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A single-step synthesis of methyl ethers of dihydro alloptaeroxylin, dihydro spathelia chromene and related dihydro pyrano coumarin derivatives

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Abstract. Treatment of hydroxy-2, 2-dimethyl chromans 1, 4, 8 with ethyl acetoacetate (EAA) in the absence of any condensing agents afforded a mixture of dihydropyrano coumarins and dihydropyrano chromones, 2 + 3, 5 + 6 and 9 + 10 respectively. Demethylation of methyl ethers of dihydro-spatheliachromene (6) and -alloptaeroxylin (10) using anhydrous $AlCl_3$–CH_3CN yielded the correspond chromans, 7 and 11.

Keywords. 2, 2-Dimethyl-2H-pyrano-coumarins and -chromones; ethyl acetoacetate; condensation.

1. Introduction

Spathelia sorbifolia Linn (Taylor *et al* 1977), *Cedrolepsin grevi* Bail and *Cueorum tricoccum* Linn (Gonzalez *et al* 1974) are prolific in the production of various 2, 2-dimethyl-2H-pyranochromones in nature. In the literature, these pyranochromones were generally synthesised from hydroxy-2-methyl chromones (Bolleter *et al* 1951; Bandaranayake *et al* 1969; Jain *et al* 1969; Bajwa *et al* 1971; Iyer *et al* 1984) and suitably substituted acetyl hydroxy chromones (Backhouse and Robertson 1939; Prasad *et al* 1982, 1983, 1988, 1989; Iyer *et al* 1983) by following two or more steps. The syntheses reported (Backhouse and Robertson 1939; Bolleter *et al* 1951; Jain *et al* 1969; Bandaranayake *et al* 1969; Bajwa *et al* 1971; Iyer *et al* 1983, 1984; Prasad *et al* 1982, 1983, 1988, 1989) so far suffer from some limitations such as complex procedures, low yield or difficult-to-access starting material. Now, we report a convenient and a single-step synthesis of the title compounds.

In the literature, the reaction of simple phenols with ethyl acetoacetate in the absence of any condensing agent (Mentzer *et al* 1951) was reported to give chromones as a major product. Hence we envisaged that such a mode of condensation would convert the respective hydroxy-2, 2-dimethyl chroman into naturally occurring dihydro pyrano chromone derivatives like spathelia chromene, alloptaeroxylin etc.

2. Experimental

Melting points were determined using the Boetius microheating table and Mettler FP_5 apparatus and are uncorrected. Column chromatography was peformed on columns of silicagel (Merck, 60-120 mesh). Analytical TLC was performed on silicagel-G

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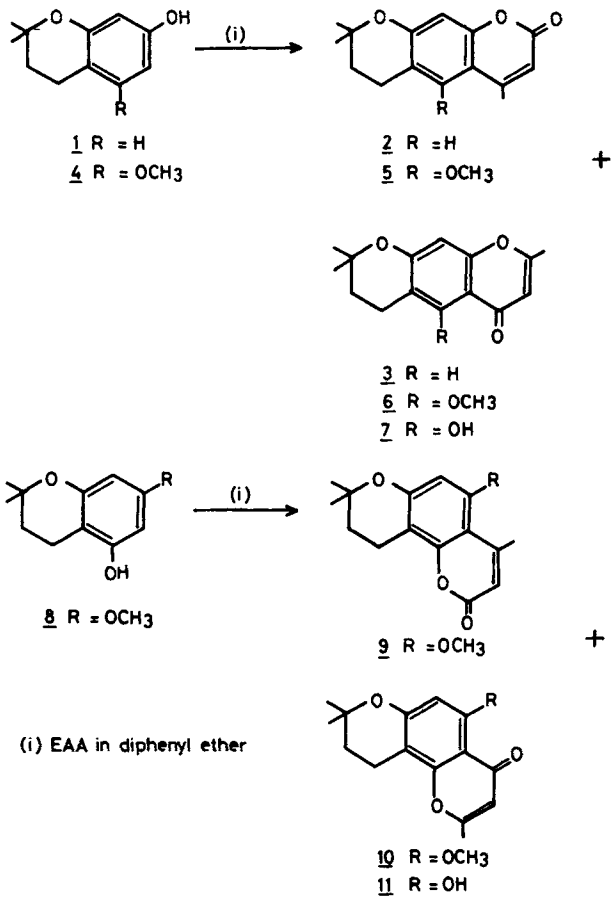

Scheme 1.

(Merck). IR were recorded on a Perkin–Elmer 597 spectrophotometer in KBr. ^1H NMR were recorded on a Varian EM-360 (90 MHz) spectrometer in solution of $CDCl_3$. Chemical shifts for ^1H NMR are reported in δ units downfield of TMS and coupling constants are in hertz. Microanalyses were performed on a Perkin–Elmer Model 240 CH analyser. Resorcinol, phloroglucinol, anhydrous $AlCl_3$, $POCl_3$, Zn dust, $HgCl_2$, $(CH_3)_2SO_4$, EAA, Na_2SO_4 and diphenyl ether were purchased from Sisco Industrial Ltd., Bombay, India. All hydroxy chromans 1, 4, 8 were prepared in our laboratory according to usual methods (Prasad and Iyer 1982) (scheme 1).

2.1 *Reaction of hydroxy-2,2-dimethylchroman with ethyl acetoacetate in diphenyl ether*

A mixture of the respective hydroxy-2,2-dimethylchroman (Prasad and Iyer 1982) (3 mmol) and EAA (0·36 ml, 3 mmol) in diphenyl ether (3 ml) was refluxed for 2h on a flame. Excess diphenyl ether was then removed under reduced pressure and the reaction mixture cooled, poured onto crushed ice (30g) with stirring, extracted with EtOAc, dried over anhydrous Na_2SO_4 and the solvent distilled off. The residual solid

obtained was found to be a mixture of two products on TLC. These two compounds namely dihydropyranocoumarin and dihydropyrano chromone, were separated by chromatography on silica gel and elution with petroleum ether–EtOAc, (47:3) and (30:20), respectively.

2.1a *Dihydro spatheliachromene* 7: A mixture of 6 (411 mg, 1·5 mmol), $AlCl_3$ (200 mg) and CH_3CN (5 ml) was refluxed for 4h on a water-bath and concentrated. The residue was treated with dilute HCl, and the separated solid filtered, dried and purified by chromatography on silica gel in petroleum ether–EtOAc (95:5) as dihydro spathelia chromene 7 (193 mg), 49·5%), m.p. 128–129° (Bolleter *et al* 1951).

2.1b *Dihydro alloptaeroxylin 11*: Demethylation of 10 as described for 6 and subsequent work-up of the reaction mixture gave 11 which crystallised from petroleum ether as cubic crystals (200 mg, 50%), m.p. 237–238° (Bolleter *et al* 1951).

3. Results and discussion

To realise our objective, 7-hydroxy-2,2-dimethyl chroman (1) was heated with ethyl acetoacetate in the absence of any condensing agent for 2h to give a mixture of two products. These two compounds were separated by passing through a column of silica gel and eluting with petroleum ether:EtOAc mixture in 47:3; 30:20 ratio respectively.

The product obtained from the first fraction was crystallised from the same solvent mixture as shiny colourless prisms, m.p. 159–160° (37%). Its IR spectrum revealed a band at 1715 cm^{-1} indicating the presence of a lactone carbonyl function. In its ^1H NMR spectrum the gem dimethyl protons appeared as a singlet at $\delta 1{\cdot}23$. The two triplets with two hydrogens each in the region at $\delta 1{\cdot}79$ and $\delta 2{\cdot}78$, having coupling constant $J = 7$ Hz, were ascribable to C_7-2H and C_6-2H protons respectively. The C_4-methyl protons and the C_3-olefinic proton appeared as two doublets at $\delta 2{\cdot}21$ and $\delta 5{\cdot}97$ with $J = 1{\cdot}8$Hz respectively. The two aromatic protons, C_{10}-H and C_5-H, appeared as two singlets at $\delta 6{\cdot}61$ and $\delta 7{\cdot}18$ respectively. Based on elemental analysis data (table 1), the structure 6,7-dihydro-4,8,8-trimethyl pyrano (3,2-*g*) chrom-2-one, 2 (Dean and Taylor 1966), was assigned to this product.

The product obtained from the second fraction was crystallised from the same solvent mixture as pale yellow prisms and was identified (mixed m.p., superimposable IR spectra) as 6,7-dihydro-2,8,8-trimethyl pyrano (3,2-g) chrom-4-one, 3, m.p. 153–154° (Iyer *et al* 1983).

Extension of this reaction to 4 and 8 led to a mixture of 5 + 6 and 9 + 10 respectively. Demethylation of dihydro spathelia chromene methyl ether (6) with $AlCl_3$–CH_3CN afforded dihydro spathelia chromene (7), whereas the same reaction of dihydro alloptaeroxylin methyl ether (10) yielded dihydro alloptaeroxylin (11). The spectral and analytical data were tabulated (table 1).

4. Conclusions

In the light of our studies on the synthesis of dihydro pyrano chromones, it is worth comparing the relative merits of this method with other methods reported in the literature. The condensation of hydroxychroman with ethyl acetoacetate in the absence of any condensing agent has the advantage that it is the simplest single route.

Table 1. Data for dihydro pyrano chromones and coumarins.

Compound	m.p.[a]	Yield (%)	Ir(KBr) max (cm^{-1})	Molecular formula	Analysis (%): observed C,H (Calcd C, H)	^1H nmr ($CDCl_3$), δ (ppm) J (Hz)
2	159–160 (94:6)	37	1715	$C_{15}H_{16}O_3$ (244·25)	73·66, 6·48 (73·75, 6·60)	1·23 (*s*, 6H, CMe_2), 1·79 (*t*, 2H 2H-7, $J = 7$), 2·21 (*d*, 3H, 4-Me, $J = 1·8$) 2·78 (*t*, 2H, 2H-6, $J = 7$), 5·97 (*d*,1H, H-3, $J = 1·8$), 6·61 (*s*, 1H, H-10), 7·18 (*s*, 1H, H-5)
3	153–154 (85:15)	47	1635	$C_{15}H_{16}O_3$ (244·25)	73, 77,6·89 (73·75, 6·61)	1·25 (*s*, 6H, CMe_2), 1·75 (*t*, 2H, 2H-7, $J = 7$), 2·25 (*s*, 3H, 2-Me), 2·80 (*t*, 2H, 2H-6, $J = 7$), 5·90 (*s*, 1H, H-3), 6·62 (*s*, 1H, H-10), 7·71 (*s*, 1H, H-5).
5	170–171 (91:9)	23	1700	$C_{16}H_{18}O_4$ (274·26)	70·11, 6·54 (70·06, 6·60)	1·40 (*s*, 6H, CMe_2), 1·80 (*t*, 2H, 2H-7, $J = 7$), 2·50 (*s*, 3H, 4-Me), 2·75 (*t*, 2H, 2H-6, $J = 7$), 3·90 (*s*, 3H-5-OCH3), 5·90 (*s*, 1H, H-3), 6·30 (*s*, 1H, H-10).
6	162–164 (60:40)	46	1655	$C_{16}H_{18}O_4$ (274·26)	70·28, 6·56 (70·06, 6·61)	1·40 (*s*, 6H, CMe_2), 1·84 (*t*, 2H, 2H-7, $J = 7$), 2·36 (*s*, 3H, 2-Me), 2·72 (*t*, 2H, 2H-6, $J = 7$), 3·96 (*s*, 3H,5-OMe), 6·00 (*s*, 1H, H-3), 6·30 (*s*, 1H, H-10).
7	128–129 (95:5)	31	1640	$C_{15}H_{16}O_4$ (260·17)	69·35, 5·99 (69·22, 6·20)	1·40 (*s*, 6H, CMe_2), 1·84 (*t*, 2H, 2H-7, $J = 7$), 2·36 (*s*, 3H, 2-Me), 2·72 (*t*, 2H, 2H-6, $J = 7$), 6·00 (*s*, 1H, H-3), 6·30 (*s*, 1H, H-10), 13·04 (*s*, 1H, 5-OH).
9	155–156 (94:6)	22	1700	$C_{16}H_{18}O_4$ (274·26)	69·96, 6·55 (70·06, 6·61)	1·36 (*s*, 6H, CMe_2), 1·83 (*t*, 2H, 2H-3, $J = 7$), 2·52 (*s*, 3H, 8-Me), 2·81 (*t*, 2H, 2H-4, $J = 7$), 3·82 (*s*, 3H, 9-OMe), 5·92 (*s*, 1H, H-7), 6·22 (*s*, 1H, H-10).
10	163–164 (60:40)	40	1665	$C_{16}H_{18}O_4$ (274·26)	70·09, 6·48 (70·06, 6·61)	1·40 (*s*, 6H, CMe_2), 1·84 (*t*, 2H, 2H-3, $J = 7$), 2·36 (*s*, 3H, 6-Me), 2·72 (*t*, 2H, 2H-4, $J = 7$), 3·96 (*s*, 3H, 9-OMe), 6·00 (*s*, 1H, H-7), 6·30 (*s*, 1H, H-10).
11	237–238 (100:0)	31	1650	$C_{15}H_{16}O_4$ (260·17)	69·12, 6·01 (69·22, 6·20)	1·38 (*s*, 6H, CMe_2), 1·84 (*t*, 2H, 2H-3, $J = 7$), 2·38 (*s*, 3H, 6-Me), 2·76 (*t*, 2H, 2H-4, $J = 7$), 6·04 (*s*, 1H, H-7), 6·24 (*s*, 1H, H-10), 12·48 (*s*, 1H, 5-OH).

[a] Solvent in each case is petroleum ether–EtOAc in the ratio shown in parentheses

References

Backhouse T and Robertson A 1939 *J. Chem. Soc.* 1257
Bajwa B S, Pyare Lal and Seshadri T R 1971 *Indian J. Chem* **9** 17
Bandaranayake W M, Crombie L and Whiting D A 1969 *J. Chem. Soc. Chem. Commun. (D)* 970
Bolleter A, Eiter K and Schmid H 1951 *Helv. Chim. Acta* **34** 186
Dean F M and Taylor D A H 1966 *J. Chem. Soc. (C)* 114
Gonzalez A G, Frager B M and Oliva Pino 1974 *Phytochemistry* **13** 2305
Iyer P R, Iyer C S R and Prasad K J R 1983 *Indian J. Chem.* **B22** 1055
Iyer P R, Iyer C S R and Prasad K J R 1984 *Indian J. Chem.* **B23** 535
Jain A C, Pyare Lal and Seshadri T R 1969 *Indian J. Chem.* **8** 1072
Mentzer C, Darius Molho and Vercier 1951 *Compt. Rend.* **232** 1488
Prasad K J R and Iyer P R 1982 *Indian J. Chem.* **B21** 255
Prasad K J R, Iyer C S R and Iyer P R 1982 *Indian J. Chem.* **B21** 570
Prasad K J R, Iyer C S R and Iyer P R 1983 *Indian J. Chem.* **B22** (a) 168, (b) 281
Prasad K J R, Vijayalakshmi C S, Mugudeswaran P N, Subramaniam E P and Shanmugam P 1988 *Indian J. Chem* **B27** 475
Prasad K J R, Iyer C S R and Iyer P R 1989 *Indian J. Chem.* **B28** 768
Taylor D R, Warner J M and Wright J A 1977 *J. Chem. Soc., Perkin Trans. 1* 397