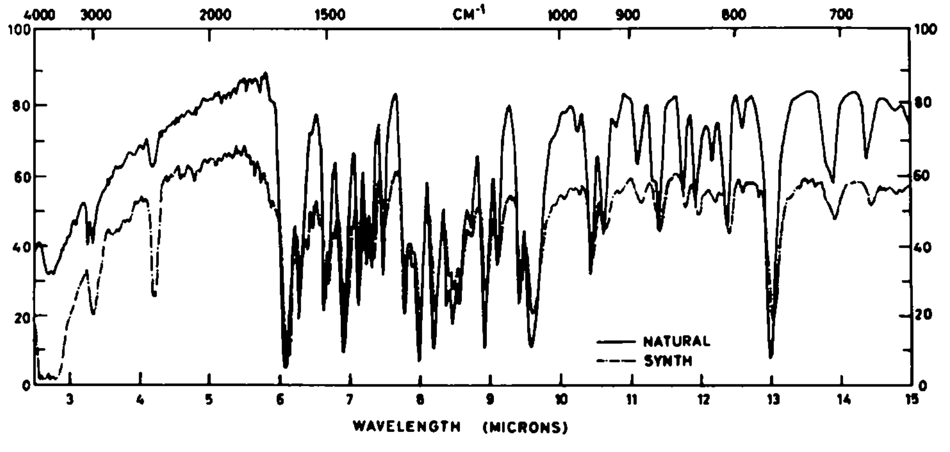
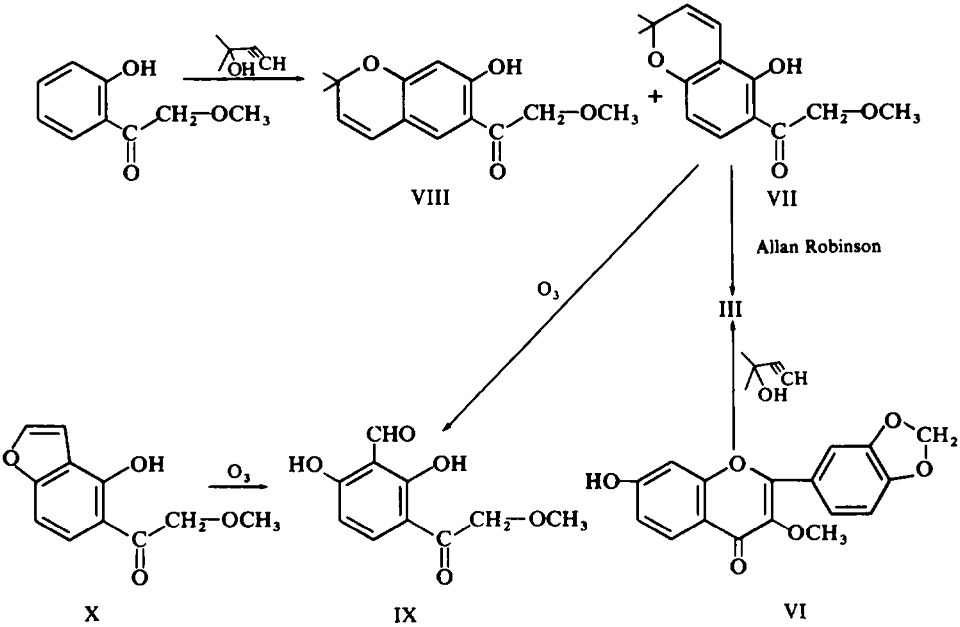


FIG. 1

An attempt to prove the structure of ketone VII by ozonolysis followed by mild alkaline hydrolysis[13] was not successful presumably because the aldehydo-ketone (IX) is very sensitive to alkali. Authentic 3-formyl-ω-methoxy resacetophenone (IX) prepared by ozonolysis of karanj ketone[14] (X) was also affected, by alkali in a similar way.

Finally Allan–Robinson condensation of the chromenoketone (VII) with sodium piperonylate and piperonylic anhydride gave pongachromene identical in all respects with the natural sample, thus confirming structure III for pongachromene.



2,2-Dimethylchromenes and other cyclic variants of C_5-type are quite prolific among isoflavones, coumarins and xanthones. Flavones, flavanones and chalkones with C_5 residues were at one time rare but are being discovered in increasing numbers. Some recent examples are bavachinol[15] (a chalkone), flemingins,[16] sorbifolin[17] and artocarpin.[18]

EXPERIMENTAL

Extraction of the bark

The coarsely powdered fresh stem-bark (fresh from the garden without drying) from a mature *Pongamia glabra* tree (2 kg) was successively extracted with (a) mixture of pet. ether (60–80°) and acetone (9:1) and (b) acetone. Extractions were done by exhaustive percolation with warm solvent. (7 days). The bark was air dried before successive extractions.

(i) *Petroleum ether–acetone* (9:1) *extract.* Solvent (5 l.) was evaporated from this extract and the residual viscous oil (10 g) was warmed in a current of N_2 to remove last traces of acetone. The oil was diluted with ether (200 ml) and allowed to stand overnight in a cool place when a pale yellow crystalline deposit was formed. The ether soln was decanted off and the deposit further washed with a small volume of ether. The almost colourless residue (2·1 g) was practically pure kanugin, colourless needles from EtOH–$CHCl_3$, m.p. 203–204° (lit. m.p. 204–205°)[2]; identical (m.m.p.) with an authentic sample. The mother liquors from the crystallization of this deposit contained a small amount of desmethoxykanugin as shown by TLC [silica gel (NCL); benzene–acetone: 92·8 v/v; R_f 0·61] and comparison with a synthetic sample.

The solvent was removed from the ethereal soln E and the residual oil diluted with pet. ether (40–60°, 150 ml) and shaken with aqueous MeOH (95:5; 100 ml). On standing in the refrigerator, a mass of yellow crystals slowly separated at the interface of the two liquids. They were separated and the pet. ether soln continuously extracted with MeOH. The methanolic extract on evaporation and trituration with a small volume of pet. ether gave more of the above solid which was combined with the crystals obtained earlier and fractionation of this total (mixture A; 22 mg) is described below.

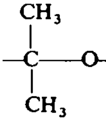
The residual oil from the pet. ether soln was fatty in nature but contained small amounts of unidentified compounds.

(ii) *Acetone extract.* Evaporation of the solvent from the extract (5 l.) gave a brown solid (950 mg) which was partly soluble in ether. The ether insoluble matter (600 mg) was inorganic in nature and was not examined further. The ether soln was washed with NaOHaq which removed a negligible amount. After evaporating the ether soln the neutral fraction (280 mg) was dissolved in hot MeOH (50 ml). On cooling the soln a solid (85 mg) separated which was identical on TLC with mixture A, and hence it was combined with it. The methanolic mother liquor was an intractable mixture but contained small amounts of desmethoxykanugin (TLC).

Separation of mixture A (desmethoxykanugin and pongachromene)

Mixture A (300 mg) melted over a range (114–160°) and contained (TLC; silica gel NCL; benzene–acetone—92:8) kanugin (R_f 0·55, trace), desmethoxykanugin (R_f 0·61, major) and new compound pongachromene (R_f 0·7, major) along with traces of several other substances. It could not be separated by fractional crystallization. A concentrated benzene soln was chromatographed on neutral alumina (activity I; 40 g; column prepared in benzene). First elution with benzene (75 ml) brought out only traces of fatty material. Next elute with benzene–$CHCl_3$ (99:1, 75 ml) contained impure pongachromene (20 mg); further 75 ml of the same eluant brought out pongachromene (155 mg). Benzene–$CHCl_3$ (98:2, 75 ml) gave a mixture separated by TLC into pongachromene and desmethoxykanugin (40 mg). Benzene–$CHCl_3$ (92:8, 150 ml) gave a mixture of kanugin containing small amounts of desmethoxykanugin (60 mg) which was not purified further. Final elution with chloroform yielded only intractable gum.

Pongachromene

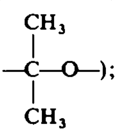
The crude pongachromene contained (TLC) traces of other impurities, specially desmethoxykanugin (which had closely similar chromatographic properties). Recrystallization several times from hot EtOH gave besides slightly impure compound (60 mg) pure pongachromene (75 mg) as pale yellow clusters of needles, m.p. 195–196°. (Found: C, 69·8; H, 5·2; —OMe, 7·9; $C_{21}H_{15}O_5$ (OMe) requires: C, 69·8; H, 4·8; —OMe, 8·2%); λ_{max}^{EtOH} 235, 280, 320 and 340 mμ; ν_{max}^{KBr} 1640 cm^{-1} (flavonoid CO), doublet at 1375 and 1360 cm^{-1} (*gem*-dimethyl), 940 cm^{-1} (—O—CH_2—O—) and 899 cm^{-1} (2,2-dimethylchromene), 770, 720 and 694 cm^{-1}(*cis* double bond). NMR ($CDCl_3$): δ 1·45 (s, 6P,  $-\underset{CH_3}{\overset{CH_3}{\mid \atop C}}-O-$); 3·85 (s, 3P, —OMe); 5·68 (d, 1P, $J_{3'',4''}$ = 10 c/s. $H_{(3'')}$); 6·00 (s, 2P, O—CH_2—O—); 6·8 (double d, 1P, $J_{4'',3''}$ = 10 c/s, $J_{4'',6}$ = 1 c/s, $H_{(4'')}$); 6·82 (complex m centre, 2P, $H_{(6)}$ and $H_{(5')}$); 7·55 (s, 1P, $H_{(6')}$); 7·69 (s, 1P, $H_{(2')}$); 7·94 (d, 1P, $H_{(5)}$, $J_{5,6}$ = 9 c/s). It gave a pink colour with Mg and HCl and crimson colour with Zn and HCl, and no ferric reaction. It gave a positive test for methylenedioxy group on heating with conc H_2SO_4 and ethanolic gallic acid.

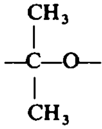
Dihydropongachromene. Pongachromene (25 mg) in EtOAc (25 ml) containing prereduced palladized charcoal (10%, 10 mg) was shaken in an atmosphere of H_2 until the absorption of gas was complete. The filtered soln on evaporation gave the dihydro compound, colourless needles, from MeOH, m.p. 223°. (Found: C, 69·6; H, 5·5, $C_{22}H_{20}O_6$ requires: C, 69·47; H, 5·26%); ν_{max}^{KBr} 1640 cm^{-1} ($\rangle$C=O).

Alkali hydrolysis of pongachromene. The chromene (60 mg) in EtOH (15 ml) was added dropwise to boiling KOHaq (15 ml; 10%) in an atmosphere of N_2. The mixture was refluxed for 3 hr, the clear soln cooled, acidified and extracted with ether. The acidic products of hydrolysis, isolated from this ether soln by extraction with sodium bicarbonate, was mixture (TLC). The mixture in ether (10 ml) was methylated with excess of ethereal diazomethane and reexamined by TLC when it showed clearly the presence of the following: (a) β-tubaic acid methyl ester (silica gel G; pet. ether: acetone—49:1, R_f 0·65; silica gel-G impregnated with $AgNO_3$, pet. ether–acetone, 49:1, R_f 0·37) was isolated by preparative TLC using the same system and cutting out the band at R_f 0·65, as a liquid whose IR and UV spectra were identical with those of methyl ester prepared from authentic β-tubaic acid, (b) a small amount of methyl piperonylate (identity by co-TLC with authentic sample; silica gel G, benzene–$CHCl_3$—96:4, R_f 0·55).

Condensation of ω*-methoxyresacetophenone with* 2*-methyl-but-*3*-yn-*2*-ol*

A mixture of ω-methoxyresacetophenone (5·0 g), 2-methylbut-3-yn-2-ol (10 ml) and basic $ZnCl_2$ (5 g) was refluxed at 110° for 30 min and then at 130° for 30 min and poured into a mixture of ether and iced dil HCl; the ether layer was separated and shaken (a) with dil HCl twice to remove Zn salts (b) with 5% Na_2CO_3 aq to remove unreacted ketone and (c) with 5% NaOH aq (3 × 50 ml) to extract the chromenoketone. The brownish yellow viscous liquid (300 mg), obtained by acidifying the NaOH extract, was dissolved in benzene (10 ml) and filtered through a short column of silica gel which was washed with a mixture of benzene–$CHCl_3$ (9:1; 50 ml). Evaporation of the combined filtrate and washings furnished a pale yellow oil (220 mg). TLC showed it to be a mixture of two ketones (silica gel-G, benzene–acetone, 96:4; R_f 0·7 and 0·6 respectively) and number of minor nonketonic compounds (R_f < 0·4; H_2SO_4 spray). The two major ketonic compounds were separated by preparative TLC (ten 20 × 20 cm plates; silica gel-G; benzene–acetone—96:4) and cutting out the band at R_f 0·7 and at R_f 0·6 and extracting separately with chloroform.

The chromenoketone [2,2-dimethyl-5-hydroxy-6(2′-methoxy acetyl) chromene] from the band at R_f 0·7, was a pale yellow liquid (70 mg) which failed to crystallize; $\nu_{max}^{CCl_4}$ 3600 cm^{-1} (OH-phenolic) 1655 cm^{-1}, 1630 cm^{-1} (Ar—C=C—), 900 cm^{-1} (2:2-dimethyl chromene). NMR (CCl_4): δ 1·40 (s, 6P,  $-\overset{CH_3}{\underset{CH_3}{C}}-O-$); 3·36 (s, 3P, —OMe); 4·38 (s, 2P, —CO—C$\underline{H}_2$—OMe); 5·45 (d, 1P, $H_{(3)}$ $J_{3,4}$ = 10 c/s); 6·18 (double d, 1P, $H_{(8)}$, $J_{8,7}$ = 9 c/s), 6·66 (double d, 1P, $H_{(4)}$, $J_{3,4}$ = 10 c/s), $J_{4,8}$ = 1 c/s); 7·55 (d, 1P, $H_{(7)}$, $J_{7,8}$ = 9 c/s). Its DNPH crystallized from $CHCl_3$–MeOH as orange prisms, m.p. 237–238°. (Found: C, 55·9; H, 4·6; $C_{20}H_{20}O_7N_4$ requires: C, 56·0; H, 4·6%).

The isomeric VIII from the band at R_f 0·6, was also a pale yellow liquid, NMR (CCl_4): δ 1·40 (s, 6P,  $-\overset{CH_3}{\underset{CH_3}{C}}-O-$); 3·37 (s, 3P, —$OCH_3$); 4·37 (s, 2P, —CO—C$\underline{H}_2$—OMe); 5·46 (d, 1P, $H_{(3)}$, $J_{3,4}$ = 10 c/s); 6·22 (double d, 1P, $H_{(4)}$ $J_{4,3}$ = 10 c/s, $J_{4,8}$ = 1 c/s); 6·24 (d, 1P, $H_{(8)}$, $J_{8,4}$ = 1 c/s); 7·38 (s, 1P, $H_{(5)}$). It gave a DNPH, brick red prisms from MeOH, m.p. 223–225°. (Found: C, 56·4; H, 4·9; $C_{20}H_{20}O_7N_4$ requires: C, 56·0; H, 4·6%).

3-*Formyl* ω*-methoxyresacetophenone*. A soln of karanj ketone (100 mg) in dry EtOAc (10 ml) was ozonolysed at −10° (excess) and the ozonide was reduced by shaking with Pd–C (5%, 10 mg) in an atmosphere of H_2 till peroxide test was negative. The filtered EtOAc soln, on evaporation, furnished the 3-formyl ketone as pale yellow needles from EtOAc–pet ether, m.p. 112–113°. (Found: C, 57·3; H, 4·5; $C_{10}H_{10}O_5$ requires: C, 57·1; H, 4·8%). Its bis DNPH, deep red prisms from chloroform, m.p. 205–206°.

Synthesis of pongachromene (III)

(a) *From* 3*-methoxy-*7*-hydroxy-*3′:4′*-methylenedioxyflavone* (VI) *with* 2*-methylbut-*3*-yn-*2*-ol*. A mixture of the hydroxyflavone (1·5 g), 2-methylbutyne-2-ol (2 ml) and basic $ZnCl_2$ (1·5 g) was refluxed under N_2 at 130° for 3 hr. The cooled mixture was treated with iced dil HCl and thoroughly extracted with ether. The ether extract was washed thrice with dil NaOH aq to remove all unreacted hydroxyflavone (1·2 g). The dried ether soln on evaporation furnished a brown gum (200 mg) which was purified by percolating its benzene soln through a small column of basic alumina and washing the column with benzene–$CHCl_3$ (9:1). The filtrate and washings on evaporation, gave a pale yellow residue (0·5 mg) which contained (TLC) pongachromene but was not pure. Co-chromatography in different solvent systems (silica gel-G; $CHCl_3$–acetone—96:4, R_f 0·8; $CHCl_3$, R_f 0·3; benzene–acetone 96:4, R_f 0·6), confirmed the presence of pongachromene in this mixture.

(b) *By Allan–Robinson condensation of 2,2-dimethyl-5-hydroxy-6-(ω-methoxyacetyl) chromene* (VII). The chromenoketone VII (40 mg), piperonylic anhydride (400 mg) and potassium piperonylate (100 mg) were intimately mixed and heated at 170–175° under reduced press. for 4 hr. The cooled mixture was extracted with dry ether several times and extract evaporated and the residue (95 mg) in benzene (10 ml) was filtered through a small column of basic alumina. The column was washed further with benzene–$CHCl_3$ (9:1). Evaporation of the combined filtrate and washings gave crude pongachromene (15 mg) which after several crystallizations from hot EtOH gave pale yellow needles, m.p. and m.m.p. with natural sample 195–196°; IR Spectrum (KBr) of these two samples was identical.

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