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NUCLEAR PRENYLATION OF 2-O-METHYL PHLOROACETOPHENONE

SYNTHESES OF PREREMIROL, ACRONYLIN, EVODIONOL AND ISOEVODIONOL*

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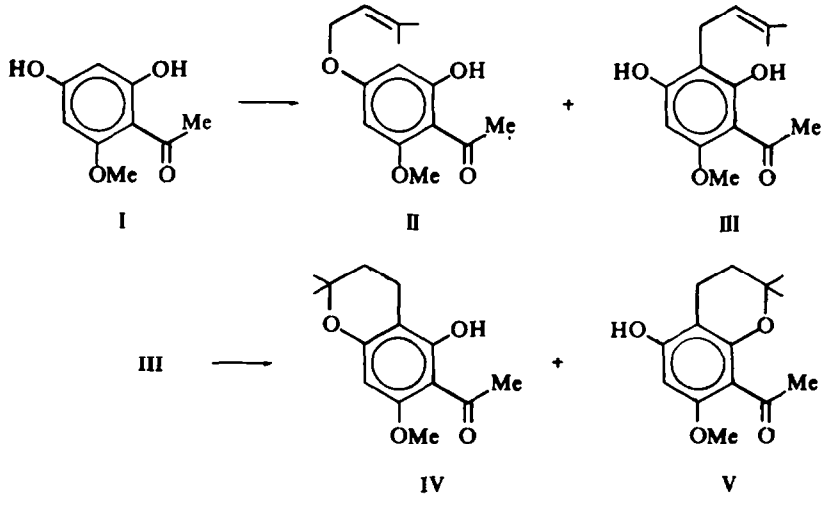
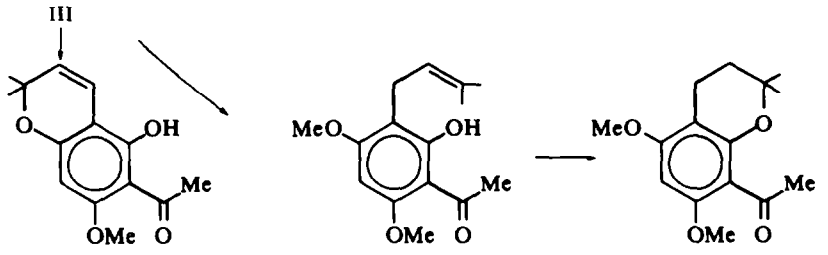
Abstract— Prenylation of 2-O-methyl phloroacetophenone with prenyl bromide in the presence of methanolic alkali yields mainly the 5-*C*-prenyl derivative; whereas with 2-methyl-2-hydroxy-3-butene in the presence of boron trifluoride etherate, both 5-*C*- and 3-*C*-prenyl derivatives are formed. These derivatives under the names preremirol (5-*C*-) and acronylin (3-*C*-) have recently been isolated from *Remirea maritima* and *Achronychia laurifolia* respectively. Their oxidative cyclization yields naturally occurring isoevodionol and evodionol respectively.

FOUR PHENOLIC KETONES all having isoprenoid units were isolated recently[2–4] from the rhizomes of the tropical sea-shore plant *Remirea maritima* Aubl. (Cyperaceae). Two of them *viz.* preremirol and iso-evodionol are related, the latter being the cyclodehydrogenated product of the former. Preremirol was shown to be 2-*O*-methyl-5-*C*-prenyl phloroacetophenone (III) on the basis of 100 MHz NMR and mass spectral data.[4] The possibility of the alternative 3-*C*-prenyl isomeric structure (IX) was ruled out because preremirol gave on acid cyclisation two 2,2-dimethyl-5-hydroxy-7-methoxy chromans (IV and V) one of which showed a ferric reaction. Similarly isoevo-



* For preliminary communication, see ref. 1.

dionol was assigned the structure of 2,2-dimethyl-5-hydroxy-6-acetyl-7-methoxy chromene (VIII) firstly on the basis of UV, NMR and mass spectral data and then by identity of its methyl ether with evodionol methyl ether and non identity of isoevodionol with evodionol.[3] Biogenetically, the formation of preremirol may involve introduction of a *C*-prenyl unit in a phloroacetophenone derivative. Following this possibility both compounds have now been synthesised, thus establishing their structures unequivocally.



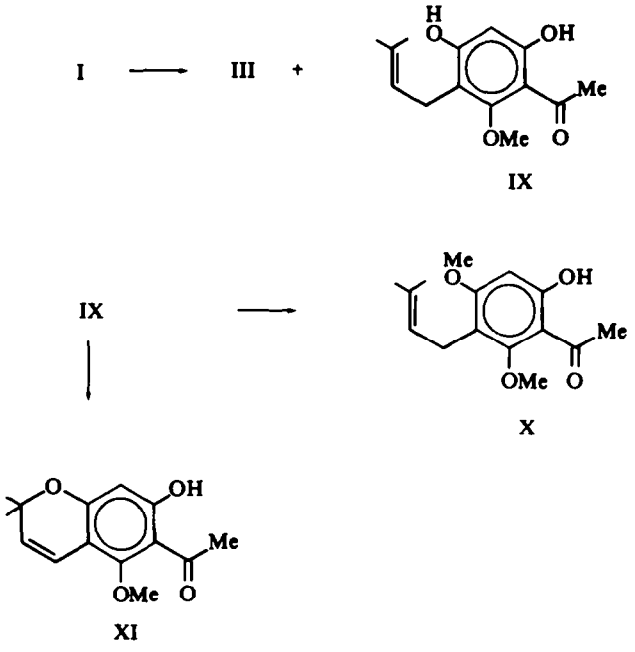
VIII VI VII

2-O-Methyl phloracetophenone (I) was prenylated with prenyl bromide in the presence of methanolic potash when a mixture of two products was obtained. The minor product was identified as 2-O-methyl-4-O-prenyl phloroacetophenone (II) by its NMR spectrum which showed characteristic resonance signals at δ 4·52 ppm (1d, J 7 Hz, 2H of O—CH_2—CH) and two *meta* coupled aromatic protons at δ 5·91, 6·05 ppm (2d, J 2 Hz) besides other signals. Its identity was established further by preparing the same ether by treating 2-O-methyl phloroacetophenone with 1 mole of prenyl bromide in the presence of K_2CO_3 and acetone.

The second major product obtained in nearly 30% yield also analysed for a monoprenyl derivative. However, its NMR spectrum showed resonance signals of only one aromatic proton as a singlet at δ 5·88 ppm and benzylic methylene of a prenyl unit as a doublet at δ 3·32 ppm (J 7 Hz). That prenylation occurred in the 5-position has been shown in two ways. (i) When it was directly cyclised in the presence of acid, a mixture of two chromans was obtained: the one showing a positive ferric reaction was given the structure of 2,2-dimethyl-5-hydroxy-6-acetyl-7-methoxychroman (IV) and the other showing a negative ferric reaction of 2,2-dimethyl-5-hydroxy-7-methoxy-8-acetyl chroman (V). The chroman structure of (IV) was established by its NMR spectrum which showed a characteristic pair of triplets at δ 1·80 and 2·52 ppm (J 6·5 Hz). (ii) When it was partially methylated to (VI) and subsequently heated with formic acid, it gave only one chroman (VII) showing a negative ferric reaction and a characteristic pair of triplets at δ 1·76 and 2·58 ppm (J 6 Hz). Thus the major prenylation product was established as 2-O-methyl-5-C-prenyl phloroacetophenone (III) which was found identical with the description of preremirol.

Cyclodehydrogenation of synthetic preremirol was accomplished with 1 mole of DDQ when 2,2-dimethyl-5-hydroxy-6-acetyl-7-methoxy chromene (VIII) formed; the chromene ring was established by a pair of doublets at δ 5·41 and 6·63 ppm (J 10 Hz) in its NMR spectrum. It agreed completely with the data given for isoevodionol (VIII).

Acronylin has recently been isolated by Biswas and Chatterjee[5] from the light



petroleum extract of the bark of *Acronychia laurifolia* BL (Family: Rutaceae). It was given the structure as 2-O-methyl-3-C-prenyl phloroacetophenone (IX) based on spectral studies. It is now synthesized unambiguously by bringing about prenylation of 2-O-methyl phloroacetophenone in another manner.

2-O-Methyl phloroacetophenone (I) was treated with 2-methyl-2-hydroxy-3-butene in the presence of boron trifluoride etherate when a mixture of two mono prenyl derivatives was obtained. One of them proved to be identical with preremirol (III) and the other one obtained in 20% yield was also shown to be a C-prenyl derivative by its NMR spectrum. Its structure as 2-O-methyl-3-C-prenyl phloroacetophenone (IX) was established by partial methylation to (X) with 1 mole of dimethyl sulphate in the presence of K_2CO_3 and acetone and subsequent treatment with acid when no cyclisation occurred. 3-C-Prenyl derivative (IX) was found completely identical with acronylin.

Oxidative cyclisation of synthetic acronylin (IX) with 1 mole of DDQ gave a chromene identical with evodionol (XI), occurring in *Evodia littoralis*[6] and *Melicope simplex*[7]; it showed a characteristic pair of doublets at δ 5·57 and 6·49 (J 10 Hz) in its NMR spectrum.

EXPERIMENTAL

Unless otherwise stated, all m.ps are uncorrected: UV spectra were taken in MeOH (log ε in parenthesis): light petroleum had boiling range 60–80°, silica gel was used for column chromatography: and TLC was carried out on silica gel G plates using either 3% alcoholic $FeCl_3$ or 10% dil H_2SO_4 as spraying reagent and one of the following solvent systems: (A) C_6H_6: (B) C_6H_6: EtOAc (95:5): (C) C_6H_6:EtOAc (90:10): (D) C_6H_6:EtOAc (75:25).

2-O-*Methyl*-4-O-*prenyl phloroacetophenone* (II). To a solution of 2-*O*-methyl phloroacetophenone (I, 100 mg) in acetone (20 ml) was added PrBr (0·06 ml) and anhydrous K_2CO_3 (500 mg) and the resulting mixture refluxed for 3 hr (water bath). The product crystallized from MeOH to give 2-*O*-methyl-4-*O*-prenyl phloroacetophenone (II) as colourless silky needles (50 mg), m.p. 72–73°: R_f 0·40 (solvent A); reddish brown ferric reaction: NMR ($CDCl_3$): δ 1·74 (broad s, 6H, $(C\underline{H}_3)_2C=$), 2·58 (s, 3H—CO—$C\underline{H}_3$), 3·82 (s, 3H, —$OC\underline{H}_3$), 4·52 (d, J = 7 Hz, 2H, —O—$C\underline{H}_2$), 5·42 (broad m, 1H, —$C\underline{H}$=), 5·91 and 6·05 ppm (2d, J = 2 Hz, 2 aromatic *meta* coupled H in 3 and 5 positions). (Found: C, 67·4: H, 7·3. $C_{14}H_{18}O_4$ requires: C, 67·2: H, 7·3%).

Nuclear prenylation of 2-O-*methyl phloroacetophenone* (I) *using prenyl bromide.* 2-Q-Methyl phloroacetophenone was prepared from 2,4-di-Q-methyl phloroacetophenone (3·7 g) by partial demethylation using Manaktala's method[8] and purified by column chromatography. The fraction eluted with benzene yielded colourless crystals (2·0 g), mp 205–206°. It (4 g) was added to a well-cooled solution of KOH (5·8 g) in absolute MeOH (34 ml) and the solution was treated with PrBr (9·4 ml). After 20 hr at room temp the mix was diluted with ice-cold water and acidified with dil HCl. The solid product was collected and examined on TLC using solvent A which showed the presence of two compounds. It was subjected to column chromatography and the column eluted with light petroleum followed by benzene: light petroleum (1:4). *Fraction* A crystallized from MeOH to give 2-Q-methyl-4-Q-prenyl phloroacetophenone (II) as colourless silky needles (50 mg), m.p. and m.m.p. with authentic sample described above 72–73°: R_f 0·40 (solvent A): reddish brown ferric reaction.

Fraction B crystallized from EtOAc: light petroleum mixture to give 2-Q-methyl-5-C-prenyl phloroacetophenone (III) as pale yellow prisms (1·5 g): m.p. 170–71°: R_f 0·31 (solvent C): violet brown ferric reaction: λ_{max} 227–30, 290, 304 (sh)nm (3·90, 4·13 and 3·19 respectively) which shifted in alkali to 228 (sh). 243, 323 nm (3·63, 3·56 and 4·30 respectively): NMR ($CDCl_3$): δ 1·73 and 1·78 (2d, J = 5 Hz, 6H, $(C\underline{H}_3)_2C=$), 2·58 (s, 3H, —CO—$C\underline{H}_3$), 3·32 (d, J = 7 Hz, 2H, —$C\underline{H}_2$—), 3·82 (s, 3H, —$OC\underline{H}_3$), 5·16 (m, 1H, —$C\underline{H}$=), and 5·88 ppm (s, 1 aromatic H at position 3). (Found: C, 67·6: H, 7·7. Calc. for $C_{14}H_{18}O_4$: C, 67·2: H, 7·3%). These data agree with those described for preremirol.[4]

2,4-*Di*-O-*methyl*-5-C-*prenyl phloroacetophenone* (VI). To a solution of preremirol (III, 250 mg), in acetone (50 ml), dimethyl sulphate (0·1 ml), anhydrous K_2CO_3 (1·25 g) were added and the mixture refluxed for 3 hr. The product was purified by column chromatography by elution with light petroleum (60–80°) and crystallized from MeOH when it formed light yellow needles (200 mg), m.p. 113–14°, green ferric reaction: R_f 0·50 (solvent A): NMR ($CDCl_3$): δ 1·68 and 1·78 (2s, 6H, $(C\underline{H}_3)_2C=$), 2·62 (s, 3H, —CO—$C\underline{H}_3$), 3·28 (d, J = 8·5 Hz, 2H, —$C\underline{H}_2$—Ar), 3·92 (s, 6H, 2, —O—$C\underline{H}_3$), 5·26 (m, 1H, —$C\underline{H}$=) and 6·0 ppm (s, 1 aromatic H at position 3). (Found: C, 68·7: H, 7·8. $C_{15}H_{20}O_4$ requires: C, 68·2: H, 7·6%).

2,2-*Dimethyl*-5,7-*dimethoxy*-8-*acetyl chroman* (VII). The above ketone (VI, 100 mg) was treated with warm HCOOH (10 ml) and the resulting solution left at room temp for 40 min. It was diluted with water (50 ml) and $CHCl_3$ extracted. The organic layer gave a residue which crystallized from MeOH as colourless rectangular prisms (70 mg), m.p. 76–77°, negative ferric reaction: R_f 0·74 (solvent C); NMR ($CDCl_3$): δ 1·28 (s, 6H, $(C\underline{H}_3)_2C$<), 1·76, 2·58 (2t, J = 6 Hz, 4H, 2—$C\underline{H}_2$), 2·45 (s, 3H, —CO—$C\underline{H}_3$), 3·78, 3·84 (2s, 6H, 2—$OC\underline{H}_3$) and 6·06 ppm (1 aromatic H at 6 position). (Found: C, 68·7: H, 7·9. $C_{15}H_{20}O_4$ requires: C, 68·2: H, 7·6%).

Acid cyclisation of preremirol (*Formation of* 2,2-*dimethyl*-5-*hydroxy*-6-*acetyl*-7-*methoxy*-(IV) *and* 5-*hydroxy*-7-*methoxy*-8-*acetyl*-(V) *chromans*: Preremirol (III, 100 mg) was dissolved in warm HCOOH (10 ml) and the solution left at room temp for 40 min. The product showed two spots on TLC, one showing a positive ferric reaction and the other not. It was chromatographed on a column of silica gel. Elution with light petroleum gave IV as white prisms (25 mg), m.p. 87–88° (lit.[4] m.p. 90°): R_f 0·46 (solvent A): violet ferric reaction: NMR ($CDCl_3$): δ 1·36 (s, 6H, $(C\underline{H}_3)_2C$<), 1·80, 2·52 (t, J = 6·5 Hz, 4H, 2—$C\underline{H}_2$—), 2·62 (s, 3H, CO—$C\underline{H}_3$), 3·84 (s, 3H, —$OC\underline{H}_3$) and 5·89 (s, 1 aromatic H at position 8). (Found: C, 67·6: H, 7·5. Calc. for $C_{14}H_{18}O_4$: C, 67·2: H, 7·3%). Further elution with benzene: EtOAc (3:1) gave V which crystallized from a light petroleum: benzene mixture to give cream coloured plates (50 mg), m.p. 182–83° (lit.[4] m.p. 184–85°): R_f 0·27 (solvent D): negative ferric reaction. (Found: C, 67·7: H, 6·9. Calc. for $C_{14}H_{18}O_4$: C, 67·2. H, 7·3%).

2,2-*Dimethyl*-5-*hydroxy*-6-*acetyl*-7-*methoxychromene* (*Isoevodionol*) (VIII). Synthetic preremirol (III, 150 mg) was dissolved in benzene (25 ml) and the solution refluxed with DDQ (135 mg) for 20 min when the colourless hydroquinone separated. It was filtered hot and washed with benzene. The benzene residue was

purified by column chromatography. Elution with light petroleum:benzene (95:5) gave the required chromene (VIII) which crystallized from light petroleum (60–80°) as large yellow needles (80 mg), m.p. 128–9°: greenish brown ferric reaction: R_f 0·81 (solvent C): λ_{max} 270, 292, 304 (sh), 350 nm (4·48, 3·98, 3·90 and 2·90 respectively), with no shift in alkali: NMR ($CDCl_3$): δ 1·42 (s, 6H, $(C\underline{H}_3)_2C$<), 2·56 (s, 3H, —CO—$C\underline{H}_3$), 3·81 (s, 3H, —O$C\underline{H}_3$), 5·41, 6·63 (2d, J = 10 Hz, 2 olefinic H at positions 3 and 4) and 5·83 (s, 1 aromatic H at position 8). (Found: C, 68·0: H, 6·6. Calc. for $C_{14}H_{16}O_4$: C, 67·7: H, 6·5%). The above data agree with those described for isoevodionol.[2]

Nuclear prenylation of 2-O-*methyl phloroacetophenone (using 2-methyl-2-hydroxy-3-butene.* To a stirred solution of 2-O-methyl phloroacetophenone (5 g) in dry dioxan (100 ml) was added gradually boron trifluoride-etherate (6 ml) at room temp. To the resulting pink red solution was added a solution of 2-methyl-2-hydroxy-3-butene (7·2 ml) in anhydrous dioxan (20 ml) and the whole solution stirred for 1 hr at room temp. After 24 hr the solution was diluted with moist ether (2 × 100 ml). The ether solution was washed with water till the water layer showed no colour. The ether solution was extracted with Na_2CO_3 to give unchanged 2-O-methyl phloroacetophenone (3 g). The ether residue showed two spots on TLC in (solvent B) and was subjected to column chromatography and eluted first with light petroleum:benzene (1:1) and then with light petroleum:benzene (1:3) to give the following two fractions.

Fraction A crystallized from EtOAc:light petroleum mixture to give preremirol (III, 0·5 g), m.p. 170–71°: TLC and m.m.p. were identical with the sample prepared earlier.

Fraction B crystallized from EtOAc: light petroleum mixture to give 2-O-methyl-3-C-prenyl-phloroacetophenone (IX) as shining white needles (1 g), m.p. 127–28°: R_f 0·5 (solvent C), violet ferric reaction: λ_{max} 235, 282, 315 nm (4·19, 4·26 and 3·81 respectively) which shifted in alkali to 250, 332 nm (3·95 and 4·46 respectively): NMR ($CDCl_3$); δ 1·75, 1·77 (2d, J = 7 Hz, 6H, $(C\underline{H}_3)_2C$=), 2·67 (s, 3H, —CO—$C\underline{H}_3$), 3·32 (d, J = 7 Hz, 2H, —$C\underline{H}_2$), 3·71 (s, 3H, —O$C\underline{H}_3$), 5·24 (m, 1H, —$C\underline{H}$=), and 6·19 ppm (s, 1 aromatic H at position 5). (Found: C, 67·1: H, 7·3. Calc. for $C_{14}H_{18}O_4$: C, 67·2, H, 7·3%). These data agree with those reported for acronylin.[5]

2,4-*Di*-O-*methyl*-3-C-*prenyl phloroacetophenone* (X). A solution of 3-C-prenyl ketone (IX, 100 mg) in dry acetone (20 ml) was refluxed with dimethyl sulphate (0·04 ml), and anhydrous K_2CO_3 (500 mg) for 3 hr. The product was purified by column chromatography. Elution with light petroleum (60–80°) yielded acronylin methyl ether (X) which crystallized from MeOH as white needles (40 mg), m.p. 78–9°: R_f 0·40 (solvent A), reddish brown ferric reaction. (Found: C, 68·6: H, 7·1. $C_{15}H_{20}O_4$ requires: C, 68·2: H, 7·6%). It was recovered unchanged when treated with HCOOH.

2,2-*Dimethyl*-5-*methoxy*-6-*acetyl*-7-*hydroxy chromene* (*Evodionol*) (XI). A solution of synthetic acronylin (IX, 150 mg) in dry benzene (30 ml) was refluxed with DDQ (135 mg) for 30 min. The product was purified by column chromatography. Elution with light petroleum gave (XI) which crystallized from MeOH as light yellow plates (80 mg), m.p. 85–86°: R_f 0·78 (solvent C): intense green ferric reaction: λ_{max} 262, 290 (sh) nm (4·39 and 4·60 respectively), with no shift in alkali: NMR ($CDCl_3$): δ 1·42 (s, 6H, $(C\underline{H}_3)_2C$<), 2·65 (s, 3H, —CO—$C\underline{H}_3$), 3·78 (s, 3H, —O$C\underline{H}_3$), 5·57, 6·49 (2d, J = 10 Hz, 2 olefinic H of chromene ring) and 6·16 ppm (s, 1 aromatic H in position 8). (Found: C, 68·2: H, 6·8. Calc. for $C_{14}H_{16}O_4$: C, 67·7: H, 6·5%). These data agree with those reported for evodionol.[7]

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