NOVEL ONE POT CONVENIENT SYNTHESIS OF 3-BENZYLIDENE-2-PHENYL-2,3-DIHYDRO-4H-1-BENZOPYRAN-4-ONES

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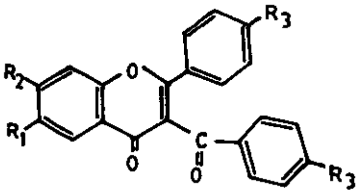
Abstract - A novel one pot good yield synthesis of 3-benzylidene-2-phenyl-2,3-dihydro-4H-1-benzopyran-4-ones by the condensation of o- hydroxyacetophenones with aromatic aldehydes has been described and the new compounds were identified by their chemical, analytical and spectroscopic data.

In connection with our investigastion into the mechanism of dye sensitized photooxygenation of naturally occurring polyphenols[1], we required alkoxy and hydroxy substituted 3-C-benzoylated-2-phenyl-4H-1-benzopyran-4-ones, 1. Literature survey indicates that there is very little work on their fruitful synthesis and C-acylations normally occur at C-6 and C-8 position of the benzopyrones[2]. One way to achieve regioselective or enantioselective synthesis of 1 would be to subject the corresponding 3-benzylidene-2-phenyl-2,3-dihydro-4H-1-benzopyran-4-ones, 2 to the ene reaction with singlet oxygen to lead to the hydroperoxide, 3 or hydroxy derivatives, 4 which could readily be converted to 5 or 1. Alternatively, the naturally occurring flavone or flavanones could be subjected to radical bromination followed by halogen exchange with benzoyl radical.[2] In our experiments, we decided to choose the former method partly because of our experience with singlet oxygen reactions and partly because the yields on the latter method (radical reactions) are expected to be low. The required starting materials for the ene reaction could be prepared by acid catalysed condensation of aromatic aldehydes with 2-phenyl-2,3-dihydro-4H-benzopyran-4-ones obtainable by cyclization of hydroxychalocones, 6, but the yields of chalcones themselves decrease rapidly with increasing hydroxylation level of the corresponding acetophenones and aldehydes from which they are derived, indicating that 2 will in any case be not obtained in more than over all 10-15% yield[3]. In this paper, we report a one pot reaction to synthesize 2 in moderate to good yields which could be converted to required compounds by reaction with singlet oxygen under controlled conditions to avoid formation of degradative products and 5.[4]



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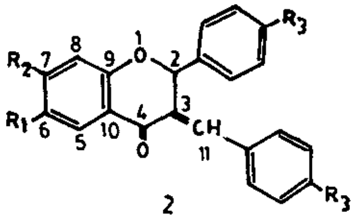

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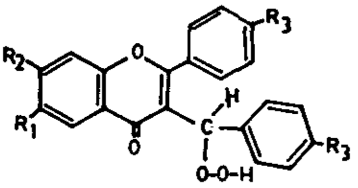

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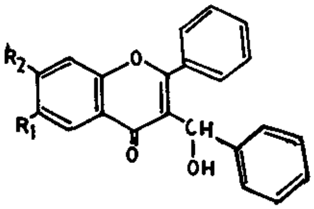

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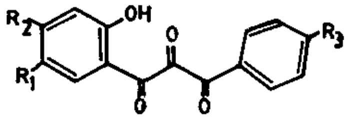

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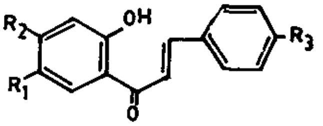


6

a. $R_1=R_2=R_3=H$ b. $R_1=R_2=H, R_3=OCH_3$ c. $R_1=R_3=H$ $R_2=OCH_3$ d. $R_1=H, R_2=R_2=OCH_3$
e. $R_1=OH, R_2=R_3=H$ f. $R_1=H, R_2=OCH_3, R_3=Cl$ g. $R_1=H, R_2=OCH_3, R_3=NO_2$

When 2-hydroxy-4-methoxyacetophenone, for instance, was reacted with benzaldehyde according to the procedure given in the experimental section, two compounds A and B were isolated purely by column chromatography over silica gel. Compound A was identified as 2'-hydroxy-4'-methoxychalcone (6c) by spectral and chemical data and by direct comparison with an authentic sample[5]. Compound B, crystallized as white needles (MeOH), mp 137°C, R_f,0.63 (benzene), IR (KBr) : ν max 1640 (C=0) and 1460 (C=C) cm^{-1}. *In its PMR spectrum, it exhibited* a three proton singlet at δ 3.72 which could be attributed to a methoxy and two one proton singlets at δ 5.30, and 6.35 which could be assigned to C-2 and C-11 protons respectively. The signals for C-5,C-6 and C-8 protons appeared as a doublet, double doublet and a doublet at δ 7.92,7.54 and 7.27 respectively[2,5]. Its mass spectrum exhibited M^+ ion at m/z 342 which lost a methoxyl and a side chain phenyl to give intense fragments at m/z 311 and m/z 265 respectively. Retro Diels-Alder fragments at m/z 192 and m/z 150 and other prominent peaks (Scheme 1) supported the structure of B as 3-benzylidene-7-methoxy-2-phenyl-2,3-dihydro-4H-1-benzopyran-4-one *(2c)*.

It has been observed that the reaction of 2-hydroxy-4-methoxyacetophenone with benzaldehyde yields compound 2c (47%) as against the expected chalcone (23%). When the ratio of aldehyde was increased, the yield of 2c was increased to 70%. The increment in yield was further observed when aldehyde component contained electron withdrawing functionality; for instance p-chlorobenzaldehyde and p-nitrobenzaldehyde gave 2f and 2g in 73% and 81% yield respectively, whereas anisaldehyde gave only 27% of 2d. The spectral characteristics of compounds 2a-g indicate that the chalcones obtained earlier in a similar reaction[3] were in fact not chalcones, but were approximately (4:1) mixture constituted chiefly of 3-benzylidene-2-phenyl-2,3-dihydro-4H-1-benzopyran-4-ones and chalcones.

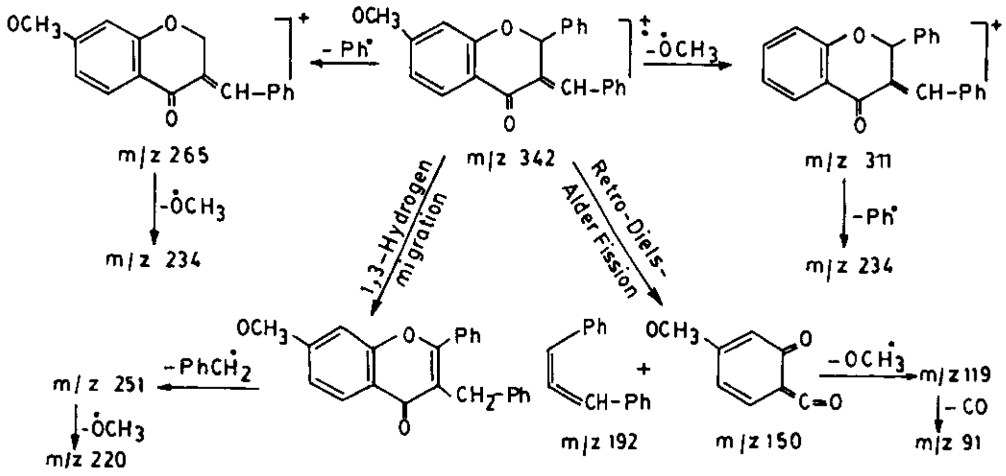
Table 1

S.No.	Acetophenone	Benzaldehyde	Reaction[a] time (h)	Products obtained[b] Chalcone Compound	Yield%[c]	3-benzylidene benzopyran-4-one Compound	Yield%[c]
1.	R_1=R_2=H	R_3=H	52	6a	38	2a	50
2.	R_1=R_2=H	R_3=OCH_3	72	6b	29	2b	38
3.	R_1=OCH_3, R_2=H	R_3=H	62	6c	30	2c	47
4.	R_1=OCH_3, R_2=H	R_3=OCH_3	78	6d	47	2d	27
5.	R_1=H, R_2=OH	R_3=H	58	6e	47	2e	36
6.	R_1=OCH_3,R_2=H	R_3=Cl	42	6f	15	2f	73
7.	R_1=OCH_3,R_2=H	R_3=NO_2	31	6g	11	2g	81

[a] All the reactions were carried out with NaOH(10%) at room temperature.

[b] All the compounds were characterised by their spectroscopic data (NMR,IR and Mass spectra)

[c] The yields are unoptimized.



SCHEME. 1

Examination of the reaction mixture by TLC and NMR measurements indicated that chalcone formation starts after about 4 h whereas 3-benzylidene-2-phenyl-2,3-dihydro-4H-1-ones were formed after approximately 12 h of reaction at room temperature. Increase of temperature did not affect the product distribution.

These observations indicate the intermediacy of a chalcone which may get isomerised to dihydroflavone which further react with benzaldehyde to give 2. Such a conclusion was supported by isolation of a minute quantity of 6-hydroxyflavanone after about 10 h of reaction besides hydroxychalcone and 3-benzylidene benzopyrone when 2',5'-dihydroxyacetophenone was condensed with benzaldehyde and the reaction followed by N.M.R. The yields obtained in the present one pot procedure are better (maximum 81% vs. 27%). and reaction times are much less(maximum of 78 h vs. 4-10 days) when compared with literature[6].

The paper also indicates that the Claisen-Schmidt chalcone synthesis does not lead to the expected Cannizzaro reaction products or conjugates polymers, as suggested earlier[7]. Since 2 could be isolated even when a much lower (approximately one half) concentration of the aldehyde or substituted aldehyde was used and in the presence of electron donating or attracting substituents, the reaction appears to be general and can profitably be employed for the synthesis of these novel unnatural products which are otherwise obtained with difficulty and by a circuitous route . Seven new 3-benzylidene-2-phenyl-2,3-dihydro-4H-1-benzopyran-4-ones (Table 1) were synthesized by the present procedure.

EXPERIMENTAL

Melting points were determined in open capillaries on an electric melting point apparatus (Adair Dutt) and are uncorrect. IR spectra were recorded in KBr on a SP-1200 Grating IR spectrophotometer and 5-DX-Nicolet FT IR spectrophotometer. ^{1}H NMR spectra were recorded on Nicolet-100Mz JEOL-FT NMR spectrometer using TMS as the internal standard and values reported are in δ scale and mass spectra on an JMS-D300 JEOL mass spectrometer at 70 eV. The time allowed for the completion of the reaction and the purity of the prepared compounds were controlled by means of TLC performed on silica gel (BDH, Bombay) plates using iodine for visualizing the spots. Organic solvent extracts were usually dried over anhydrous $MgSO_4$ and solvents used were freshly distilled and purified before use. Petroleum ether solvent refers to the one with the boiling range of 60-80°.

GENERAL REACTION PROCEDURE

In a typical experiment, a solution of 2-hydroxyacetophenone (0.0125 mol) and benzaldehyde (0.0124 mole) in ethanol (15 ml) was added dropwise to an aqueous solution of NaOH (10%, 25 ml) and the mixture stirred vigorously with cooling to keep the temperature well below 5°C. A distinct colour change was observed and progress of the reaction was monitored by TLC. The reaction mixture was left at room temperature for 38-78h, diluted with ice cold water (20 ml) and extracted with diethyl ether (3 x 75 ml) to remove unreacted benzaldehyde. The aqueous portion was acidified with dilute HCl (10%, 10 ml) to yield an orange yellow solid which was subjected to column chromatography over silica gel

(100 g) using petroleum ether, benzene, chloroform and methanol either alone or in the combination mentioned along with description of the compounds as eluting solvents to yield 6 and 2. Physical, spectroscopic and chromatosgraphic data of the compounds are given

2'-hydroxychalcone, 6a (38%), eluted from a mixture of petroleum ether-benzene (5:2), recrystallized from methanol as yellow needles, mp 88^{o}c, Rf, 0.82 (benzene). IR (KBr) : ν max 3350 (OH), 1635 (C=0) and 1440 (C = C) cm^{-1}. PMR (CDCl$_3$, δ): 12.62 (bs, 1H, OH), 7.26 and 6.65 (J=17 Hz,2H, α- and β -H) 6.32-6.81 (m, 9H, aromatic protons). M/z (% abundance): 224(62.5), 207 (12.5), 147(30.0), 131(34.0), 121(100) 103 (20.0). Anal. Found C, 81.30; H, 5.26. $C_{15}H_{12}O_2$ requires C, 80.35 and H, 5.35%.

2'-hydroxy-4-methoxychalcone, 6b (29%), eluted from a mixture of petroleum ether-benzene(4:1), recrystallized from methanol as pale yellow needles, mp 93^{o}c, Rf, 0.88 (benzene).,IR (KBr): ν max 3400 (OH), 1650 (C=0) and 1440(C=C) cm^{-1}. PMR (CDCl$_3$,δ); 12.86 (bs,1H,OH), 3.86 (s.3H,OCH$_3$), 7.25 and 6.86 (J=16 Hz, 2H, α -and β -H), 6.45-7.86 (m,8H,aromatic protons), M/z(% abundance): 254 (92.0), 237 (9.7), 223 (31.5), 161 (14.6), 147(14.6), 133 (100), 121 (78.0), 107(29.2).Anal. Found C, 75.13; H, 5.48 .

$C_{16}H_{14}O_3$, requires C, 75.59 and H, 5.51% .

2'-hydroxy-4'-methoxy chalcone, 6c (30%), eluted from a mixture of benzene-chloroform (10:1), recrystallized from benzene-methanol (3:1) as yellow needles, mp 105^{o}c , Rf, 0.76 (benzene). IR(KBr); ν max. 3400 (OH), 1625 (C=O)and 1460 (C=C) cm^{-1}. PMR (CDCl$_3$,δ) : 12.92 (bs,1H,OH), 3.83 (s,3H,OCH$_3$), 7.26 and 6.54 (J=16Hz, 2H,α-and β-H), 7.91 (d, 1H,6'-H), 7.45 (dd, 1H,5'-H) and 7.19 (d,1H,3'-H). M/z (% abundance): 254(93.7),237(62.5), 223(25.0), 206(38.7), 177(100), 151(58.0), 131(25.0), 103(31.0). Anal. Found. C, 75.13; H, 5.48.$C_{16}H_{14}O_3$ requires C, 75.59 and H, 5.51%.

2'-hydroxy-4,4'-dimethoxychalcone, 6d (47%), eluted from a mixture of benzene-chloroform (5:3), recrystallized from methanol as pale yellow shining crystals , mp 92^{o}c, Rf, 0.84 (benzene). IR(KBr) ν max. 3400 (OH), 1630 (C=O) and 1420 (C=C) cm^{-1}, PMR (CDCl$_3$, δ); 12.90 (s, 1H,OH), 3.85 (s,6H, OCH$_3$), 7.30 and 6.45 (J=17Hz, 2H,α-and β -H), 7.94 (d, 1H,6'-H), 7.56 (dd, 1H,5'H), 7.25 (d, 1H,3'-H). Anal.Found, C, 71.48; H,5.78. $C_{17}H_{16}O_4$ requires C, 71.83 and H,5.63%.

2',5'- dihydroxychalcone, 6e (47%), eluted from a mixture of benzene-chloroform (6:1), recrystallized from methanol as yellow needles, mp 173^{o}c, Rf,0.78 (benzene). IR (KBr): ν max 3350 (OH), 1650 (C=O) and 1420 (C=C) cm^{-1}. PMR (CDCl$_3$,δ); 13.06 (bs,2H, OH), 7.32 and 6.45 (J=17Hz, 2H, α- and β-H), 7.81 (d, 1H, 6'-H), 7.41 (d,1H 3'-H), 7.37 (dd,1H,4'-H). M/z (% abundance): 240 (25.0), 223(15.3), 163(68.2), 137(100),109(13.6),103(23.6).Anal.Found,C,75.93; H, 4.83. $C_{15}H_{12}O_3$ requires C, 75.00 and H, 5.00%.

2'-hydroxy-4'-methoxy-4-chlorochalcone, 6f (15%), eluted from a mixture of petroleum- benzene (1:4),recrystallized from benzene as light yellow needles, mp 96°c, Rf,0.69 (benzene). IR (KBr):νmax 3350 (OH), 1625 (C=O) and 1460(C=C) cm^{-1} PMR (CDCl$_3$ δ); 13.05 (s,1H,OH), 3.86 (s,3H, OCH$_3$), 7.25 and 6.42 (J=16Hz,2H, α- and β-H),7.35 (d, 1H,3'-H), 7.59(dd, 1H,5'-H), 7.91 (s, 1H,6'-H). M/x (% abundance): 289 (35.0), 271(50.0), 253(32.7), 177 (55.0) 165(23.7) 158 (32.7), 151 (50.0), 137 (100), 123(30.0), 111(47.5). Anal.Found C, 66.51; H, 5.42; Cl, 12.03. $C_{16}H_{13}O_3Cl$ requires C,66.66; H, 5.51, and Cl, 12.15%.

2'-hydroxy-4'-methoxy-4-nitrochalcone, 6g (11%), eluted from a mixture of petroleum ether-benzene (1:2) recrystallized from methanol as yellow needles, mp 176°c, Rf, 0.67 (benzene). IR (KBr):νmax. 3340 (OH), 1660(C=O) and 1460 (C=C) cm^{-1}. PMR (CDCl$_3$, δ) 12.30 (bs, 1H, OH), 3.86 (s, 3H,OCH$_3$), 7.25 and 6.43 (J=16Hz, 2H,α- and β-H), 7.32 (d, 1H, 3'-H), 7.43 (dd, 1H, 5'-H), 7.91 (d, 1H, 6'-H). M/z (% abundance): 299 (32.5),, 287(17.2), 253(52.4), 251(31.7), 177 (40.0), 176 (95.0), 151 (100), 148(42.3), 123 (44.0). AnalFound. C, 64.07; H, 4.46; N, 4.52.$C_{16}H_{13}NO_5$ requires C, 64.21; H, 4.34 and N,4.68%.

3- benzylidene-2-phenyl-2,3-dihydro-4H-1-benzopyran-4-one, 2a(50%), eluted from a mixture of cloroform-methanol (5:3), recrystallized from benzene-methanol (4:1) as white needles, mp 198°c, Rf, 0.63 (benzene). IR (KBr):νmax 1680 (C=O) and 1465 (C=C) cm^{-1}. PMR (CDCl$_3$, δ): 5.38 (s,1H,2-H), 6.37 (s,1H,11-H), 6.45-7.82 (m, 14H, aromatic protons). M/z (% abundance): 312 (62.5), 235 (7.5), 221 (100), 192(27.5), 120(95.0) 115 (35.0), 91(17.5). Anal.FoundC, 84.52; H, 5.02.$C_{22}H_{16}O_2$ requires C, 84.61 and H, 5.12%.

3-(4''-methoxy benzylidene)-2-(4'-methoxyphenyl)-2,3-dihydro-4H-1-benzopyran-4-one, 2b (38%), eluted from a mixture of chloroform-methanol (10.3), recrystallized from methanol as white crystals , mp 168°c,Rf, 0.76 (benzene). IR (KBr):νmax. 1680 (C=O) and 1475 (C=C) cm^{-1}. PMR (CDCl$_3$, δ): 3.81 (s,6H,OCH$_3$), 5.36 (s,1H,2-H), 6.09(s,1H,11-H), 6.43- 7.81 (m, 12H, aromatic protons). M/z (% abundance): 372 (29.2), 341 (20.4), 265 (23.7), 252(100), 145 (95.1), 121 (95.0), 120(95.0), 107(41.7). Anal.Found C,76.91; H, 5.29.$C_{24}H_{20}O_4$ requires C, 77.41 and H, 5.37%.

3-benzylidene-2-phenyl-7-methoxy-2,3-dihydro-4H-1-benzopyran-4-one, 2c (47%), eluted from a mixture of chloroform- methanol (10.1), recrystallized from ethanol as white needles, mp 137°c, Rf, 0.63 (benzene). IR (KBr):νmax 1640 (C=O) and 1460 (C=C) cm^{-1}. PMR (CDCl$_3$, δ); 3.72 (s,3H, OCH$_3$), 5.30 (s, 1H, 2-H), 6.35 (s,1H, 11-H), 7.27(d,1H, 8-H), 7.54 (dd, 1H,6-H), 7.92 (d, 1H,5-H). M/z (% abundance) : 342 (17.5), 311 (22.5), 265 (10.0) 251 (10.0), 234(22.5), 192(42.4), 150(100), 119(10.0), 91(15.0). AnalFound C, 79.87; H, 5.20, $C_{23}H_{18}O_3$ requires C, 80.07 and H, 5.26%.

3-(4$''$-methoxybenzylidene)-2-(4$'$-methoxyphenyl)-7-methoxy-2,3-dihydro-4H-1-benzopyran-4-one, 2d (27%), eluted from a mixture of chloroform methanol (10:4), recrystallized from methanol as white crystals mp 121^{o}c, Rf, 0.53 (benzene). IR(KBr): ν max 1665 (C=O)and 1475(C=C) cm^{-1}. PMR ($CDCl_3$, δ); 3.83 (s,9H,OCH_3), 5.38(s,1H,2-H), 6.05 (s,1H,11-H), 7.29(d,1H,8-H), 7.62 (dd, 1H, 6-H), 7.89(d,1H,5-H). M/z (% abundance): 402 (32.6), 371 (52.3), 295 (41.2), 281(27.3), 252(52.3), 150(59.6), 145(58.3), 121 (82.2), 119(49.3), 107(22.3). Anal. FoundC,74.68; H, 5.52.$C_{25}H_{22}O_5$ requires C, 74.62 and H, 5.47%.

3-benzylidene-2-phenyl-6-hydroxy-2,3-dihydro-4H-1-benzopyran-4-one, 2e (36%), eluted from a mixture of chloroform-methanol (10: 1), recrystallized from methanol as white crystals, mp 211^{o}c, Rf, 0.67 (benzene). IR (KBr): νmax. 3400 (OH), 1680 (C=O) and 1460 (C=C) cm^{-1}. PMR ($CDCl_3$, δ): 12.81 (bs, 1H, OH), 5.41 (s, 1H, 2-H), 6.33 (s, 1H, 11-H), 7.96 (d, 1H,5-H), 7.51 (dd,1H,7-H), 7.31 (d, 1H, 8-H). M/z (% abundance) : 328 (7.5), 311 (20.4), 251 (2.5), 237 (97.5), 192 (77.5), 136 (100), 119(8.0), 115 (32.5). Anal.Found C, 79.90; H, 4.83.$C_{22}H_{16}O_3$ requires C, 80.48 and H, 4.87%.

3-(4$''$-chlorobenzylidene)-2-(4$'$-chlorophenyl)-7-methoxy-2,3-dihydro-4H-1-benzopyran-4-one, 2f (73%), eluted from a mixture of chloroform-methanol (5:2), recrystallized from ethanol as white crystals, mp 124^{o}c, Rf, o.37(benzene). IR (KBr): ν max 1680 (C=O),and 1460(C=C) cm^{-1}. PMR ($CDCl_3$, δ): 3.84 (s,3H, OCH_3), 5.32 (s, 1H,2-H), 6.32 (s,1H,11-H), 7.21 (d, 1H,8-H), 7.38(dd, 1H,6-H), 7.91 (s,1H,5-H), M/z (% abundance): 413 (14.6), 412 (29. 2), 382(52.3), 378 (4.8), 301 (23.0), 287(100), 263 (29.2), 228(52.3), 152(13.8), 150 (9.8), 126(9.8). Anal.Found C, 66.61; H, 4.23; Cl, 16.84. $C_{23}H_{16}O_3Cl_2$ requires C, 66.82; H, 4.35 and Cl, 17.10 %.

3-(4$''$-nitrobenzylidene)-2-(4$'$-nitrophenyl)-7-methoxy-2,3-dihydro-4H-1-benzopyran -4-one,2g (81%), eluted from a mixture of chloroform-methanol (3:2), recrystallized from methanol as light yellow crystals, mp 168^{o}c, Rf. 0.31 (benzene). IR(KBr): ν max 1680 (C=O) and 1460(C=C) cm^{-1}. PMR ($CDCl_3$, δ): 3.80 (s,3H, OCH_3), 5.38 (s,1H,2-H), 6.65 (s,1H,11-H), 7.26 (d,1H,8-H), 7.42(dd, 1H,6-H), 8.02(d,1H, 5-H). M/z (% abundance): 432 (26.4), 401(27.5), 386 (32.0), 340(52.4), 310(34.0), 296(72.6), 282(82.0), 150(100), 136(32.0), 122(52.6). Anal.Found C; 63.32; H, 3.61; N, 6.41.$C_{23}H_{16}N_2O_7$ requires C,62.88; H, 3.70 and N, 6.48%.

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