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# A STUDY OF NUCLEAR PRENYLATION OF β-RESACETOPHENONE—II

## SYNTHESIS OF BAVACHALCONE, 4'-O-METHYLBAVACHALCONE AND BAVACHIN*

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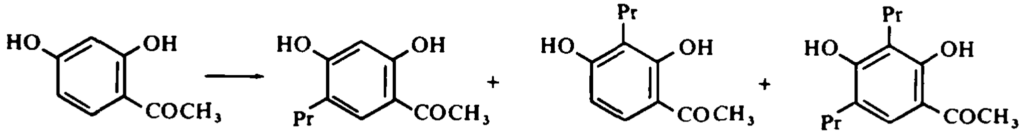
**Abstract**—Reaction of β-resacetophenone with 2-methyl-but-3-en-2-ol in the presence of boron trifluoride-etherate at room temperature is found to yield a mixture of three separable 5-C-prenyl-(40%), 3-C-prenyl-(25%) and 3,5-di-C-prenyl-(15%) resacetophenones. 5-C-Prenylresacetophenone and its 4-methyl ether have been condensed separately with *p*-hydroxybenzaldehyde obtaining bavachalcone and 4'-O-methylbavachalcone respectively. The former on cyclization gives the natural flavanone, bavachin.

In part I,[1] the nuclear prenylation of β-resacetophenone, under conditions analogous to C-methylation,[2] was described. A mixture of three compounds was obtained, the major component being the 3-C-prenyl derivative which was used for the synthesis of isobavachalcone and the flavanone isobavachin. No 5-C-prenyl derivative was formed in the above prenylation; it has now been obtained by the reaction of β-resacetophenone (I) with 2-methyl-but-3-en-2-ol in the presence of boron trifluoride-etherate according to the general procedure of Bohlmann and Kleine.[3]



I II III IV

In the above reaction, a mixture of three products was obtained. The major component was identified as 5-C-prenylresacetophenone (II) as follows. It was soluble in aqueous sodium carbonate and showed positive ferric reaction. Its elemental analysis indicated the introduction of only one prenyl unit and the NMR spectrum (see Experimental) indicated its placement in one of the available nuclear

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* The names given by discoverers to this group of compounds require a change in order to make the relationships easily understandable. The names of the flavanones bavachin and isobavachin are taken as the basis; bavachinin is then 7-O-methylbavachin. Just as isobavachalcone is related to isobavachin, so the name bavachalcone should appropriately be assigned to the chalcone corresponding to bavachin; it may be expected to occur in this plant and elsewhere. So the chalcone named earlier as "bavachalcone" will now be 4'-O-methylbavachalcone and it rightly corresponds to 7-O-methylbavachin. We have adopted this change in this paper.

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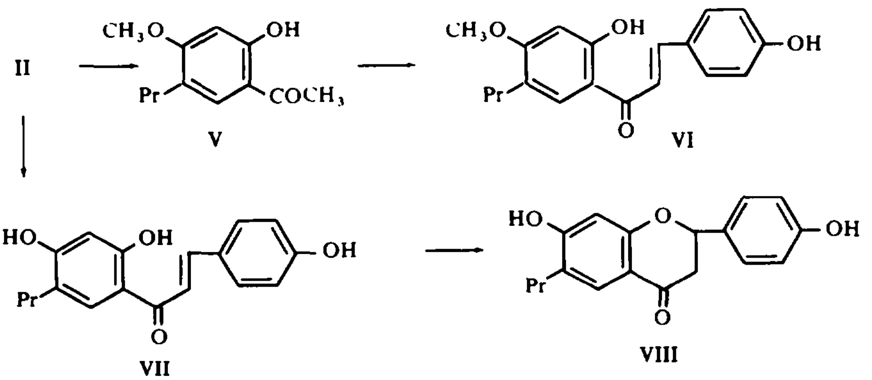
positions. Since there were no signals of *ortho*-coupled aromatic protons, the C-prenyl unit should be in the 5-position. This ketone was partially methylated; the NMR spectrum of the resulting 4-methyl ether (V) further substantiated the structure of the major prenylated product as 5-C-prenylresacetophenone (II).

The next major product was identical with 3-C-prenylresacetophenone (III) already characterized.[1] The third product, obtained in the smallest yield was found to be 3,5-di-C-prenylresacetophenone (IV) corresponding to the sample prepared earlier.[1] Thus treatment of β-resacetophenone with 2-methyl-but-3-en-2-ol under Lewis acid conditions gives products somewhat different from those obtained by carrying out the nuclear prenylation under alkaline conditions.[1] These results are parallel to those obtained with β-resorcylaldehyde in this laboratory.[4] One of the products obtained from this aldehyde in small amount was tentatively assigned the structure of 3-C-prenyl-β-resorcylaldehyde. Since the analogous 3-C-prenylresacetophenone (III) has now been isolated and characterized beyond doubt, the tentative structure for 3-C-prenylresorcylaldehyde may also be considered to be correct.

Recently[5] from the chloroform extract of light petroleum exhausted whole seeds of *Psoralea corylifolia L*, two new chalcones and three new flavanones were isolated and their constitutions deduced on the basis of degradation and spectral data. We recently carried out the synthesis of two of them, isobavachalcone and isobavachin,[1] from 3-C-prenylresacetophenone. The synthesis of the other three flavonoids has now been accomplished from 5-C-prenylresacetophenone as follows.

5-C-Prenyl-4-methoxy-2-hydroxyacetophenone (V) was condensed with *p*-hydroxybenzaldehyde in the presence of concentrated alcoholic alkali, when 5′-C-prenyl-4′-methoxy-4,2′-dihydroxychalcone (VI) was obtained in rather poor yields; changes in concentration of alkali and the period of the reaction did not help. This chalcone was found to agree with the description given[5] for natural 4′-O-methylbavachalcone. Since the chalcone has already been converted into its flavanone 7-O-methyl bavachin, this constitutes the total synthesis of 7-O-methyl bavachin also.

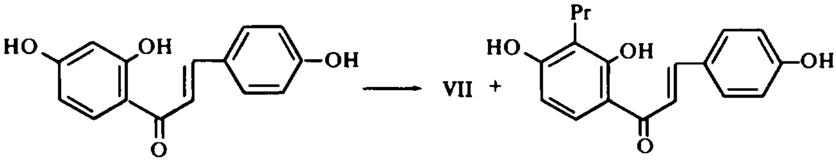


5-C-Prenylresacetophenone (II) on condensation with *p*-hydroxybenzaldehyde gave bavachalcone (VII) also in poor yield. Subsequent cyclization with dilute alkali yielded 6-C-prenyl-7,4′-dihydroxyflavanone (VIII) identical with the description given[5] for bavachin. Its structure was further supported by its spectral data. Thus its NMR spectrum indicated the resonance signals of one prenyl unit, two aromatic protons of ring A in 5- and 8-positions, two multiplets characteristic of protons in 2- and 3-positions of flavanones and other expected signals of the side phenyl.

### *Biogenetic considerations*

Bhalla *et al.*[5] have suggested that an intermediate with a phloroglucinol A ring is first formed which undergoes ring closure in different ways and subsequent dehydroxylation to produce bavachin and isobavachin. Since resorcinol derivatives are very common among chalcones, e.g. butein and isoliquiritigenin, it appears more rational to consider isoliquiritigenin as the primary member of this series. By analogy with β-resacetophenone it should undergo prenylation at both 5′- and 3′-positions yielding bavachalcone and isobavachalcone, which by ring closure would yield bavachin and isobavachin. The partial methylation of the 4′-position of the chalcone or the 7-position of the flavanone is an easy reaction both in nature and in the laboratory and accounts for the presence of 4′-O-methylbavachalcone and 7-O-methylbavachin.

In support of the above hypothesis for the evolution of prenylated chalcones, isoliquiritigenin (IX) has been condensed with 2-methyl-but-3-en-2-ol in the presence of boron trifluoride-etherate. The resulting product was found to be a mixture of two compounds along with a large amount of unreacted isoliquiritigenin, separable by column chromatography. The major compound to be eluted was found to be identical with 5′-C-prenylisoliquiritigenin (bavachalcone, VII) and the minor product was identified as 3′-C-prenylisoliquiritigenin[1] (isobavachalcone, X).



IX X

## EXPERIMENTAL

Unless otherwise stated, m.ps are uncorrected and were taken in a sulphuric acid bath; UV spectra were taken in methanolic solution, values in brackets for UV spectra represent log ε values; IR spectra were taken in KBr disc; NMR spectra were recorded on a Varian A-60 spectrometer; light petroleum had boiling range 60–80°; silica gel was used for column chromatography; $R_f$ values are those recorded on TLC plates using the solvent systems (A) chloroform and (B) benzene:EtOAc (4:1).

*Reaction of β-resacetophenone with* 2-*methyl-but*-3-*en*-2-*ol.* To a stirred soln of β-resacetophenone (1·1 g) in dry dioxan (8 ml) was added gradually $BF_3$-$Et_2O$ (0·3 ml) at room temp, when the soln acquired a pink-red colour. To this was added a soln of 2-methyl-but-3-en-2-ol (0·5 g) in anhyd dioxan (5 ml) and the whole soln stirred for 1 hr at room temp. After dilution with moist $Et_2O$ (100 ml), the soln was washed with water (3 × 50 ml) thus discharging the colour. The soln was then extracted with 1 % $Na_2CO_3$ aq (3 × 50 ml), which on acidification gave unreacted β-resacetophenone (0·3 g). The remaining ethereal soln on examination by TLC (solvent A) showed the presence of three compounds. Hence it was subjected to column chromatography and the column eluted successively with (i) benzene:light petroleum (1:3), (ii) benzene:light petroleum (1:1) and (iii) benzene:light petroleum (2:1) giving the following three main fractions. *Fraction A*, crystallized from light petroleum yielding IV (120 mg), m.p. and m.m.p. with an authentic sample[1] 109–110°; TLC ($R_f$ 0·74, solvent A); IR spectrum identical. *Fraction B*, crystallized from benzene giving III (200 mg), m.p. and m.m.p. with the sample prepared earlier[1] 155–156°; identical TLC ($R_f$ 0·34, solvent A) and superimposable IR spectrum. *Fraction C*, crystallized from benzene–petroleum ether mixture affording II as colourless plates (310 mg), m.p. 144–145°; red ferric reaction; soluble in $Na_2CO_3$ soln; $R_f$ 0·11 (solvent A); $\lambda_{max}$ 234, 278, 325 nm (3·54, 3·55, 3·00 resp.); $\nu_{max}$ 1635 $cm^{-1}$ ($>C=O$); NMR ($CDCl_3$) with TMS as internal reference: $\delta$ 1·77, 1·80 (2s, 6H of $(CH_3)_2C=$), 2·53 (s, 3H of $-CO-CH_3$), 3·30 (d, $J$ = 8 c/s, 2H of $Ar-CH_2-$), 5·38 (m, 1H of triply substituted methane group $-CH=$), 6·40 (s, 1 aromatic H in 3-position) and 7·47 ppm (s, 1 aromatic H in 6-position). (Found: C, 70·4; H, 7·1. $C_{13}H_{16}O_3$ requires: C, 70·9; H, 7·3%).

*5-C-Prenyl-4-methoxy-2-hydroxyacetophenone* (V). A soln of II (1·8 g) in acetone (50 ml) was refluxed with dimethyl sulphate (0·9 ml) and $K_2CO_3$ (4 g) for 3 hr. Acetone was distilled off and water added to the residue and the whole soln extracted with ether. Removal of ether gave an oily residue which after purification by column chromatography gave the required ketone (V) as a colourless oil (1·7 g), red-brown ferric reaction; NMR ($CCl_4$): $\delta$ 1·64, 1·69 (2s, 6H of one $(CH_3)_2C=$), 2·39 (s, 3H of $-CO-CH_3$), 3·08 (d, $J$ = 7·8 c/s, 2H of $Ar-CH_2-$), 3·78 (s, 3H of $-O-CH_3$), 5·18 (m, $-C\underline{H}=$ of prenyl unit), 6·23 (s, one H in 3-position) and 7·27 ppm (s, 1H in 6-position). These data agree with those reported earlier[5] for this compound, obtained by degradation of 7-O-methylbavachin.

*5′-C-Prenyl-4′-methoxy-4,2′-dihydroxychalcone* (*4′-O-methylbavachalcone*, VI). To a soln of V (1·5 g) and *p*-hydroxybenzaldehyde (1·9 g) in alcohol (10 ml) was added KOHaq (13 g/15 ml water) and the whole soln kept out of contact with air for 3 days at room temp. The deep red soln was diluted with ice cold water, acidified with AcOH and extracted with ether. The ether extract was washed first with 5% aq $NaHCO_3$ soln and then with water. Removal of ether gave a yellow residue which was subjected to column chromatography. Elution first with benzene–light petroleum mixture (1:3) gave the unchanged ketone (1·2 g) as an oil, then benzene–light petroleum mixture (3:2) afforded VI as an orange red solid. It crystallized from benzene as orange red plates (100 mg), m.p. 163–164° (lit[5] 161°); red ferric reaction; $R_f$ 0·80 (solvent B); $\lambda_{max}$ (MeOH) 235, 372 nm (4·14, 4·64); $\lambda_{max}$ (MeOH–NaOH) 436 nm (4·67); $\nu_{max}$ 1630 $cm^{-1}$. (Found: C, 74·4; H, 7·0. $C_{21}H_{22}O_4$ requires: C, 74·5; H, 6·6%).

*5′-C-Prenyl-4,2′,4′-trihydroxychalcone* (*bavachalcone*, VII). To a soln of II (1 g) and *p*-hydroxybenzaldehyde (1·3 g) in alcohol (8 ml) was added KOHaq (9 g/11 ml water) and the whole soln was kept out of contact with air at room temp for 4 days as described earlier. The product was found to be a mixture of two compounds on TLC (solvent B). It was subjected to column chromatography: elution first with benzene gave unreacted II (0·8 g, $R_f$ 0·79 in solvent B) and then with EtOAc–benzene mixture (3:97) yielded VII as an orange red solid which crystallized from benzene as orange red crystals (120 mg), m.p. 178–179°; red-brown ferric reaction; $R_f$ 0·56 (solvent B); $\lambda_{max}$ (MeOH) 228 and 373 nm (4·20 and 4·59 resp.); $\lambda_{max}$ (MeOH–NaOH) 438 nm (4·69); $\nu_{max}$ 1640 $cm^{-1}$. (Found: C, 73·9; H, 6·7. $C_{20}H_{20}O_4$ requires: C, 74·1; H, 6·2%).

*6-C-Prenyl-7,4′-dihydroxyflavanone* (*bavachin*, VIII). A soln of VII (600 mg) in alcohol (5 ml) was refluxed with NaOHaq (1·5%, 8 ml) for 0·5 hr and then left aside for 16 hr at room temp. The soln was diluted with ice-cold water, acidified with dil AcOH and the solid filtered. It was found to be a mixture of two compounds by TLC (solvent B) and subjected to column chromatography. Elution first with benzene–EtOAc (98:2) mixture, gave VII unchanged (300 mg). Then benzene–EtOAc mixture (95:5) gave VIII (200 mg) which crystallized from benzene–ethyl acetate mixture as colourless needles, m.p. 183–184° (lit[5] 189°); no ferric reaction; $R_f$ 0·43 (solvent B); $\lambda_{max}$ 235, 277, 322 nm (4·50, 4·31 and 3·99 resp.); NMR: $\delta$ (DMSO) 7·46 (s, one aromatic H in 5-position), 7·31 (d, $J$ = 8·4 c/s, 2′-, 6′-protons), 6·78 (d, $J$ = 9 c/s, 3′-, 5′-protons), 6·39 (s, one aromatic proton in 8-position), 5·35 (broad multiplet, one $-C\underline{H}=$ of the prenyl unit buried under the resonance of $C_2$-proton); $\delta$ (Pyridine): 0·94 (broad singlet, one $(C\underline{H}_3)_2C=$ group), 2·38 (m, two protons in 3-position) and 2·84 ppm (d, $J$ = 7·2 c/s, two protons of $Ar-C\underline{H}_2-CH=$ group of the prenyl unit). (Found: C, 71·9; H, 6·5. $C_{20}H_{20}O_4 \cdot \frac{1}{2}H_2O$ requires: C, 72·1; H, 6·4%).

*Reaction of isoliquiritigenin* IX *with 2-methyl-but-3-en-2-ol.* To a soln of IX[6] (0·5 g) in dry dioxan (8 ml) $BF_3$–$Et_2O$ (0·35 ml) was added, the soln attaining a red colour. To this was added 2-methyl-but-3-en-2-ol (175 mg) and the whole soln stirred for 1 hr at room temp. To the resulting mixture was added moist ether and the ethereal soln was first washed with water and then kept in contact with water for 24 hr. Removal of ether gave a solid which was found to be a mixture of two products together with a large amount of unreacted material (300 mg) as shown by TLC (solvent B). This was subjected to column chromatography and the column eluted successively with (i) benzene, (ii) benzene–EtOAc (97:3) and (iii) benzene–EtOAc (95:5). The major eluent was identified as VII (100 mg), identical in TLC and IR spectrum with sample prepared as described above, and the minor product as X, m.p. and m.m.p., with sample prepared earlier,[1] 155–156°.

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