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SYNTHESIS OF SOME NEW PHENYL 2H-1-BENZOPYRAN-2-ONES: NOVEL STRUCTURE FOR NIVEGIN

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Abstract - The constitution of nivegin, occurring in Echinops niveus has been revised by synthesising 5,7-dihydroxy-4-(4-hydroxyphenyl)-2H-1-benzopyran-2-one(1), 5,7-dihydroxy-3-(4-hydroxyphenyl)-2H-1-benzopyran-2-one(2) and their derivatives **3** - **6**. It has been assigned a novel structure having the phenyl substituent in the benzenoid ring of the coumarin nucleus - 4,5-dihydroxy-7-(4-hydroxyphenyl)-2H-1-benzopyran-2-one(**11**).

INTRODUCTION

Recently Singh et al.[1] reported the isolation of nivegin [5,7-dihydroxy-4-(4-hydroxyphenyl)-2H-1-benzopyran-2-one (**1**)] from Echinops niveus and have claimed it to be a new compound, but a compound of structure **1** has earlier been synthesised by Monache et al[2]. The m.p. and spectral data reported by Singh et al[1]. for nivegin were found quite different from those reported by Monache et al.[2] for the synthetic **1** as summarised in Table 1.

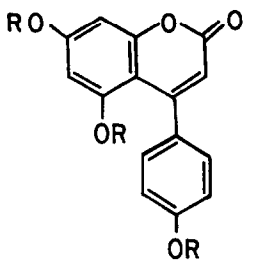
Table 1 M.p. and spectral data of nivegin and synthetic 1

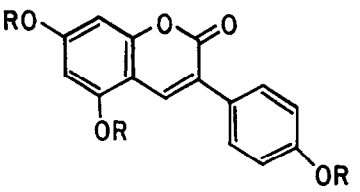
Data	Nivegin[1]	Synthetic 1[2]
M.P.	262-64°C	294-95°C
λ_{max}	267,338 nm (in ethanol)	262,324 (in methanol)
ν_{max}^{KBr} (cm^{-1})	3300, 1660, 1610, 1550, 1500, 1445	3510, 3235, 1662, 1590, 1550, 1510
^{1}H-NMR (δ)	(in DMSO-d_6)	(in Me_2CO-d_6)
H-3	6.65 (s)	5.74 (s)
(the chemical shift value of the H-3 in 4-phenylcoumarins is normally in the range δ 5.70-6.15 ppm)		
H-6 & H-8	6.44 & 6.16 (2d, J=2.12 Hz)	6.35 (s,2H)
H-2',6'	7.86 (d, J=8.76 Hz)	7.22 (d,J=8.5 Hz)
H-3',5'	6.89 (d,J=8.76 Hz)	6.83 (d,J=8.5 Hz)

Singh et al.[1] have prepared the triacetyl derivative of nivegin and reported a broad singlet at δ 2.32 (9H) for the three acetoxyl groups in its ^{1}H-NMR spectrum; the m.p., chemical shift values of other protons in the ^{1}H-NMR spectrum, UV, IR and mass spectra of this compound are not given. Monache et al.[2] have also reported the triacetate of **1** and they have mentioned two peaks - at δ 2.31 (6H) for the C-7 and C-4 acetoxyl groups and at δ 1.42 (3H) for the C-5 acetoxyl group. In order to assign the correct structure to nivegin, we have synthesised the phenylcoumarins **1**&**2**, and their triacetyl and trimethyl derivatives **3**-**6**; the compounds **2**, **5** and **6** have been synthesised by us for the first time.

RESULTS AND DISCUSSION

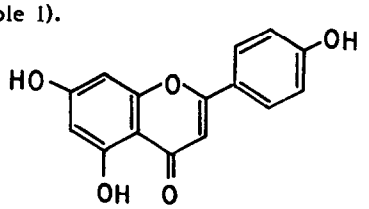
The compounds **1,3** and **4** have been synthesised by the method of Monache et al.[2] and their complete spectral data is given for the first time. The refluxing of an equimolar mixture of phloroglucinaldehyde[3] and sodium p-hydroxyphenyl acetate in dry acetic anhydride gave **6**, which on deacetylation in ethanol with NH_3 solution (15%) yielded **2**; its various spectral data (UV, IR, ^{1}H-NMR, ^{13}C-NMR and mass) and those of its trimethyl derivative **5** were compatible with the structure. The different data (m.p., UV, IR, PMR, CMR and MS) reported by Singh et al.[1] for the natural sample of nivegin were found quite different from those of our synthetic **1** and **2**, thus ruling out these structures for nivegin.





1. R = H **2.** R = H
3. R = CH_3 **5.** R = CH_3
4. R = $CO\,CH_3$ **6.** R = $COCH_3$

The close scrutiny of UV and ^{1}H-NMR spectral data of nivegin revealed them to agree well with those of 5, 7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one (apigenin) (**7**), but the m.p. (347°C)[4] of the latter is different from that of nivegin (262-64°C). Moreover the mass spectra of flavones generally do not exhibit the (M^+-CO) fragment, but nivegin exhibited a strong (M^+-CO) peak at m/z 242. The ^{13}C-NMR spectrum[5] of apigenin also showed remarkable differences from that of nivegin. Similarly, the isomeric structure —5,7-dihydroxy-3-(4-hydroxyphenyl)-4H-1-benzopyran-4-one (genistein) (**8**) was ruled out for nivegin as the m.p. (290-91°C)[6] and the UV spectral data [λ_{max}^{EtOH} : 263, 325 (sh) nm][7] of the former are quite different from those of the natural sample (cf Table 1).



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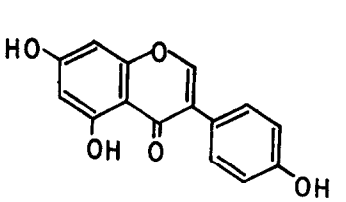

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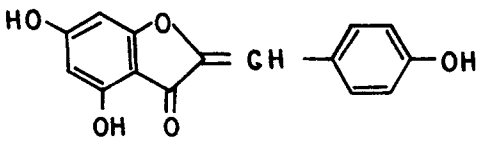
The 2-benzylidene-2-H-1-benzofuran-3-ones(aurones) exhibit a strong (M^+CO) peak in their mass spectra[8], also the bezylic proton in these compounds appears as a singlet in the range δ 6.37 - 5.94[8]. This led us to believe the structure 4,6-dihydroxy-2-(4-hydroxybenzylidene) -2H-1-benzofuran-3-one (**9**) for nivegin, again the m.p. [295-300°C (decomposition)][9] and the UV

spectral data [λ_{max}^{EtOH}: 225,245(sh), 345(sh), 392 mm][10] of the former are quite different than those of nivegin (cf Table 1).



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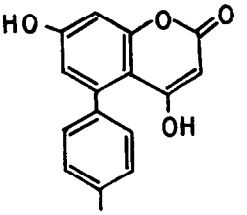

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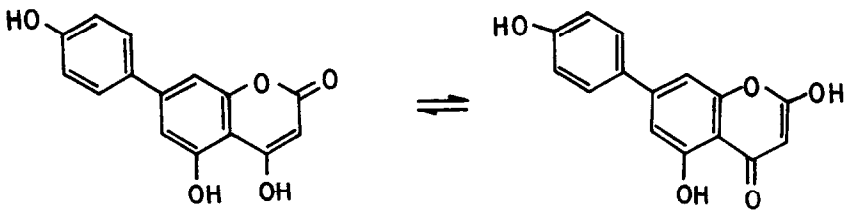
However, based upon the data reported by Singh et al.[1] for the natural product, nivegin could have the structure —4,7-dihydroxy-5-(4-hydroxyphenyl)-2H-1-benzopyran-2-one (**10**) or 4,5-dihydroxy-7-(4-hydroxyphenyl)-2H-1-benzopyran-2-one (**11**). The ^{1}H-NMR spectrum of nivegin triacetate exhibited a broad singlet at δ 2.32(9H), which cannot be explained for **10**, because one acetoxyl group in the ^{1}H-NMR spectrum of the triacetates **4** and **6** exhibited a different chemical shift value than the other two, probably because of the anisotropic effect of the phenyl group on the neighboursing carbon; however, the triacetate of **11** can exhibit the same chemical shift value for the three acetoxyl groups. The relatively downfield δ value of the H-3 in the ^{1}H-NMR spectrum of nivegin (δ 6.65) can be explained on the basis that the structure **11** may exist in the tautomeric form **12** and the H-3 in chromones appears reversibly between δ 6.30 - 6.90 ppm[11]. The ^{13}C-NMR spectra of nivegin[1] and its UV and IR spectral absorption maxima[1] are also in conformity with the structure **11** (and **12**).



11 12

On the basis of the spectral data reported for the natural product occuring in Echinops niveus by Singh et al.[1], the structure of nivegin should be: 4,5-dihydroxy-7-(4-hydroxyphenyl)-2H-1-benzopyran-2-one (**11**). To the best of our knowledge this is a new compound and is perhaps the first example of naturally occurring flavonoid compound having the phenyl group in the benzenoid ring of the benzopyranone nucleus[12].

EXPERIMENTAL

All m.ps. were measured on a H_2SO_4 bath and are uncorrected. The UV spectra were recorded on Perkin-Elmer model 554 spectrophotometer and IR spectra were recorded on Perkin-Elmer model 710 FT-IR spectrometer. The ^{1}H-NMR spectra were recorded either on Perkin Elmer R-32 (90 MHz) spectrometer or on Bruker AM-250 FT-NMR spectrometer with reference to tetramethylsilane as internal standard. The ^{13}C-NMR spectra were also recorded on Bruker AM-250 NMR spectrometer with reference to TMS as internal standard. The mass spectra were recorded on Varian Mat 311A instrument. For chromatographic separations, silica gel was used as the absorbent.

5,7-Dihydroxy-4-(4-hydroxyphenyl)-2H-1-benzopyran-2-one (1), m.p. 267-69° (lit.[2] m.p. 294-95°C); λ_{max}^{MeOH} (log ε): 258 (3.82), 320(3.90); +NaOAc:270(3.87), 316 (sh), 368(3.82); +NaOMe: 282(3.71), 364(3.71); +NaOH: 276(3.66), 364(3.73) nm; ν_{max} (KBr): 3430, 3240, 1665, 1608, 1590, 1508, 1368, 1285, 1260, 1235, 1165, 1098, 1030 and 825 cm^{-1}; ^{1}H-NMR(DMSO-d_6) : 5.71(1H, s, H-3), 6.20 (1H, s, H-6), 6.25(1H, s, H-8), 6.75(2H, d, J=8.5 Hz, H-3', H-5'), 7.17(2H, d, J=8.5 Hz, H-2', H-6'), 9.60(1H, bs, -OH), 10.11(2H, bs, 2 x -OH); ^{1}H-NMR (acetone-d_6): 5.77(1H, s, H-3), 6.29 (1H, d, J=2.5Hz, H-6), 6.35(1H, d, J=2.5 Hz, H-8), 6.87(2H, d, J=8.5 Hz, H-3', H-5'), 7.22(2H, d, J=8.5 Hz, H-2', H-6'); ^{13}C-NMR (DMSO-d_6): 94.56(C-8), 99.16(C-6), 100.67(C-10), 109.64(C-3), 113.96 (C-3', C-5'), 129.01(C-2', C-6'), 129.90(C-1'), 156.16(C-5), 156.78(C-4'), 157.10 (C-9), 157.45 (C-4), 159.97(C-7), 161.40(C-2); ^{13}C-NMR(acetone-d_6): 95.27(C-8), 99.42(C-6 , C-10), 110.82(C-3), 114.33(C-3', C-5'), 129.11(C-2', C-6') , 130.62(C-1'), 156.50(C-5), 156.96(C-4'), 157.42(C-9), 157.77 (C-4, C-7), 161.47(C-2); eims(m/z) (rel. int.): 271(17), 270(100), 256(6), 243(16), 242(98), 241(8), 213(21), 131(6), 121(16), 115(7), 77(7), 69(23), 55(6), 39(7), 18(8).

5,7-Dyhydroxy-3-(4-hydroxyphenyl)-2H-1-benzopyran-2-one(2). To a solution of **6** (2 g) in 20 ml of ethanol was added NH_3 solution (30 ml, 15%) and the reaction mixture was left for 2 h. Excess of NH_3 and ethanol were removed under reduced pressure and the solid thus obtained crystallized from methanol as light reddish crystals (**2**, 1g), m.p. more than 320°C; λ_{max}^{MeOH} (log ε): 262 (3.87), 360 (4.12); +NaOAc: 273 (4.07), 372 (4.09); NaOMe: 284 (4.04), 421 (4.04); +NaOH: 284(4.02), 419(4.01) nm: ν_{max} (KBr): 3400, 2360, 1705, 1605, 1515, 1455, 1370, 1280, 1235, 1160, 1130, 1075 and 820 cm^{-1}; ^{1}H-NMR (DMSO-d_6): 6.24 (1H, s, H-6), 6.32 (1H, s, H-8), 6.62 (2H, d, J=8.5 Hz, H-3', H-5'), 7.51 (2H, d, J=8.5 Hz, H-2', H-6'), 7.97 (1H, s, H-4), 9.64 (1H, s, -OH), 10.38 (1H, s, -OH), 10.71 (1H, s, -OH); ^{13}C-NMR (DMSO-d_6): 93.53 (C-8), 98.28 (C-6), 102.36 (C-10), 114.95 (C-3', C-5'), 119.71 (C-3), 126.00 (C-1'), 129.25 (C-2', C-6'), 133.96 (C-4), 155.36 (C-9), 155.78 (C-4'), 157.18 (C-7), 160.41 (C-2), 161.48 (C-5); eims (m/z) (rel. int.): 271 (17), 270(100), 243(7), 242(46), 241(4), 213(6), 131(4), 121(18), 77(5), 69(17), 51(4), 43(6), 18(8).

5,7-Dimethoxy-4(4-methoxyphenyl)-2H-1-benzopyran-2-one (3), m.p. 151-52° (lit.[2] m.p. 151-52°C); λ_{max}^{MeOH} (log ε): 257 (3.97) and 318 (4.04) nm; ν_{max} (KBr): 3070, 2975, 2940, 2830, 1710, 1625, 1590, 1510, 1460, 1425, 1355, 1350, 1320, 1282, 1245, 1225, 1205, 1180, 1160, 1110, 1055, 1025, 950, 860, 847 and 800 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.50 (3H, s, C-5-OCH_3), 3.86 (6H, s, C-7- and C-4' - OCH_3), 5.96 (1H, s, H-3), 6.22 (1H, d, J=2.5 Hz, H-6), 6.50 (1H, d, J=2.5 Hz, H-8), 6.87 (2H, d, J=8.5 Hz, H-3', H-5'), 7.20 (2H, d, J=8.5 Hz, H-2', H-6'); ^{13}C-NMR ($CDCl_3$): 54.44 (OCH_3), 55.01 (OCH_3), 55.16 (OCH_3): 93.99 (C-8), 95.44 (C-6), 103.29 (C-10), 112.17 (C-3), 112.46 (C-3', C-5'), 128.43 (C-2', C-6'), 131.77 (C-1'), 155.18 (C-5), 156.93 (C-4'), 158.03 (C-9), 159.33 (C-4), 160.56 (C-2), 163.00 (C-7); eims (m/z) (rel. int.): 313(26), 312 (100), 285(18), 284(61), 270(4), 269(16), 226(3), 198(2), 183(1), 169(1), 156(7), 135(4), 126(2), 77(1), 69(4), 63(2), 32(2), 31(2), 15(3). Anal: $C_{18}H_{16}O_5$ requires : C, 69.23; H, 5.12; found: C, 69.21; H, 5.33%.

4-(4-Acetoxyphenyl)-5,7-diacetoxy-2H-1-benzopyran-2-one (4), m.p 181-82°C (lit[2] m.p. 186-87°C); λ_{max}^{MeOH} (log ε): 282 (4.21) nm; ν_{max}(KBr): 1762, 1750, 1730, 1635, 1625, 1475, 1425, 1362, 1195, 1125, 1075 and 1030 cm^{-1}; ^{1}H-NMR($CDCl_3$): 1.51 (3H, s, C-5-$OCOCH_3$), 2.35 (6H,

s, C-4' - and C-7 - $OCOCH_3$), 6.29 (1H, s, H-3), 6.89 (1H, d, J=2.5 Hz, H-6), 7.30 (3H, m, H-8, H-3', H-5'), 7.46 (2H, d, J=8.5 Hz, H-2', H-6'); ^{13}C-NMR($CDCl_3$): 19.40 ($OCO\underline{C}H_3$), 20.79 ($OCO\underline{C}H_3$), 20.85 ($OCO\underline{C}H_3$), 108.47(C-8), 110.33 (C-10), 113.48 (C-6), 117.31(C-3), 121.60(C-3', C-5'), 128.63 (C-2', C-6'), 134.83 (C-1'), 147.69 (C-5), 150.95(C-4'), 151.99 (C-9), 152.67(C-4), 155.06(C-7), 158.6 (C-2), 167.93($O\underline{C}OCH_3$), 168.59 ($O\underline{C}OCH_3$), 169.15($O\underline{C}OCH_3$); eims (m/z) (rel. int.): 397(4), 396 (15), 355(6), 354(27), 326(5), 313(9), 312(50), 284(7), 271(17), 270(100), 269(23), 242(32), 241(7), 213(8), 178(7), 150(3), 115(2), 85(1), 69(5), 57(4), 41(1), 15(5); Anal: $C_{21}H_{16}O_8$ requires: C, 63.63; H, 4.04; found: C, 63.19; H, 4.41%.

5,7-Dimethoxy-3-(4-methoxyphenyl)-2H-1-benzopyran-2-one(5). To a solution of 2 (0.5 g) in dry acetone (20 ml), anhydrous K_2CO_3 (2.5g) and dimethyl sulphate (0.4 ml) were added. The reaction mixture was worked up after refluxing for 4 hour and the solid obtained crystallized from methanol as brownish crystals (5, 600 mg), m.p. 160-61°C; λ^{MeOH}_{max} (log ε): 350(4.03), 246(4.09) nm; ν_{max} (KBr):2880, 2840, 1715, 1605, 1515, 1460, 1370, 1282, 1250, 1155, 1110, 1025, 952, 835 and 815 cm^{-1}; ^{1}H-NMR ($CDCl_3$): 3.74 (6H, s, C-4' and C-5-OCH_3), 3.78 (3H, s, C-7-OCH_3), 6.18 (1H, s, H-6), 6.31 (1H, s, H-8), 6.85 (2H, d, J=8.5 Hz, H-3', H-5'), 7.51 (2H, d, J=8.5 Hz, H-2', H-6'), 7.92 (1H, s, H-4); ^{13}C-NMR($CDCl_3$): 55.24 (OCH_3), 55.67 (OCH_3), 55.84 (OCH_3), 92.31(C-8), 94.68 (C-6), 104.75 (C-10), 113.69(C-3', C-5'), 122.15(C-3), 127.74 (C-1'), 129.50(C-2', C-6'), 133.92(C-4), 155.74(C-9), 156.65(C-4'), 159.53(C-7), 161.15(C-2), 163.09(C-5); eims (m/z) (rel. int.): 313(21), 312(100), 297(22), 270(7), 269(37), 241(5), 226(11), 183(5), 142(9), 127(5), 77(3), 69(6), 59(2), 15(6); Anal. $C_{18}H_{16}O_5$ requires C, 69.23; H, 5.12; found; C, 69.34; H, 5.62%.

3-(4-Acetoxyphenyl)-5,7-diacetoxy-2H-1-benzopyran-2-one (6). A mixture of phloroglucinaldehyde (3 g) and sodium 4-hydroxyphenylacetate (4.5 g) was refluxed in dry acetic anhydride (30 ml) for 8 h; the reaction mixture on cooling was poured into ice bath, the solid thus obtained crystallized from methanol as light greenish crystals (6, 2.5 g), m.p. 198-99°C; λ^{MeOH}_{max} (log ε): 320(4.17) and 238 (4.15) nm; ν max (KBr): 1780, 1760, 1740, 1620, 1510, 1435, 1370, 1290, 1230, 1200, 1180, 1125, 1105, 1060, 1020, 910 and 890 cm^{-1}; ^{1}H-NMR($CDCl_3$): 2.32 (6H, s, C-4'-and C-5-$OCOCH_3$) 2.44 (3H, s, C-7-$OCOCH_3$), 7.12 (1H, d, J=2.5 Hz, H-6), 7.20 (1H, d, J=2.5 Hz, H-8), 7.33 (2H, d, J=8.5 Hz, H-3', H-5'), 7.85 (2H, d, J=8.5 Hz, H-2', H-6'), 7.94 (1H, s, H-4); ^{13}C-NMR ($CDCl_3$): 20.73 ($OCO\underline{C}H_3$), 20.91 ($OCO\underline{C}H_3$), 20.95 ($OCO\underline{C}H_3$), 107.36 (C-8), 110.94 (C-10), 112.08(C-6), 121.56 (C-3', C-5'), 126.79(C-3), 129.67 (C-2', C-6'), 131.90 (C-1'), 133.16 (C-4), 147.18(C-9), 151.12 (C-4'), 152.37(C-7), 154.06(C-5), 159.46(C-2), 168.03 ($O\underline{C}OCH_3$); 168.10($O\underline{C}OCH_3$), 169.15 ($O\underline{C}OCH_3$); eims (m/z) (rel. int.): 397(31), 396(15), 355(4), 354(20), 313(7), 312(34), 271(16), 270(95), 269(14), 242(17), 241(5), 213(5), 178(3), 150(4), 121(3), 107(15), 77(2), 69(8), 44(2), 43(100), 18(2), 17(7). Anal. $C_{21}H_{16}O_8$ requires; C, 63.63; H, 4.04, found: C, 63.57; H, 4.24%.

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