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SYNTHESES OF 5-METHYL ETHERS OF NATURALLY OCCURRING ISOPENTENYLATED 1,3,5-TRIHYDROXYXANTHONES

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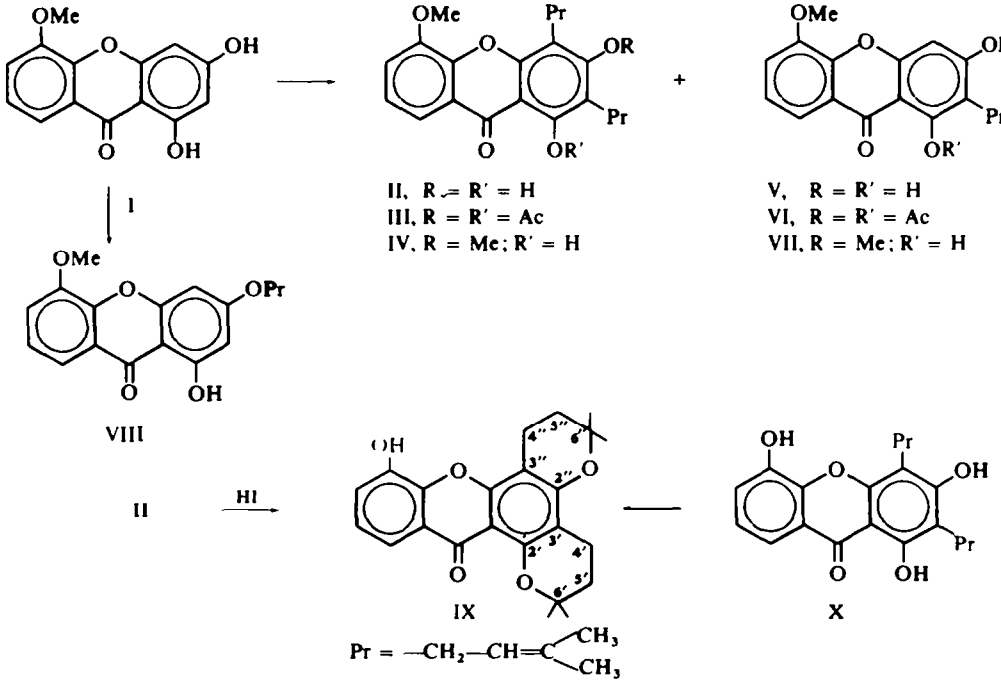
Abstract—Prenylation of 5-methoxy-1, 3-dihydroxyxanthone with prenyl bromide in the presence of methanolic methoxide yields in the ratio of 2:1,2,4-di-CC-prenyl and 2-C-prenyl derivatives which are 5-methyl ethers of natural xanthones isolated from *Garcinia mangostana* and *Calophyllum scriblitifolium* respectively. The structures of these natural compounds are supported by syntheses of their derivatives. Oxidative cyclization of the synthetic 2-C-prenyl compound with DDQ yields the 5-methyl ether of natural xanthone *viz.* 6-desoxyjacareubin.

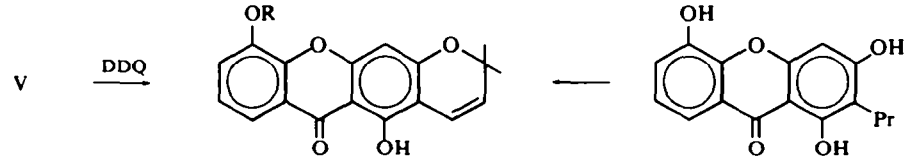
THREE isopentenylated 1,3,5-trioxygenated xanthones have been isolated recently from various plants of the Guttiferae family. 2-C-Prenyl 1,3,5-trihydroxyxanthone (XI) (isolated as 3,5-dimethyl ether, VII) and 6-desoxyjacareubin (XIII) were the first to be obtained from the heartwood of *Calophyllum scriblitifolium*.[1] The latter xanthone (XIII) has also been isolated from a number of other natural sources, such



as *C. brasiliense* and *Kielmeyera speciosa*[2] and *C. inophyllum*.[3] More recently, 2,4-di-CC-prenyl-1,3,5-trihydroxyxanthone (X) has been found to occur in very ripe fruits of *Garcinia mangostana Linn.*[4] The structures of these xanthones were established mainly from spectral data. They seem to be biogenetically inter-related involving C prenylation of the same precursor *viz.* 1,3,5-trihydroxyxanthone. Based on this idea, nuclear prenylation of 5-methoxy-1,3-dihydroxyxanthone has now been carried out and the products characterized and related to the natural compounds.

5-Methoxy-1,3-dihydroxyxanthone (I) prepared from phloroglucinol and *o*-vanillic acid by the method of Grover *et al.*,[5] was subjected to nuclear prenylation with PrBr in the presence of methanolic $\bar{O}Me$. The product was a mixture of mainly two components which could be separated by column chromatography. The major product formed in nearly 13% yield was identified as 2,4-di-CC-prenyl-5-methoxy-1, 3-hydroxyxanthone (II). On the basis of analytical data it was found that two prenyl units had entered into the starting material. These were found to be in 2 and 4 positions with the help of NMR data which showed resonance signals for the two prenyl units compared to a singlet for the OMe protons and aromatic protons of only ring B and not of ring A; the NMR spectrum of the diacetate (III) was also in agreement with structure II.

The second product, isolated in about 8% yield was a mono C-prenyl derivative as shown by analytical and NMR data. Thus there was a singlet (prenyl protons) in comparison with OMe protons and in the aromatic region, besides resonance signals of three vicinal aromatic protons of ring B (downfield multiplet and quartet), there was a sharp singlet at δ 6·58 ppm. This aromatic proton could be attributed either to the 2 or 4 position and the latter (structure V) is preferred by analogy with a similar reaction with 7-methoxy-1, 3-dihydroxyxanthone.[6] The NMR spectrum of the diacetate (VI) in which the aromatic singlet underwent a marked downfield shift and appeared at δ 7·42 ppm[7] was also in accord with structure V. It may be remarked that in the above nuclear prenylation experiment, 3-prenyl ether (VIII) could neither be isolated nor detected in TLC unlike the nuclear prenylation of 7-methoxy-1,3-dihydroxyxanthone.[6] The authentic sample of 3-prenyl ether (VIII) was, however, obtained for comparison purposes by prenylation of 5-methoxy-1,3-dihydroxy-xanthone with PrBr in the presence of K_2CO_3 and acetone.



XII, R = Me
XIII, R = H; 6-Desoxyjacareubin

XI

In order to establish the structure of the natural compound (X) isolated by Govindachari *et al*,[4] synthetic 2,4-di-C,C-prenyl-5-methoxy-1,3-dihydroxyxanthone (II) was cyclised under demethylative conditions with HI, when it formed 5-hydroxy-6′,6′-dimethyl-4′,5′-dihydropyrano (2′,3′: 1,2), 6″,6″-dimethyl-4″,5″-dihydropyrano (2″,3″: 3,4) xanthone (IX) identical with the one obtained by acid cyclisation of the

natural compound (X). The NMR spectrum supported the assigned structure; four benzylic protons appearing as a multiplet centered at δ 2·69 ppm and four other methylene protons again as a multiplet centered at δ 1·80 ppm.

Similarly the constitution of natural 2-C-prenyl 1,3,5-trihydroxyxanthone (XI) was supported by partial methylation of synthetic 2-C-prenyl-5-methoxy-1,3-dihydroxyxanthone (V) to 2-C-prenyl-3,5-dimethoxy-1-hydroxyxanthone (VII) which agreed in its description with that obtained from the natural compound.

2-C-Prenyl-5-methoxy-1,3-dihydroxyxanthone (V) was also subjected to oxidative cyclization with DDQ in benzene. The product was identical (m.p. and NMR) with the compound (XII) obtained by Gottlieb *et al.*[2] by the partial methylation of natural 6-desoxyjacareubin (XIII).

EXPERIMENTAL

All m.ps are uncorrected; UV spectra were taken in MeOH (figures in brackets represent log ε values); light petroleum b.p. 60°-80°; silica gel was used for column chromatography and TLC was carried out on silica gel G chromoplates using the following solvent systems: (A) Benzene: light petroleum, 50:50, (B) benzene, (C) benzene: MeOH, 97:3, (D) benzene: MeOH, 95:5.

Nuclear prenylation of 5-methoxy-1,3-dihydroxyxanthone (I). To a solution of 5-methoxy-1,3-dihydroxyxanthone (10 g) in anhyd. MeOH (500 ml) was added methanolic NaOMe (15 g Na/150 ml MeOH). The mixture was cooled, treated with PrBr (20 ml) in one lot and refluxed for 3 hr. After removal of solvent, the mixture was treated with water and acidified with HCl. The solid was collected and examined on TLC (solvent B) which showed the presence of a number of compounds. It was subjected to column chromatography and the column eluted successively with (i) benzene: light petroleum, 30:70 and benzene: light petroleum 60:40 to give the following two main fractions

Fraction A was crystallized from benzene-light petroleum when 2,4-di-CC-prenyl-5-methoxy-1,3-dihydroxyxanthone (II) was obtained as yellow flakes (2 g), m.p. 126-128°; green ferric reaction; R_f 0·41 (solvent A): λ_{max} 245, 260 and 315 nm (4·37, 4·24 and 4·05 respectively); NMR ($CDCl_3$): δ 1·84 (m, 12H, $2(C\underline{H}_3)_2C=$), 3·51, 3·65 (2d, J = 8 Hz, 4H, $2\text{-}CH_2-$), 4·02 (s, 3H, -OMe), 5·40 (m, 2H, $2\text{-}C\underline{H}=$), 7·28 (m, 2 aromatic H in positions 6 and 7) and 7·89 ppm (q, 1 aromatic H in position 8). (Found: C, 72·8; H, 6·7 $C_{24}H_{26}O_5$ requires: C, 73·1; H, 6·6%). The diacetate (III) prepared by Ac_2O-py. crystallized from EtOAc-light petroleum as white flakes, m.p. 134°; no ferric reaction; R_f 0·58 (solvent B): λ_{max} 250 and 355 nm (4·68 and 4·81 respectively); NMR ($CDCl_3$): δ 1·69 (m, 12 H, $2(C\underline{H}_3)_2C=$), 2·36, 2·50 (2s, 6 H, 2-O.CO.$C\underline{H}_3$), 3·45 (m, 4H, $2\text{-}C\underline{H}_2-$), 4·01 (s, 3H, -OMe), 5·28 (m, 2H, $2\text{-}C\underline{H}=$), 7·28 (m, 2 aromatic H in positions 6 and 7) and 7·89 ppm (q, 1 aromatic H in position 8). (Found: C, 70·6; H, 6·3. $C_{28}H_{30}O_7$ requires: C, 70·3; H, 6·3%).

Fraction B was crystallized from benzene when 2-C-prenyl-5-methoxy 1,3-dihydroxyxanthone (V) was obtained as light yellow needles (1 g), m.p 212-214°; green ferric reaction; R_f 0·47 (solvent C): λ_{max} 240-244, 256 and 313 nm (4·53, 4·38 and 4·28 respectively); NMR ($CDCl_3$): δ 1·83 (m, 6H, $(C\underline{H}_3)_2C=$), 3·52 (d, J = 7 Hz, 2H, $-C\underline{H}_2-$), 4·06 (s, 3H, -OMe), 5·34 (m, 1H, $-C\underline{H}=$), 6·58 (s, 1 aromatic H in position 4), 7·32 (m, 2 aromatic H in positions 6 and 7) and 7·92 ppm (q, 1 aromatic H in position 8). (Found: C, 70·0; H, 5·9. $C_{19}H_{18}O_5$ requires: C, 69·9; H, 5·6%). The diacetate (VI) prepared from Ac_2O-py. crystallized from EtOAc-light petroleum as white flakes, m.p. 204-206°; no ferric reaction; R_f 0·4 (solvent C); λ_{max} 241, 257 and 310 nm; NMR ($CDCl_3$): δ 1·77 (d, J = 5 Hz, 6H, $(C\underline{H}_3)_2C=$), 2·37, 2·52 (2s, 6H, 2-O.CO.$C\underline{H}_3$), 3·35 (d, J = 7 Hz, 2H, $-C\underline{H}_2-$), 4·05 (s, 3H, 1-OMe), 5·19 (m, 1H, $=C\underline{H}-$), 7·30 (m, 2 aromatic H in positions 6 and 7), 7·43 (s, 1 aromatic H in position 4) and 7·89 ppm (q, 1 aromatic H in position 8). (Found: C, 67·2; H, 5·5. $C_{23}H_{22}O_7$ requires: C, 67·3; H, 5·4%).

3-Prenyloxy-5-methoxy-1-hydroxyxanthone (VIII). To an acetone solution of 5-methoxy-1,3-dihydroxyxanthone (250 mg) was added PrBr (0·2 ml) and dry K_2CO_3 (1 g) and the resulting mixture refluxed for 4 hr. Acetone was removed and water added. The solid crystallized from benzene-light petroleum as light yellow needles (200 mg), m.p. 159-161°; green ferric reaction; R_f 0·57 (solvent B); λ_{max} 245 and 305 nm (3·6 and 4·3 respectively); NMR ($CDCl_3$): δ 1·79 (m, 6H, $(C\underline{H}_3)_2C=$), 4·01 (s, 3H, -OMe), 4·58 (m, 2H, $-O-C\underline{H}_2-$), 5·50 (m, 1H, $-C\underline{H}=$), 6·33 and 6·51 (2s, 2 aromatic H in positions 2 and 4), 7·26 (m, 2 aromatic H in positions 6 and 7) and 7·78 ppm (q, 1 aromatic H in position 8). (Found: C, 69·5; H, 5·2. $C_{19}H_{18}O_5$ requires: C, 69·9; H, 5·6%).

5-Hydroxy-6',6'-dimethyl-4',5'-dihydropyrano(2',3':1,2)-6'',6''-dimethyl-4''-5''-dihydropyrano (2'',3'':3,4)-xanthone (IX). 2,4-Di-C,C-prenyl-5-methoxy-1,3-dihydroxyxanthone (250 mg) was dissolved in AcOH (10 ml) and the solution heated with HI (iodine free, 55%, 10 ml) at 130° for 3 hr. The product was poured over ice and treated with $NaHSO_3$. The solid was collected, washed thoroughly with water, dried and repeatedly crystallized from MeOH–water when compound IX was obtained as yellow plates (150 mg), m.p. 255–257°. (Lit.[4] 259–262°); no ferric reaction; R_f 0·65 (solvent D); λ_{max} 259 and 310 nm; NMR ($CDCl_3$): δ 1·35, 1·42 (2s, 12H, 2($C\underline{H}_3)_2C<$), 1·79, 2·70 (2m, 8H, 4-$C\underline{H}_2$—), 7·17 (m, 2 aromatic H in positions 6 and 7) and 7·72 ppm (q, 1 aromatic H in position 8). (Found: C, 72·3; H, 6·8. $C_{23}H_{24}O_5$ requires: C, 72·3; H, 6·6%).

2,4-Di-C,C-prenyl-3,5-dimethoxy-1-hydroxyxanthone (IV). An acetone solution of 2,4-di-C,C-prenyl-5-methoxy-1,3-dihydroxyxanthone (200 mg), dimethyl sulphate (0·06 ml) and K_2CO_3 (1 g) was refluxed for 4 hr. The product crystallised from light petroleum as light yellow needles (185 mg), m.p. 106–108°; green ferric reaction; R_f 0·8 (solvent A); λ_{max} 257 and 310 nm (4·19 and 4·59 respectively). (Found: C, 73·0; H, 7·1. $C_{25}H_{28}O_5$ requires: C, 73·5; H, 6·9%).

2-C-Prenyl-3,5-dimethoxy-1-hydroxyxanthone (VII). 2-C-Prenyl-5-methoxy-1,3-dihydroxyxanthone (200 mg) was methylated with dimethyl sulphate (0·06 ml) K_2CO_3 (1 g) and acetone (15 ml). The product was crystallized from $CHCl_3$–MeOH as yellow plates (180 mg), m.p. 169°. (Lit.[1] 167–170°); green ferric reaction; R_f 0·7 (solvent C); λ_{max} 245, 256–261 and 306 nm (4·56, 4·44, and 4·34 respectively); NMR ($CDCl_3$): δ 1·81 (m, 6H, $(C\underline{H}_3)_2C=$), 3·45 (d, J = 7 Hz, 2H, —$C\underline{H}_2$—), 4·01, 4·11 (2s, 6H, 2-OMe), 5·33 (m, 1H, =CH—), 6·68 (s, 1 aromatic H in position 4), 7·37 (m, 2 aromatic H in positions 6 and 7) and 7·96 ppm (q, 1 aromatic H in position 8). (Found: C, 70·4; H, 6·1. $C_{20}H_{20}O_5$ requires: C, 70·6; H, 6·0%).

5-O-Methyl-6-desoxyjacareubin (XII). 2-C-Prenyl-5-methoxy-1,3-dihydroxyxanthone (200 mg) was dissolved in dry benzene (15 ml) and heated with DDQ (150 mg) over a steam bath for 15 min. The insoluble residue was filtered and the filtrate evaporated to dryness. The resulting solid was purified by column chromatography, when the fraction eluted with benzene–light petroleum (75:25) recrystallized from benzene as light yellow needles (170 mg); m.p. 178–180. (Lit.[2] 170–172°, Lit.[1] 182–184°); green ferric reaction; R_f 0·75 (solvent C); λ_{max} 240, 250 and 285 nm (4·30, 4·28 and 4·56 respectively); NMR ($CDCl_3$): δ 1·54 (s, 6H, $(C\underline{H}_3)_2C<$), 4·1 (s, 3H, —OMe), 5·72, 6·85 (2d, J = 10 Hz, 2 olefinic H of chromene ring), 6·55 (s, 1 aromatic H in position 4), 7·33 (m, 2 aromatic H in positions 6 and 7) and 7·91 ppm (q, 1 aromatic H in position 8). (Found: C, 70·2; H, 4·9. $C_{19}H_{16}O_5$ requires: C, 70·4; H, 5·0%).

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