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BENZOPYRANS. PART 44.[1] SYNTHESIS OF 3-(4-OXO-4*H*-1-BENZOPYRAN-2-YL)INDOLIZINES

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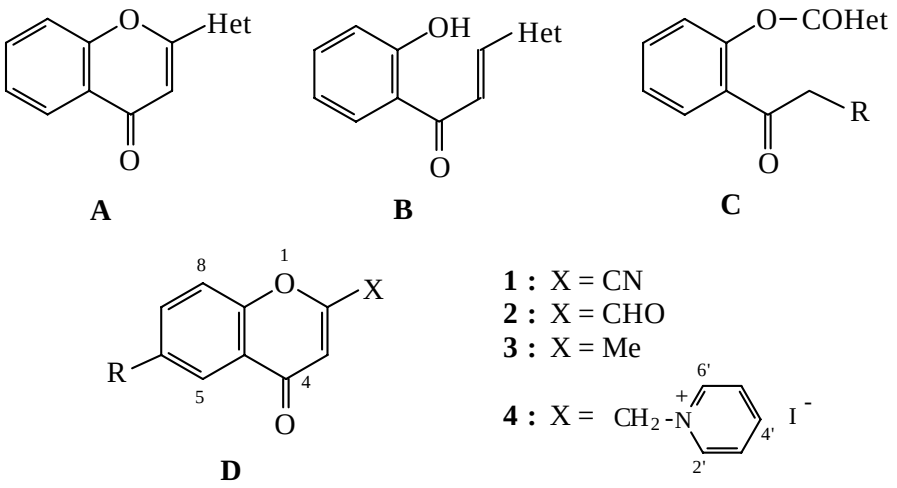
Abstract – The pyridinium methylid (**5**), generated from 1-(4-oxo-4*H*-1-benzopyran-2-yl)methylpyridinium iodide (**4**) in the presence of a base, undergoes [3+2] cycloaddition with dimethyl acetylenedicarboxylate and ethyl propiolate, the cycloadducts rapidly aromatising to the indolizines (**8**) and (**9**), respectively. Similar cycloaddition of **5** with ethyl acrylate and acrylonitrile is also followed by dehydrogenation giving respectively the indolizines (**9**) and (**10**).

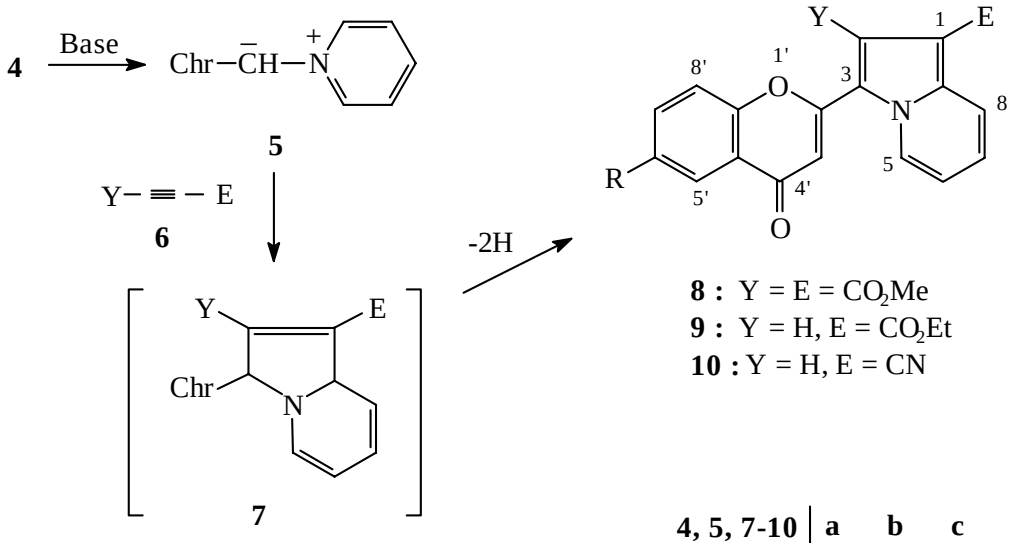
The finding of biological activity of 2-(5-tetrazolyl)chromone[2] has led to a spate of synthesis of various heterocycles directly linked to 2-position of 1-benzopyran-4-one (chromone) as generally represented by **A**. These can be prepared by (i) dehydrogenative cyclisation of the chalcones B, derived from hetaryl aldehydes and 2-hydroxyacetophenone,[3] (ii) Baker-Venkataraman transformation of appropriate *O*-acylacetophenones **C** (R = H, Ph),[4] and (iii) elaboration of X functionality of **D** to a heterocyclic system without affecting its chromone moiety. Preparation of 2-(5-tetrazolyl)chromone by heating the nitrile (**1**) with sodium azide – ammonium chloride in DMF[2,5] and that of the Hantzsch ester substituted with the chromon-2-yl moiety at 4-position by treating the aldehyde (**2**) with ethyl β-aminocrotonate[6] illustrate the last named method which has recently been gaining popularity. Another addition to this illustration is the conversion of 2-methylchromone (**3**) into the title indolizines as described in this paper.

Methyl group of 2-methylchromone (**3**) is sufficiently active so as to react with iodine and pyridine forming the 1-alkylpyridinium iodide (**4**)[7] which is likely to form the ylid (**5**) in the presence of a base. The formation of indolizine derivatives by [3+2] cycloaddition of pyridine related ylids with acetylenic esters is well known. As for example, 1-pyridinium phenacylid and dimethyl acetylenedicarboxylate



(DMAD) in the presence of palladium on charcoal gives dimethyl 3-benzoylindolizine-1,2-dicarboxylate.[8] The intermediate dihydroindolizines obtained by addition of pyridinium ylids with DMAD and other activated acetylenes usually undergo rapid aromatisation even in the absence of any exogenous dehydrogenating agent.[9] The pyridinium iodide (**4**) with equimolar amount of DMAD (**6**, Y = E = CO_2Me) in refluxing acetone containing potassium carbonate yielded in our hands the 3-substituted indolizine (**8**) (Tables 1-3), the intermediate dihydroindolizine (**7**) resulting from [3+2] cycloaddition of pyridinium methylid (**5**) with DMAD not being isolated (Scheme 1). Ethyl propiolate (EP) (**6**, Y = H, E = CO_2Et) like DMAD reacted with **4** giving the indolizine (**9**) (Tables 1-3) *via* **7** (Y = H, E = CO_2Et). Similar treatment of **4** with ethyl acrylate and acrylonitrile gave respectively the indolizines (**9**) and (**10**) (Tables 1-3) albeit in low yield evidently *via* the tetrahydroindolizine intermediate (**7**, Y = H; E = CO_2Et or CN; 1,2-double bond reduced). These results indicate that the ylid (**5**) is highly reactive towards activated alkynes as well as alkenes. All the indolizines (**8**-**10**) when dissolved in chloroform give blue fluorescence.

Scheme 1



Chr = 4-oxo-4*H*-1-benzopyran-2-yl

4, 5, 7-10	**a**	**b**	**c**
R =	H	Me	Cl

Table 1 – Analytical data of the indolizines (**8**-**10**)

Compd	Yield (%)	Mp (ºC)	Analysis					
			Calculated			Found		
			C	H	N	C	H	N
8a	54		66.8	4.0	3.7	66.5	3.7	3.9
8b	44	186	67.5	4.4	3.6	67.7	4.2	3.4
8c	67	232	61.2	3.4	3.4	61.6	3.5	3.2
9a	48	199	72.1	4.5	4.2	72.4	4.7	4.0
9b	43	186	72.6	4.9	4.0	72.3	4.5	4.2
9c	70	206	65.3	3.8	3.8	65.7	3.4	3.6
10a	28	220(decomp)	75.5	3.5	11.2	75.2	3.7	11.0
10b	37	224	76.0	4.0	9.3	76.3	3.7	9.6
10c	25	227(decomp)	67.4	2.8	8.7	67.6	3.0	9.0

Table 2 – ^{1}H-NMR spectral data[a] (δ in $CDCl_3$) of the indolizines (**8**-**10**)

Compd	5-H, 8-H	5´-H	2-H (s)	7´-H, 8´-H	7-H, 6-H	3´-H (s)	CO_2Me (s) or CO_2CH_2Me(q)	CH_2*Me* (t), 6´-Me (s)
8a[b]	8.55, 8.37	8.25		7.72, 7.47	7.32, 7.00	6.67	3.99, 3.93	
8b	8.50, 8.25	7.91		7.45, 7.30	7.24, 6.94	6.56	3.94, 3.87	—, 2.40
8c	8.52, 8.32	8.14		7.62, 7.40	7.32, 7.01	6.63	3.97, 3.94	
9a[b]	8.82, 8.30	8.17	7.75	7.68 ——— 6.22			4.33	1.40, —
9b	8.73, 8.19	7.83	7.62	7.37, 7.29	7.16, 6.87	6.48	4.30	1.36, 2.33
9c	8.76, 8.29	8.07	7.72	7.56, 7.46	7.23, 6.95	6.56	4.35	1.40, —
10a[b]	8.86, 7.80	8.25	7.60	7.73 7.55	7.32, 7.05	6.69		—,
10b	8.85 7.77	8.00	7.56	7.52 7.43	7.30 7.04	6.63		2.37
10c	8.83, 7.82	8.22	7.62	7.68, 7.52	7.34 7.07	6.69		

[a]Aryl protons and indolizinyl protons at positions 5-8 show normal splitting pattern.
[b] 6´-H of **8a**, **9a** and **10a** appears at around δ 7.47.

Table 3 – ^{13}C-NMR spectral data ($CDCl_3$) of the indolizines (**8-10**[a])

Carbon No./ Type	**8a**	**8b**	**8c**	**9a**	**9b**	**9c**	**10a**	**10b**
1	103.9	103.9	104.3	106.8	nd	107.1	nd	86.4
2	126.8	126.6	127.1	120.9	120.6	121.2	121.0	120.9
3	nd	115.5	nd	117.1	117.0	116.7	nd	118.3
5	125.5	125.5	125.4	126.3	126.3	126.3	126.6	126.7
6	115.2	155.1	115.3	114.4	114.3	114.6	115.1	115.0
7	125.1	125.2	125.2	124.5	124.3	124.7	124.7	124.7
8	120.8	120.6	120.9	120.4	120.3	120.5	118.6	118.6
8a	137.3	137.2	137.5	139.0	138.8	139.2	nd	140.7
2′	156.0	154.6	155.1	157.6	157.0	157.4	156.2	156.0
3′	110.7	110.6	110.6	106.9	106.3	106.5	108.2	108.0
4′	177.5	177.3	176.0	177.1	177.0	175.7	177.1	177.2
4′a	124.0	123.7	125.2	124.2	123.7	125.0	124.3	124.0
5′	125.9	125.2	125.5	125.8	125.0	125.2	126.0	125.4
6′	125.7	135.6	131.8	125.4	135.3	131.4	125.7	135.9
7′	134.1	135.1	134.2	133.5	134.5	133.6	133.9	135.1
8′	117.7	117.3	119.4	117.5	117.1	119.1	117.6	117.4
8′a	154.8	154.3	154.4	155.7	153.7	153.9	155.8	154.1
CO_2R	165.8	165.3	165.5	163.7	163.6	163.6		
	163.3	163.1	163.2					
CO_2*Me*	53.1	52.8	52.9					
	51.7	51.4	51.5					
CO_2*C*H_2Me				60.0	59.9	60.0		
CO_2CH_2*Me*				14.5	14.4	14.5		
6′-Me		20.8			20.7			20.9

[a]Cyano carbon of **10** evades detection; nd = not detected.

In the NMR spectrum of unsubstituted indolizine in CCl_4 as well as $CDCl_3$ solution, its 5- and 8-H appear at δ *ca.* 7.70 and 7.25, respectively.[10] Methoxycarbonyl group at 1-position of indolizine deshields 8-H and that at 3-position deshields 5-H by *ca.* 1.0 and 1.6 ppm, respectively.[11] So in the ^{1}H-NMR spectra of **8** and **9**, the appearance of 8-H at δ *ca.* 8.30 is quite expected, the chromone moiety at their 3-position also exerting a deshielding effect on 5-H by the extent of nearly 0.8 ppm. Furthermore, $J_{5,6}$ and $J_{7,8}$ values

respectively as *ca.* 7.0 and 9.0 Hz conform to the values recorded for several substituted and unsubstituted indolizines.[10]

Carbons at positions 1-3 and 5-8 of unsubstituted indolizine appear at δ *ca.* 99, 114, 113, 125, 110, 117 and 120 ppm, respectively.[12] The ^{13}C-chemical shift data (Table 3) of substituted indolizines (**8**) and (**9**) reveal that an alkoxycarbonyl group at 1-position brings about a downfield shift of both 1-C and 2-C by nearly 6 ppm, the latter peak being shifted further downward by introduction of a second alkoxy group at 2-position. A downfield shift by about 4 ppm of 3-C of 3-substituted indolizines (**8**-**10**) *vis-à-vis* that of the unsubstituted one is quite expected whereas the substitution at 1-3 positions have little effect on 5-8 carbon peaks.

EXPERIMENTAL

Yields and uncorrected melting points of the crystallised products are reported and no attempt was made to optimise the yield. IR spectra were recorded on a Perkin-Elmer 782 and NMR on a Bruker AM 300L spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C NMR spectra, respectively.

1-(4-Oxo-4*H*-1-benzopyran-2-yl)methylpyridinium iodides (**4a-c**).

These were prepared in 50-70% yield by heating the appropriate 2-methylchromone (**3**) dissolved in pyridine with powdered iodine as described in the literature[7] and crystallised from DMF. The pyridinium iodide (**4a**) had mp 220ºC (DMF) (lit.,[7] mp 200-205 ºC); δ_H (DMSO-d_6) : 9.22 (2H, d, J = 6.0, 2´,6´-H), 8.70 (1H, t, J = 7.8, 4´-H), 8.23 (2H, dd, J = 7.8, 6.0 Hz, 3´-,5´-H), 7.98 (1H, dd, J = 7.8, 1.3, 5-H), 7.78 (1H, ddd, J = 8.4, 7.8, 1.5, 7-H), 7.55 (1H, d, J = 8.4, 8-H), 7.47 (1H, dd, J = 8.5, 7.4, 6-H), 6.59 (1H, s, 3-H) and 5.95 (2H, s, CH_2); δ_C (DMSO-d_6) : 176.7 (CO), 159.5 (2-C), 155.8 (8a-C), 147.0 (4´-C), 145.7 (2´-,6´-C), 134.8 (7-C), 128.6 (3´-,5´-C), 126.0 (5-C), 124.9 (6-C), 123.2 (4a-C), 118.4 (8-C), 112.2 (3-C) and 60.5 (CH_2).

4b : mp 224ºC (DMF). Anal. Calcd for $C_{16}H_{14}NO_2$ I : C, 50.7; H, 3.7; N, 3.7. Found : C, 50.4; H, 3.3; N, 3.9. δ_H (DMSO-d_6) : 9.27 (2H, d, J = 5.9, 2´-, 6´-H), 8.71 (1H, t, J = 7.8, 4´-H), 8.25 (2H, dd, J = 7.8, 5.9, 3´-, 5´-H), 7.67 (1H, ill split d, 5-H), 7.54 (1H, dd, J = 8.6, 1.7, 7-H), 7.42 (1H, d, J = 8.6, 8-H), 6.57 (1H, s, 3-H), 5.99 (2H, s, CH_2) and 2.31 (3H, s, Me); δ_C (DMSO-d_6) : 176.6 (4-C), 159.2 (2-C), 153.9 (8a-C), 146.9 (4´-C), 145.6 (2´-, 6´-C), 135.6 (7-C), 135.5 (6-C), 128.5 (3´-, 5´-C), 124.0 (5-C), 122.8 (4a-C), 118.1 (8-C), 111.9 (3-C), 60.4 (CH_2) and 20.4 (Me).

4c : mp. 234ºC (DMF). Anal. Calcd for $C_{15}H_{11}N\,O_2Cl$ I. C, 45.1; H, 2.8; N, 3.5. Found : C, 44.8; H, 3.0; N, 3.2. δ_H (DMSO-d_6) : 9.23 (1H, d, J = 5.8, 2´-, 6´-H), 8.70 (1H, t, J = 7.8, 4´-H), 8.24 (2H, dd, J = 7.8, 5.8, 3´-, 5´-H), 7.84 (1H, d, J = 2.6, 5´-H), 7.79 (1H, dd, J = 8.9, 2.6, 7-H), 7.62 (1H, d, J = 8.9, 8-H), 6.65

(1H, s, 3-H) and 6.00 (2H, s, CH_2); δ_C (DMSO-d_6) : 175.6 (4-C), 159.7 (2-C), 154.3 (8a-C), 146.9 (4´-C), 145.7 (2´-, 6´-C), 134.5 (7-C), 130.2 (6-C), 128.5 (3´-, 5´-C), 124.2 (4a-C), 123.6 (5-C), 120.9 (8-C), 112.1 (3-C) and 60.4 (CH_2).

General procedure for the treatment of **4** with acetylenic and olefinic esters

The pyridinium iodide (**4**) (1 mmol) and DMAD or EP (0.2-0.3 mL, 2-3 mmol) were refluxed together in dry acetone (200 mL) containing anhydrous potassium carbonate (~ 10 g) for 10-12 h, the color of the solution changing from yellow to reddish violet. The solution was filtered hot, the filtrate concentrated, the deposited solid filtered off and crystallised from chloroform-light petroleum. By this method the pyridinium salt (**4**) gave the yellow colored indolizines (**8**) and (**9**) (Tables 1-3) with DMAD and EP, respectively. Similar treatment of **4c** with ethyl acrylate gave in 27% yield a product identical (mp, mixed mp, TLC and IR) with indolizine (**9c**). IR (KBr) for **8a** : 1730 (ester CO), 1697 (ester CO) and 1649 (pyrone CO) cm^{-1}. IR (KBr) for **9c** : 1697 (ester CO) and 1650 (pyrone CO) cm^{-1}.

3-(4-Oxo-4*H*-1-benzopyran-2-yl)indolizine-1-carbonitriles (**10**)

The pyridinium iodide (**4**) (1 mmol) was reacted with excess acrylonitrile (~ 0.2 mL) similarly as described for the treatment of **4** with acetylenic esters. The filtrate obtained after filtering the reaction mixture gave on concentration an oily mass which was chromatographed over a column of silica gel. The yellow solid material eluted by a mixture of ethyl acetate-light petroleum (1:4) was found to be a mixture of two components having very close R_f values. The relatively more polar component separated by preparative TLC of the above mixture was crystalized from chloroform-light petroleum to yield **10** (Tables 1-3) as shining yellow crystals; the other minor component of the mixture could not be obtained in pure form and it remained unidentified. IR (KBr) for **10a** : 2218 (CN) and 1629 (CO) cm^{-1}. IR (KBr) for **10b** : 2211 (CN) and 1614 (CO) cm^{-1}.

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