A NEW ROUTE TOWARDS THE SYNTHESIS OF DIHYDROPYRANOXANTHONES

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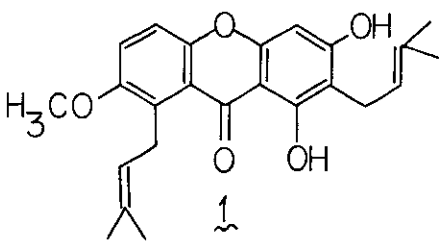
Abstract - A new route towards the synthesis of dihydropyranoxanthones using carboxy-2,2-dimethylchromans as starting material is described.

The occurrence of isoprenoid units (3-methylbut-2-enyl and 2,2-dimethylchromene) in both A and B ring of xanthone nucleus is frequent among naturally occurring xanthones, viz., calocalabaxanthone[1] (1), toxyloxanthone D[2] (2), calabaxanthone[3] (3), pyranojacareubin[4] (4) and thwaitesixanthone[5] (5) and their number has been increasing[6,7]. It is difficult to achieve selective orientation in good yield, in an attempt towards their synthesis involving building up of isoprenoid unit on the preformed xanthone nucleus. An unambiguous approach towards their synthesis could be to start with preformed isoprenoid units on o-hydroxybenzoic acids and phenols and then build up the xanthone nucleus. The 2,2-dimethylchroman moiety is most stable amongst the isoprenoid units to resist the reaction conditions employed for xanthone synthesis. Once xanthone nucleus is build up to give dihydropyranoxanthone, the 2,2-dimethylchroman moiety may then be transformed[8,9] into the desired isoprenoid unit i.e. 3-methylbut-2-enyl or 2,2-dimethylchromene. Carboxy-2,2-dimethylchromans and hydroxychromans are therefore the desired starting material.



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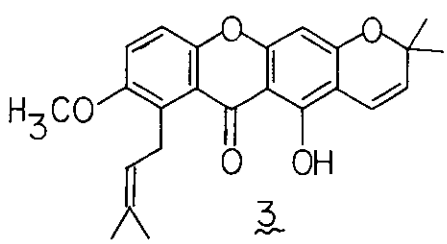

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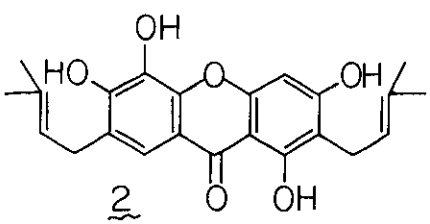

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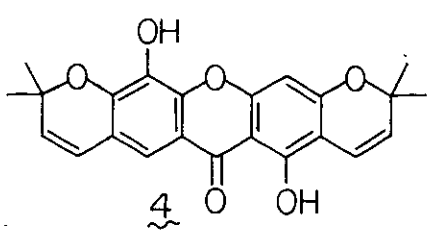

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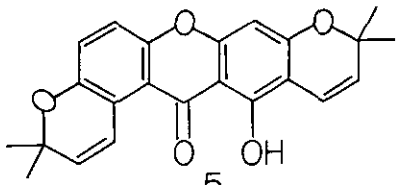

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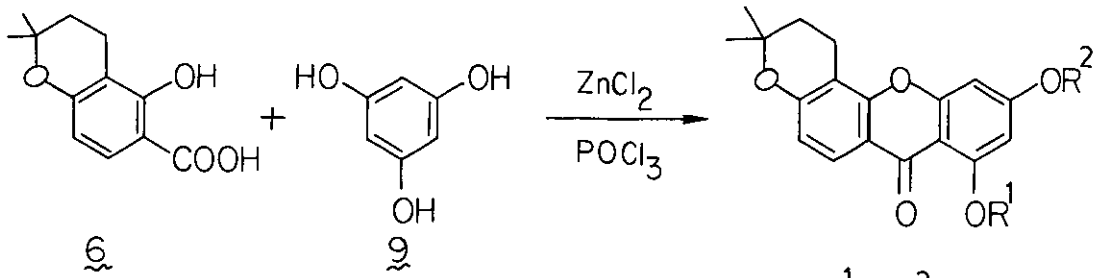
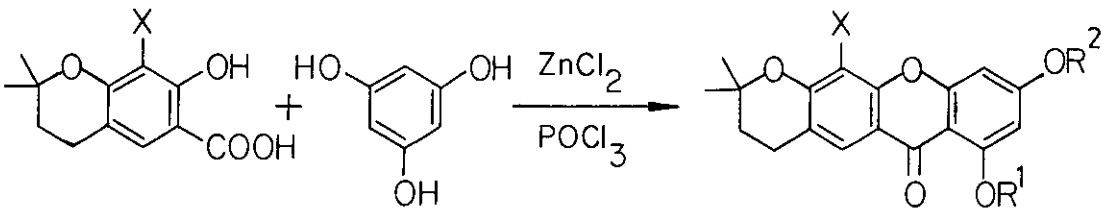
In this communication, we report a new route towards the synthesis of dihydropyranoxanthones using carboxy-2,2-dimethylchromans as starting material. Carboxy-2,2-dimethylchromans used are 5-hydroxy (6)-, 7-hydroxy (7)- and 7,8-dihydroxy (8)- 3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-6-carboxylic acid[10]. Condensation of these acids (6-8) has been carried out initially with 1,3,5-trihydroxybenzene (9) in presence of zinc chloride and phosphorus oxychloride and then with 3,4-dihydro-5,7-dihydroxy-2,2-dimethyl-2H-1-benzopyran[11] (10) under similar conditions to give the corresponding dihydropyranoxanthones.

Initially, the condensation of 9 with 6 in presence of zinc chloride and phosphorus oxychloride (1:3) has been carried out as follows. A mixture of 9 (0.57 g, 4.5 mmol), 6 (1.0 g, 4.5 mmol), freshly fused zinc chloride (3.0 g) and phosphorus oxychloride (9.0 ml) was heated in an oil bath at 70-75° C for 1h. The product was poured over crushed ice and left overnight. The solid so obtained was filtered, dried and chromatographed over silica gel. Elution of the column with benzene gave 1,2-dihydro-8,10-dihydroxy-3,3-dimethyl-3H,7H-pyrano [2,3-c] xanthen-7-one (11) which crystallised from alcohol as yellow prisms; yield: 0.85 g (60%); mp 285-286°C. Similar condensation of 9 with carboxy-2,2-dimethylchromans, viz., 7 and 8 in presence of zinc chloride and phosphorus oxychloride (1:3) gave 3,4-dihydro-7,9-dihydroxy-2,2-dimethyl-2H,6H-pyrano [3,2-b] xanthen-6-one (12) and 3,4-dihydro-7,9,12-trihydroxy-2,2-dimethyl-2H,6H-pyrano [3,2-b] xanthen-6-one (13) respectively (yield 55-62%). Partial methyl ethers, viz., 14, 15 and 16 of above formed dihydropyranoxanthones have been prepared by methylation with appropriate moles of dimethyl sulphate in acetone in presence of potassium carbonate. The assigned structures were in agreement with their elemental analysis and ^{1}H-NMR spectral data.



6 9

11 $R^1=R^2=H$
14 $R^1=H$, $R^2=CH_3$



7 X=H
8 X=OH

9

12 $R^1=R^2=X=H$

13 $R^1=R^2=H$, X=OH

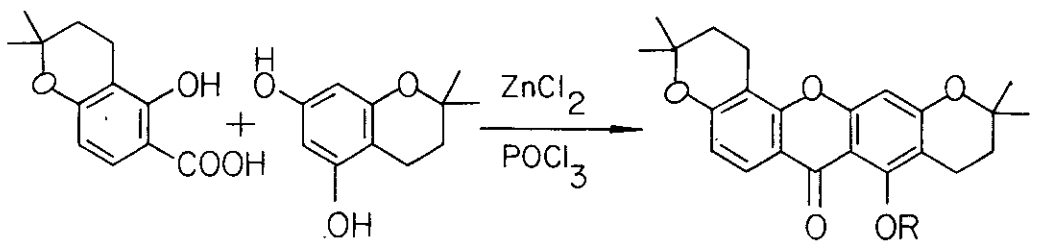
15 $R^1=X=H$, $R^2=CH_3$

16 $R^1=H$, $R^2=CH_3$, $X=OCH_3$

Condensation of 10 with 6 in presence of zinc chloride and phosphorus oxychloride (1:3) gave only one product, A (yield 53%). Compound A gave positive ferric reaction and showed in its ^{1}H-NMR spectrum, the presence of two 2,2-dimethylchroman rings, an aromatic singlet, two ortho coupled aromatic protons and a low field hydroxyl singlet. Since 10 offers two reaction sites (6 and 8) for acylation, compound A could, therefore, be assigned the structure 5-hydroxy-3,4,11,12-tetrahydro-2,2,10,10-tetramethyl-2H,6H,10H-dipyrano [3,2-b:3',2'-d] xanthen-6-one (17) or 6-hydroxy-1,2,12,13-tetrahydro-3,3,11,11-tetramethyl-3H,7H,11H-dipyrano [2,3-c:3',2'-d] xanthen-7-one (18) or 5-hydroxy-3,4,8,9-tetrahydro-2,2,10,10-tetramethyl-2H,10H,14H-dipyrano [2,3-a:3',2'-d] xanthen-14-one (19). The third possibility 19 was

ruled out since compound A showed the presence of a chelated hydroxyl group.

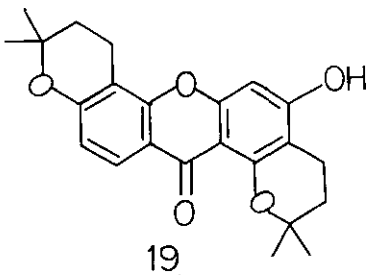
The structure 17 was assigned to compound A as it did not react with 2-methylbut-1,3-diene[9] in presence of orthophosphoric acid; A was recovered unchanged from the reaction mixture. Had it been the alternate structure 18, the reaction with 2-methylbut-1,3-diene may have led to the structure 20. The assigned structure 17 was further supported by methoxy benzene-induced shift study made as follows: The environment of methoxyl group is different in 21 and 22, which are the possible structures for methyl ether of compound A. The possibility whether methoxy benzene-induced shift can be used to differentiate 21 and 22 and hence 17 and 18 was examined first in known[9] linear and angular dihydropyranoxanthones (23 and 24). The solvent shift of methoxyl group at 1 position in 24 was 0.3 ppm $\left[\Delta = \delta^{3.89}_{CDCl_3} - \delta^{3.59}_{C_6H_6} \right]$. However, there was no solvent shift of methoxyl group in 23 ($\Delta = 0$). The difference in solvent shift of methoxyl group in 23 and 24 can be explained as follows: In structure 24, the 2,2-dimethylchroman ring is fused between 3 and 4 position of xanthone nucleus with an ortho aromatic proton to the methoxyl group. However, in structure 23, the linearly fused 2,2-dimethylchroman ring between 2 and 3 position, caused steric inhibition of benzene solvation of the methoxyl group. Prompted by the successful results in 23 and 24, methoxy benzene-induced shift study was then used in the present case. The methoxyl group in methyl ether of compound A exhibit no solvent shift; $\Delta = \left[\delta^{3.92}_{CDCl_3} - \delta^{3.92}_{C_6H_6} \right] = 0$, thereby suggesting structure 21 for methyl ether of compound A and structure 17 for compound A itself.



6 10

17 R=H

21 R=CH_3



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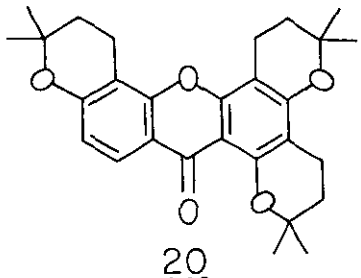

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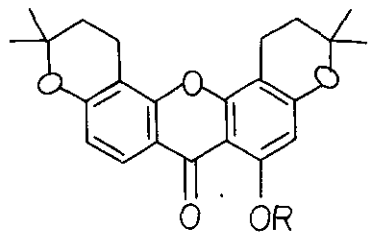
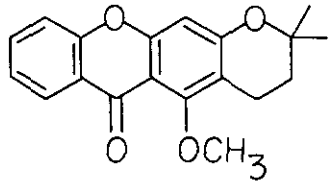


18 R = H
22 R = CH_3



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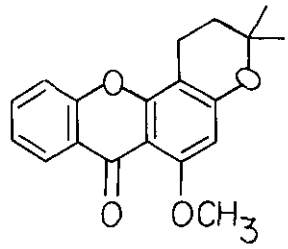
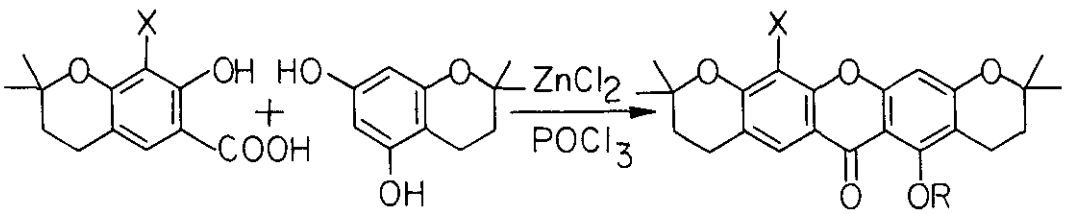


24

Similar condensation of 10 with 7 and 8 gave 5-hydroxy-3,4,8,9-tetrahydro-2,2,10,10-tetramethyl-2*H*,6*H*,10*H*-dipyrano [3,2-b:2',3'-e] *xanthen-6-one (25) and 5,12-dihydroxy-3,4,8,9-tetrahydro-2,2,10,10-tetramethyl-2H,6H,10H-dipyrano* [3,2-b:2',3'-e] xanthen-6-one (26) respectively. 26 is tetrahydro derivative of naturally occurring pyranojacareubin[4] (4). 25 and 26 on methylation gave 27 and 28 respectively.



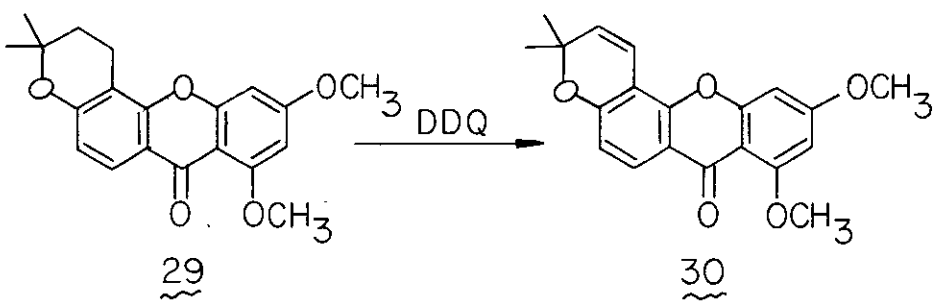
7 X = H
8 X = OH

10

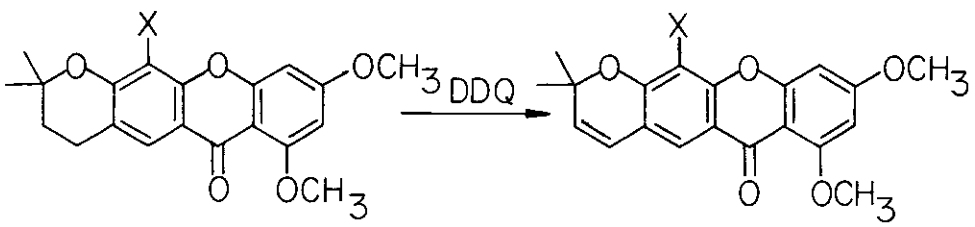
25 R = X = H
26 R = H, X = OH
27 R = CH_3, X = H
28 R = CH_3, X = OCH_3

In the past, dihydropyranoxanthones with 2,2-dimethylchroman ring in both A and B ring of xanthone nucleus have been synthesised[8] by cyclization of the corresponding dihydropyranobenzophenones effected with tetramethylammonium hydroxide in refluxing pyridine. The synthesis of required benzophenones was achieved[8] in number of steps and in poor yield. However, in the present communication, synthesis of dihydropyranoxanthones has been achieved in good yield (50-60%) and in one step.

The dihydropyranoxanthones obtained above are intermediates for the synthesis of pyranoxanthones, e.g. dihydropyranoxanthone (29; methyl ether of 11) on dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dry benzene gave the corresponding pyranoxanthone, 8,10-dimethoxy-3,3-dimethyl-3H,7H-pyrano [2,3-c] xanthen-7-one (30) in 80% yield. Similar dehydrogenation of 31 (methyl ether of 12) and 32 (methyl ether of 13) with DDQ gave the corresponding pyranoxanthones, viz., 33 and 34. Table-1 summarises the yield, mp and spectral data of all the prepared compounds.



29 30



31, 32 33, 34

31, 33 X = H
32, 34 X = OCH_3

Table - 1: Compounds 11-17, 21 and 25-34 prepared

Product[a]	Yield[b] (%)	mp (°C)	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
11	60 (1:10)	285-286	*
12	55 (1:0)	293-294	*
13	62 (1:0)	339-340	*
14	90	220-221	1.40(s, 6H); 1.92(t, 2H, J=7 Hz); 2.94(t, 2H, J=7 Hz); 3.88(s, 3H); 6.21(d, 1H, J=2.5 Hz); 6.28(d, 1H, J=2.5 Hz), 6.70(d, 1H, J=9 Hz); 7.87(d, 1H, J=9 Hz); 13.10(s, 1H, exchanged with D_2O).
15	80	162-163	1.37(s, 6H); 1.84(t, 2H, J=7 Hz); 2.86(t, 2H, J=7 Hz); 3.80(s, 3H); 6.19(d, 1H, J=2.5 Hz); 6.25(d, 1H, J=2.5 Hz); 6.62(s, 1H); 7.81(s, 1H); 13.10(s, 1H, exchanged with D_2O).
16	87	159-160	1.46(s, 6H); 1.89(t, 2H, J=7 Hz); 3.00(t, 2H, J=7 Hz); 3.86(s, 3H); 3.96(s, 3H); 6.18(d, 1H, J=2.5 Hz); 6.37(d, 1H, J=2.5 Hz); 7.63(s, 1H); 12.80(s, 1H, exchanged with D_2O).
17	53 (0:1)	198-199	1.34(s, 12H); 1.68-1.94(m, 4H); 2.56-2.94(m, 4H); 6.22(s, 1H); 6.70(d, 1H, J=9 Hz); 7.89(d, 1H, J=9 Hz); 13.50(s, 1H, exchanged with D_2O).
21	82	210-211	1.34(s, 12H); 1.71-1.95(m, 4H); 2.73-2.97(m, 4H); 3.92(s, 3H)[c]; 6.58(s, 1H); 6.70(d, 1H, J=9 Hz); 7.98(d, 1H, J=9 Hz).
25	50 (0:1)	192-193	1.33(s, 12H); 1.68-1.93(m, 4H); 2.56-2.91(m, 4H); 6.23(s, 1H); 6.66(s, 1H); 7.85(s, 1H); 13.70(s, 1H, exchanged with D_2O).

26	55 (0:1)	221-222	1.32(s, 6H); 1.36(s, 6H); 1.66-1.92(m, 4H); 2.54-2.89(m, 4H); 5.70(s, 1H, exchanged with D_2O); 6.30(s, 1H); 7.42(s, 1H); 13.60(s, 1H, exchanged with D_2O).
27	85	181-182	1.37(s, 12H); 1.72-1.95(m, 4H); 2.72-2.98(m, 4H); 3.95(s, 3H)[c]; 6.50(s, 1H); 6.60(s, 1H); 7.90(s, 1H).
28	80	172-173	1.35(s, 6H); 1.40(s, 6H); 1.70-1.93(m, 4H); 2.72-2.98(m, 4H); 3.90(s, 6H)[c]; 6.57(s, 1H); 7.62(s, 1H).
29	85	161-162	1.33(s, 6H); 1.82(t, 2H, J=7 Hz); 2.83(t, 2H, J=7 Hz); 3.80(s, 3H); 3.86(s, 3H); 6.22(d, 1H, J=2.5 Hz); 6.35(d, 1H, J=2.5 Hz); 6.66(d, 1H, J=9 Hz); 7.92(d, 1H, J=9 Hz).
30	80 (4:1)	209-210	1.32(s, 6H); 3.85(s, 3H); 3.95(s, 3H); 5.54(d, 1H, J=10 Hz); 6.13(d, 1H, J=2.5 Hz); 6.27(d, 1H, J=2.5 Hz); 6.65(m, 2H); 7.90(d, 1H, J=9 Hz).
31	90	175-176	1.40(s, 6H); 1.88(t, 2H, J=7 Hz); 2.87(t, 2H, J=7 Hz); 3.85(s, 3H); 3.89(s, 3H); 6.28(d, 1H, J=2.5 Hz); 6.41(d, 1H, J=2.5 Hz), 6.58(s, 1H); 7.78(s, 1H).
32	80	214-215	1.40(s, 6H); 1.82(t, 2H, J=7 Hz); 2.85(t, 2H, J=7 Hz); 3.81(s, 3H); 3.90(s, 6H); 6.32(d, 1H, J=2.5 Hz); 6.58(d, 1H, J=2.5 Hz); 7.76(s, 1H).
33	80 (4:1)	203-204	1.42(s, 6H); 3.84(s, 3H); 3.93(s, 3H); 5.50(d, 1H, J=10 Hz); 6.12-6.37(m, 3H); 6.50(s, 1H); 7.71(s, 1H).
34	90 (3:1)	170-171	1.40(s, 6H); 3.85(s, 3H); 3.97(s, 3H); 4.02(s, 3H); 5.55(d, 1H, J=10 Hz); 6.16(d, 1H, J=2.5 Hz); 6.30(d, 1H, J=10 Hz) 6.40(d, 1H, J=2.5 Hz); 7.54(s, 1H).

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* ^{1}H-NMR spectrum could not be recorded due to poor solubility of compound in $CDCl_3$/ DMSO-d_6.

a Satisfactory microanalysis obtained for all the products.

b Values in the parenthesis given after the yield are the ratio of benzene-petroleum ether used as eluent in column chromatography over silica gel.

c No solvent shift, $\Delta = \left[\delta_{CDCl_3} - \delta_{C_6H_6} \text{ ppm} \right] = 0$.

ACKNOWLEDGEMENTS

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