

## Synthesis and Reactions of 4-[(4-Oxo-4H-1-Benzopyran-2-yl) Methylene]-2-Phenyl-5(4H)-Oxazolone

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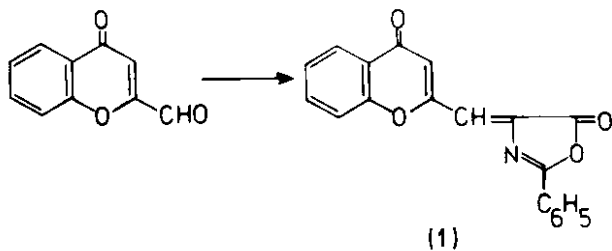
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**Summary:** Azlactone 1 reacted with hydrazines and some amino compounds gave the corresponding hydrazides and amides. Treatment of 1 with sodium hydroxide or sodium acetate gave 3 a or b respectively. Also 1 reacted with Grignard reagents to give 4a-e. Configurational assignment of the new compounds was based on elemental analysis, IR and NMR spectroscopic evidences.

Interest in azlactones is due to their importance as versatile synthetic 507 intermediate as well as to some pharmacological activity, accordingly a variety of aryl- and hetero-aryl- substituted azlactones have been reported<sup>1,2</sup>.

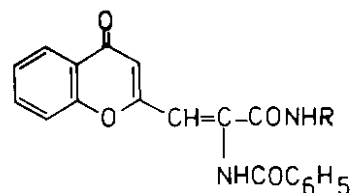
Condensation of chromone-2-carboxaldehyde<sup>3</sup> with hippuric acid in acetic anhydride-sodium acetate gave 4-[(4-oxo-4H-1-benzopyran-2-yl) methylene]-2-phenyl-5(4H)-oxazolone (1), characterized by its IR spectrum, bands at 1800 (C=O of oxazolone), 1710 (C=O of  $\gamma$ -pyrone) 1655 (C=N), and 1612  $\text{cm}^{-1}$  (C=C). The NMR spectrum of 1 in  $\text{CDCl}_3$  showed signals at  $\delta$ 7.3 (s, 1H, C<sub>3</sub>-H), 7.4–7.9 (m, 9H, Ar-H), and 7.8 ppm (s, 1H, C<sub>2</sub>-CH=).



The azlactone 1 behaves for the most part like anhydrides towards nucleophilic reagents, which is usually at the electrophilic carbonyl carbon atom with ring opening.

Treatment of oxazolone 1 with hydrazines, amines, benzamide, and glycine gave the corresponding 2-(benzoylamino)-3-(4-oxo-4H-1-benzopyran-2-yl)-2-propenoic acid hydrazides (2a and b), or *N*-(2-(4-oxo-4H-1-benzopyran-2-yl)-1-(aralkylamino) carbonylethenyl) benzamides (2c-k) respectively.<sup>4</sup> The IR spectra of compounds 2 showed the absence of  $\nu$  C=O of oxazolone and presence of  $\nu$  NH in the range 3200 - 3300  $\text{cm}^{-1}$  while 2K showed bands at 1720 and 3420  $\text{cm}^{-1}$  (COOH). The NMR spectrum of 2b in DMSO showed signals at  $\delta$ 6.7 (s, 1H, C<sub>2</sub>-CH=), 7.2 (s, 1H, C-H), 7.4–7.9 (m, 14H, Ar-H) and

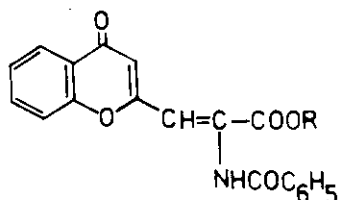
8.1, 8.4 & 8.9 ppm (s, 3H, three NH). The NMR spectrum of 2i in DMSO showed signals at  $\delta$ 3.7 (s, 3H, OCH<sub>3</sub>), 6.8 (s, 1H, C<sub>2</sub>-CH=), 7.1 (s, 1H, C<sub>3</sub>-H), 7.5 - 7.9 (m, 13H, Ar-H), and 8.5 & 8.9 ppm (s, 2H, two NH). The NMR spectrum of 2k in  $\text{CDCl}_3$  showed signals at  $\delta$  1.2 (t, 2H, N-CH<sub>2</sub>), 3.8 (t, 1H, =C-OH), 6.1 (s, 1H, C<sub>2</sub>-CH=), 7.1 (s, 1H, C<sub>3</sub>-H), 7.3 - 8.0 (m, 9H, Ar-H), 10.5 (s, H, COOH) and 8.7 ppm (s, 1H, NH).



- |   |   |  |
|---|---|--|
| a) R = NH <sub>2</sub>                                    | : | b) R = NHC <sub>6</sub> H <sub>5</sub>                   |
| c) R = C <sub>2</sub> H <sub>5</sub>                      | : | d) R = n-C <sub>4</sub> H <sub>9</sub>                   |
| e) R = iso-C <sub>4</sub> H <sub>9</sub>                  | : | f) R = furfuryl  |
| g) R = CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>      | : | h) R = C <sub>6</sub> H <sub>4</sub> -CH <sub>3</sub> -p |
| i) R = C <sub>6</sub> H <sub>4</sub> -OCH <sub>3</sub> -p | : | j) R = COC <sub>6</sub> H <sub>5</sub>                   |
| k) R = CH <sub>2</sub> COOH                               | : |  |

Azlactone 1 is not hydrolyzed by water but is easily cleaved by treatment with aqueous ethanolic sodium hydroxide to give 2-(benzoylamino)-3-(4-oxo-4H-1-benzopyran-2-yl)-2-propenoic acid (3a). Methanoylsis with sodium acetate give methyl 2-(benzoylamino)-3-(4-oxo-4H-1-benzopyran-2-yl)-2-propenoate (3b). The IR spectrum of 3a showed bands at 1680 and 3320  $\text{cm}^{-1}$  (COOH), while for 3b at 1730 (C=O of ester) and 3180  $\text{cm}^{-1}$  (NH). The NMR spectrum of 3a in  $\text{CDCl}_3$  showed signals at  $\delta$ 6.7 (s, 1H, C<sub>2</sub>-CH=), 7.1 (s, 1H, C<sub>3</sub>-H), 7.3-7.7 (m, 9H, Ar-H), 8.7 (s, 1H, NH), and 12.2 ppm (s, 1H, COOH). The NMR spectrum of 3b in  $\text{CDCl}_3$  showed signals at  $\delta$ 4.0 (s, 3H, COOCH<sub>3</sub>), 6.8

(s, 1H, C<sub>2</sub>-CH=), 7.2 (s, 1H, C<sub>3</sub>-H), 7.3-7.9 (m, 9H, Ar-H) and 8.3 ppm (s, 1H, NH).

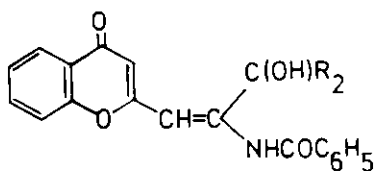


(3)

a) R = H

b) R = CH<sub>3</sub>

Treatment of the azlactone 1 with Grignard reagents<sup>4,5</sup> gave *N*-[1-(hydroxydiaralkylmethyl)-2-(4-oxo-4*H*-1-benzopyran-2-yl) vinyl] benzomides (4a-e). The IR spectra of 4 showed bands at 3400 cm<sup>-1</sup> (OH) and the absence of νC=O of 5-oxazolone. The NMR spectrum of 4a in CDCl<sub>3</sub> showed signals at δ1.4 (s, 1H, OH), 2.3 (s, 6H, two CH<sub>3</sub>), 7.0 (s, 1H, C<sub>2</sub>-CH=), 7.3 (s, 1H, C<sub>3</sub>-H), 7.4-7.7 (m, 9H, Ar-H), and 8.7 ppm (s, 1H, NH), while for 4C signals centered at 2.1 (s, 1H, OH), 6.9 (s, 1H, C<sub>2</sub>-CH=), 7.2 (s, 1H, C<sub>3</sub>-H), 7.4-7.9 (m, 19H, Ar-H), and 8.5 ppm (s, 1H, NH).



(4)

a) R = CH<sub>3</sub>b) R = cyclo-C<sub>3</sub>H<sub>5</sub>c) R = C<sub>6</sub>H<sub>5</sub>d) R = C<sub>6</sub>H<sub>4</sub>-CH<sub>3</sub>-pe) R = C<sub>6</sub>H<sub>4</sub>-OCH<sub>3</sub>-p

## Experimental

All melting points are not corrected. The infrared absorption spectra were determined with a Beckmann IR-20A Spectrophotometer using KBr Wafer technique. The NMR spectra were measured by Varian T60 Spectrophotometer using TMS as internal standard.

### 4-[(4-Oxo-4*H*-1-benzopyran-2-yl)methylene]-2-phenyl-5(4*H*)-oxazolone (1).

An equimolar mixture of chromone-2-carboxaldehyde and finely powdered hippuric acid (0.1 mol) was heated on a steam-bath with addition of sodium

acetate (0.05 mol) and acetic anhydride (0.3 mol) for 2 hr. The mixture was then cooled and after addition of ethanol (20 ml) kept overnight. The solid product was filtered off, washed with water (100 ml) followed by ice-cold ethanol (20 ml), and crystallized to give oxazolone 1 as yellow crystals (cf. Table.1).

### Reaction of the azlactone 1 with amino compounds. Formation of 2a-k.

A solution of azlactone 1 (0.01 mol) and the required hydrazine, amine, benzamide, or glycine (0.01 mol) in ethanol (50 ml) was refluxed for 8 hr. The solid which separated after concentration and cooling was filtered and crystallized from the proper solvent to give the corresponding hydrazide or amide 2a-k as yellow crystals. The results are listed in Table.1.

### 2-(Benzoylamino)-3-(4-oxo-4*H*-1-benzopyran-2-yl)-2-propenoic acid (3a).

The azlactone 1 (0.01 mol) was refluxed in ethanol (50 ml) containing sodium hydroxide (0.01 mol/2ml H<sub>2</sub>O) for 3 hr. The solution was concentrated and poured into water (100 ml) and then acidified with HCl (2% solution). The solid was filtered, washed with water, dried, and crystallized to give 3a as pale yellow crystals (cf. Table 1).

### Methyl-2-(benzoylamino)-3-(4-oxo-4*H*-1-benzopyran-2-yl)-2-propenoate (3b).

A suspension consisting of methanol (30 ml), the oxazolone 1 (0.01 mol), and sodium acetate (0.05 mol) was kept under reflux for 30 hr. The solid product which separated after concentration and cooling was filtered off and recrystallized to give the ester 3b as yellow crystals (cf. Table 1).

### Reaction of the azlactone 1 with Grignard reagents.

#### Formation of 4a-e.

An ethereal solution (100 ml) of methylmagnesium iodide, cyclopropyl, phenyl, *p*-tolyl, or *p*-methoxyphenylmagnesium bromide (0.05 mol) was added during 30 min. to a fine suspension of azlactone 1 (0.01 mol) in ether (50 ml). The mixture was refluxed on steam-bath for 4 hr., left overnight, and finally hydrolyzed with saturated aqueous ammonium chloride. The ether was evaporated and the residue was filtered, washed with water, and crystallized to give 4a-e respectively as yellow crystals. The results are listed in Table 1.

Table 1.

Physical data of the products 1-4.

Comp.	M.P. °C	Yield %	Solvent crystn.	Mol. Formula	Analysis %		
					C	H	N
1	176	93	A	$C_{19}H_{11}NO_4$	71.92	3.47	4.42
					71.76	3.36	4.34
2a	155	67	E	$C_{19}H_{15}N_3O_4$	65.33	4.30	12.03
					65.18	4.21	11.87
2b	218	74	A	$C_{25}H_{19}N_3O_4$	70.59	4.47	9.88
					70.38	4.40	9.69
2c	172	61	E	$C_{21}H_{18}N_2O_4$	69.61	4.97	7.73
					69.37	4.85	7.62
2d	228	73	E	$C_{23}H_{22}N_2O_4$	70.77	5.64	7.18
					70.62	5.57	7.09
2e	223	75	E	$C_{23}H_{22}N_2O_4$	70.77	5.64	7.18
					70.54	5.58	7.03
2f	249	78	A	$C_{24}H_{18}N_2O_5$	69.57	4.35	6.76
					69.48	4.30	6.69
2g	201	72	E	$C_{26}H_{20}N_2O_4$	73.58	4.72	6.60
					73.50	4.68	6.47
2h	234	78	A	$C_{26}H_{20}N_2O_4$	73.58	4.72	6.60
					73.53	4.66	6.49
2i	209	77	A	$C_{26}H_{20}N_2O_5$	70.91	4.55	6.36
					70.80	4.52	6.28
2j	230	68	E	$C_{26}H_{18}N_2O_5$	71.23	4.11	6.39
					71.11	4.07	6.27
2k	190	63	A	$C_{21}H_{16}N_2O_6$	64.29	4.08	7.14
					64.17	4.00	7.11
3a	108	60	M	$C_{19}H_{13}NO_5$	68.06	3.88	4.18
					67.93	3.82	4.08
3b	153	57	M	$C_{20}H_{15}NO_5$	68.77	4.30	4.01
					68.72	4.24	3.93
4a	274	64	B	$C_{21}H_{19}NO_4$	72.21	5.44	4.01
					72.08	5.42	3.93
4b	250	60	B	$C_{25}H_{23}NO_4$	74.81	5.74	3.49
					74.73	5.71	3.34
4c	265	76	B	$C_{31}H_{23}NO_4$	78.65	4.86	2.96
					78.57	4.78	2.88
4d	262	74	B	$C_{33}H_{27}NO_4$	79.04	5.39	2.79
					78.96	5.32	2.72
4e	266	78	B	$C_{33}H_{27}NO$	74.30	5.07	2.63
					74.26	5.00	2.54

A = Acetic acid; B = Benzene; E = Ethanol; M = Methanol

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