A CONVENIENT SYNTHESIS OF PROPYL SUBSTITUTED BENZOFUROCOUMARINS

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Abstract – A convenient synthesis of propyl substituted benzofurocoumarins has been achieved by condensation of 2-bromocyclohexan-1-one with hydroxy-4-propyl-2H-1-benzopyran-2-ones followed by ring closure with PPA and subsequent dehydrogenation using DDQ.

Benzofuranocoumarins constitute a group of naturally occurring compounds of biological interest. Many of them are associated with estrogenic[1], insecticidal[2] and antibacterial[3] activities. They are also known to play an important role as phytoalexins[4]. Further, 4-propyl-2H-1-benzopyran-2-ones are found to possess insecticidal[5,6] and antibacterial[6] activities. In view of the above, it was considered of interest to construct benzofuran ring on 4-propyl-2H-1-benzopyran-2-ones. The resulting propyl substituted benzofuranocoumarins may have better physiological activities. In this communication, we report an efficient method for the synthesis of propyl substituted benzofuranocoumarins. It involves the etherification[7] of hydroxy-2H-1-benzopyran-2-ones with 2-bromocyclohexan-1-one followed by cyclisation with polyphosphoric acid (PPA) and subsequent dehydrogenation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

Initially, the synthesis of 9-propyl-7H-benzofuro [2,3-h] [1] benzopyran-7-one (1) has been carried out as follows. A mixture of 7-hydroxy-4-propyl-2H-1-benzopyran-2-one[8] (2 g, 10.4 mmol), 2-bromocyclohexan-1-one[9] (1.2 ml, 10.46 mmol), anhydrous acetone (75 ml) and anhydrous potassium carbonate (6 g) was refluxed for 24 h and the reaction mixture was filtered. Evaporation of the solvent and treatment of residue with crushed ice gave a solid which crystallised from ethanol as rectangular plates (2.35 g), $C_{18}H_{20}O_4$. It responded to DNP, indicating the presence of a ketonic group. Its ^{1}H-NMR spectrum showed a triplet at δ 1.08 (J 7 Hz)

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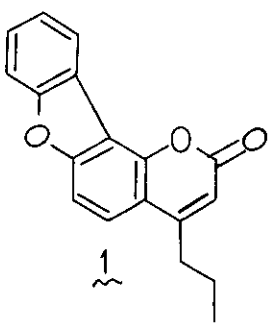
for methyl group of propyl chain; the signals for two methylene groups of propyl chain were mixed with methylene protons of cyclohexanone ring, thereby, appearing as two multiplets at δ 1.57-2.18 and 2.32-2.72 integrating for eight and four protons respectively. A multiplet at δ 4.60-4.78, integrating for one proton, was assignable to methineoxy group. Therefore, the product was assigned the structure of 7-(2-oxo-cyclohexanyloxy)-4-propyl-2H-1-benzopyran-2-one (2). Compound 2 (1 g, 3.47 mmol) on heating with polyphosphoric acid (10 ml) at 95-100°C for 10 h yielded a mixture of two products (overall yield 80%). The products were isolated from the reaction mixture by pouring it over the crushed ice, extraction with ether and washing the organic layer with aqueous sodium bicarbonate solution (5%) followed by purification by column chromatography over silica gel. Both of them analysed for $C_{18}H_{18}O_3$ and did not give any DNP test. The ^{1}H-NMR spectrum of the first compound showed two doublets at δ 7.15 and 7.23 (J 9.5 Hz) for ortho coupled protons at C-10 and C-11 respectively while that of second showed two singlets at δ 7.20 and 7.40 for para protons of C-6 and C-11 besides other usual signals. Moreover, the ^{1}H-NMR spectrum of both the compounds showed the absence of methineoxy group. Hence, the first and second products were assigned the structures, 2,3,4,5-tetrahydro-9-propyl-7H-benzofuro [2,3-h] [1] benzopyran-7-one (3) and 2,3,4,5-tetrahydro-7-propyl-9H-benzofuro [3,2-g] [1] benzopyran-9-one (4), respectively. Exclusive formation of compound 4 could also be achieved by cyclisation[7] of 2 (1 g, 3.47 mmol) with ethanolic potassium hydroxide (0.1 N, 200 ml) at 80-90°C (18 h refluxing). Dehydrogenation of 3 (0.2 g, 0.74 mmol) with DDQ (0.35 g, 1.54 mmol) in anhydrous benzene (25 ml) (36 h refluxing) afforded the required 1 (0.15 g) as colourless crystals. However, dehydrogenation of 4 with DDQ furnished 7-propyl-9H-benzofuro [3,2-g] [1] benzopyran-9-one (5). The structures of 1 and 5 were established on the basis of their elemental analysis and ^{1}H-NMR spectral data (Table -1).

11-Methyl-7-propyl-9H-benzofuro [3,2-g] [1] benzopyran-9-one (6) was synthesised starting from 7-hydroxy-8-methyl-4-propylcoumarin.[10] The latter on condensation with 2-bromocyclohexan-1-one in acetone/potassium carbonate afforded 7-(2-oxo-cyclohexanyloxy)-8-methyl-4-propyl-2H-1-benzopyran-2-one (7). Compound 7 was cyclised by heating with PPA to give a product which analysed for $C_{19}H_{20}O_3$. It was assigned the structure, 2,3,4,5-tetrahydro-11-methyl-7-propyl-9H-benzofuro [3,2-g] [1] benzopyran-9-one (8) on the basis of its

^{1}H-NMR spectral data (Table-1). Dehydrogenation of 8 with DDQ in anhydrous benzene furnished the required 6. The structure of 6 was confirmed on the basis of microanalysis and ^{1}H-NMR spectral data (Table -1).

Similarly, 6-methyl-11-propyl-9H-benzofuro [2,3-f][1] benzopyran-9-one (9) was synthesized by condensation of 5-hydroxy-7-methyl-4-propylcoumarin[8] with 2-bromocyclohexanone followed by cyclisation of the intermediate ether viz., 5-(2-oxo-cyclohexanyloxy)-7-methyl-4-propyl-2H-1-benzopyran-2-one (10) with PPA to give 2,3,4,5-tetrahydro-6-methyl-11-propyl-9H-benzofuro [2,3-f] [1] benzopyran-9-one (11) and subsequent dehydrogenation with DDQ. The structures of 9, 10 and 11 were in agreement with their elemental analyses and ^{1}H-NMR spectral data (Table -1). Compounds 8 and 11 could also be prepared by cyclisation of 7 and 10 respectively with ethanolic potassium hydroxide.



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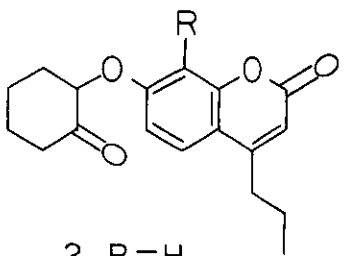
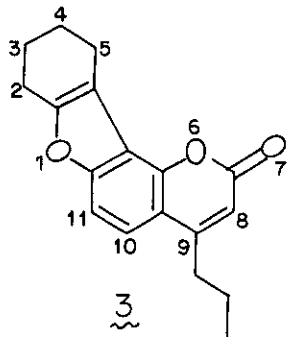


2, R=H
7, R=CH$_3$



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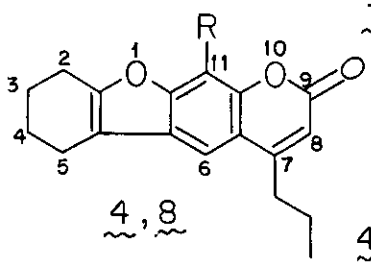
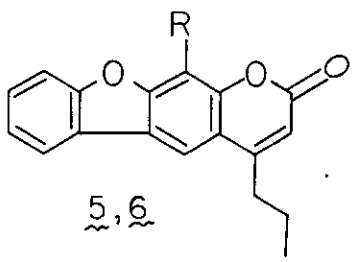
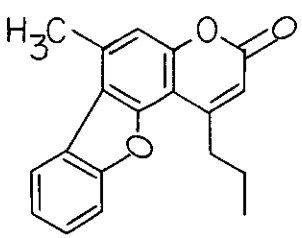


4, 8



5, 6

4, 5; R=H
6, 8; R=CH$_3$



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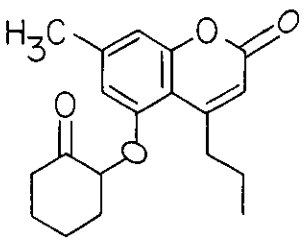

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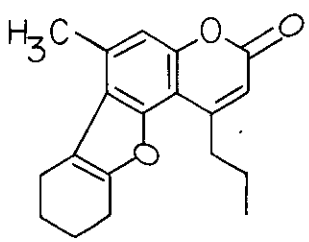

11

Table - 1 : Compounds 1 - 11 prepared

Product[a, b]	Yield (%)	m.p.[c] (°C)	^{1}H-NMR($CDCl_3$/TMS) δ (ppm)
1	75	140-141	1.08(t, J 7 Hz, 3H), 1.50-1.80(m, 2H), 2.65(t, J 7 Hz, 2H), 5.99(s, 1H), 7.10-7.98(m, 6H).
2	80	172-173	1.08(t, J 7 Hz, 3H), 1.57-2.18(m, 8H), 2.32-2.78(m, 4H), 4.60-4.78(m, 1H), 6.01(s, 1H), 6.60(d, J 2.5 Hz, 1H), 6.75(dd, J 9.5 Hz, 2.5 Hz, 1H), 7.41(d, J 9.5 Hz, 1H).
3	40	153-155	1.07(t, J 7 Hz, 3H), 1.51-2.15(m, 6H), 2.32-2.78(m, 6H), 6.10(s, 1H), 7.15(d, J 9.5 Hz, 1H), 7.23(d, J 9.5 Hz 1H).
4	40	168-169	1.00(t, J 7 Hz, 3H), 1.60-1.90(m, 6H), 2.50-2.80(m, 6H), 6.08(s, 1H), 7.20(s, 1H), 7.40(s, 1H).
5	75	220-221	1.10(t, J 7 Hz, 3H), 1.60-1.92(m, 2H), 2.82(t, J 7 Hz, 2H), 6.18(s, 1H), 7.20-7.98(m, 6H).
6	75	218-219	1.04(t, J 7 Hz, 3H), 1.60-1.90(m, 2H), 2.59(s, 3H), 2.81(t, J 7 Hz, 2H), 6.20(s, 1H), 7.20-7.97(m, 5H).
7	80	193-194	1.08(t, J 7 Hz, 3H), 1.60-2.10(m, 8H), 2.40(s, 3H), 2.52-2.85(m, 4H), 4.55-4.75(m, 1H), 6.03(s, 1H), 6.52(d, J 9.5 Hz, 1H), 7.26(d, J 9.5 Hz, 1H).
8	70	146-147	1.06(t, J 7 Hz, 3H), 1.50-2.08(m, 6H), 2.50(s, 3H), 2.51-2.92(m, 6H), 6.01(s, 1H), 7.30(s, 1H).
9	75	145-146	1.08(t, J 7 Hz, 3H), 1.58-1.81(m, 2H), 2.62(s, 3H), 2.95(t, J 7 Hz, 2H), 6.01(s, 1H), 6.95(s, 1H), 7.12-7.89(m, 4H).
10	80	153-154	1.05(t, J 7Hz, 3H), 1.52-2.15(m, 8H), 2.40(s, 3H), 2.65-3.40(m, 4H), 4.20-4.41(m, 1H), 5.98(s, 1H), 6.70(d, 1H, J 2.5 Hz), 7.20(d, J 2.5 Hz, 1H).

11	70	169-170	1.03(t, J 7 Hz, 3H), 1.44-2.89(m, 6H), 2.50(s, 3H), 2.65-3.00(m, 6H), 6.02(s, 1H), 6.80(s, 1H).

a Satisfactory microanalysis obtained for all the products.

b The screening of all these compounds for antifertility activity is in progress and will be reported separately.

c Not corrected.

ACKNOWLEDGEMENTS

We are thankful to the University Grants Commission, New Delhi for financial help.

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Received, 5th July, 1984