Some New 4-Oxo-4H-1-Benzopyran Derivatives

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Summary: Some 4-oxo-4H-1-benzopyrans bearing the 1,3,4-thiadiazole moiety were prepared. These include 2(2'-amino or acylamino-1,3,4-thiazol-5'-yl)-4-oxo-4H-1-benzopyrans (flavone analog) and some N-(1,3,4-thladiazolyl-4-oxo-4H-1-benzpyran-2-carboxamides.

2-(1,3,4-thiadiazolyl) analogues of flavone

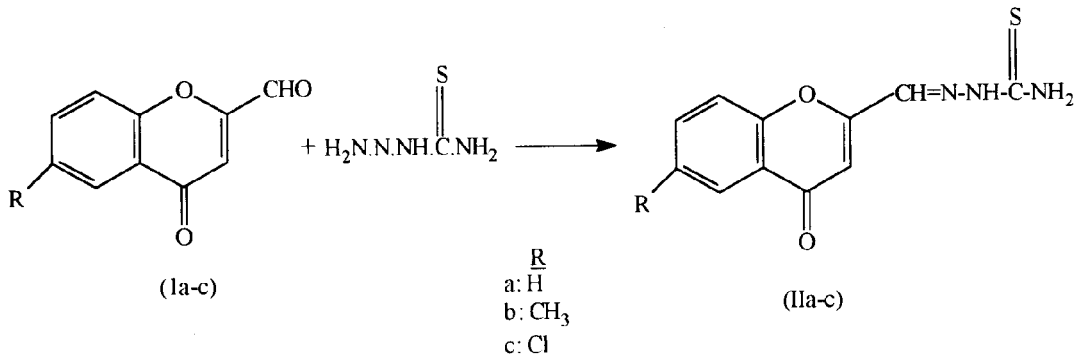
Many publications describing the synthesis of 2-heterocyclic chromones (flavone analogues), have prompted us to prepare other heterocyclic analogues. Herein we take the 1,3,4-thiadiazole moiety as the heterocyclic ring because of its pharmacological importance [1]. In this work we describe the synthesis of 2-(2'-amino or acylamino-1,3,4-thiazol-5'-yl)-4-oxo-4H-1-benzopyrans (IV). There are two routes for the synthesis of 2-amino-1,3,4-thiadiazole ring, one starts from 1-acylthiosemicarbazides followed by elimination of water [2]. The other employes aldehydes thiosemicarbazone, which are cyclized by oxidation with ferric chloride [3].

Attempted synthesis of 2(2'-amino-1,3,4-thiadiazol-5'-yl)-4-oxo-4H-1-benzopyrans through the first route was unsuccessful. However on trying the second route, through cyclization of 4-oxo-4H-1-benzopyran-2-carboxaldehyde thiosemicarbazone with ferric chloride satisfactory results were obtained.

When 4-oxo-4H-1-benzopyran-2-carboxaldehydes **Ia-c** were allowed to react with thiosemicarbazide at room temperature, the corresponding thiosemicarbazones **IIa-c** were formed.

All compound **IIa-c** have correct analytical data; their IR spectra showed bands at 3380-3330, 3270, 3180-3160 (NH), 1640 (C=O pyrone) and at 1620-1605 cm^{-1} (C=N). The PMR spectrum of compound **IIc** taken as an example showed the following signals at δ 12.3 (1H, s, N-N-H-C=S), exchangeable with D_2O), 8.5 (2H, d, S=C-NH_2, exchangeable with D_2O), 7.97-7.79 (4H, m, ArH + -CH=N-), and 7.12 (1H, s, H-3).

It is known that oxidation of aldehydes thiosemicarbazones gives different heterocyclic systems depending on the reagent used for oxidation [4]. For obtaining the 2-aminothiadiazole ring, the oxidation is usually carried out with aqueous ferric chloride [3,5]. Thus, when thiosemicarbazones **IIa-c** were allowed to react with two equivalents of ferric chloride in aqueous dioxane, they underwent oxidative cyclization to give 2(2'-amino-1',3',4'-thiadiazol-5'-yl)-4-oxo-4H-1-benzopyrans hydrochloride **IIIa-c**, which upon treatment with aqueous sodium carbonate gave the free amines **IVa-c.** The amino compounds **(IVa-c)** were acylated with a mixture of acetic anhydride and acetic acid or with benzoyl chloride to give the 2-acetamine or 2-benzamino derivatives **(Va-f)**.



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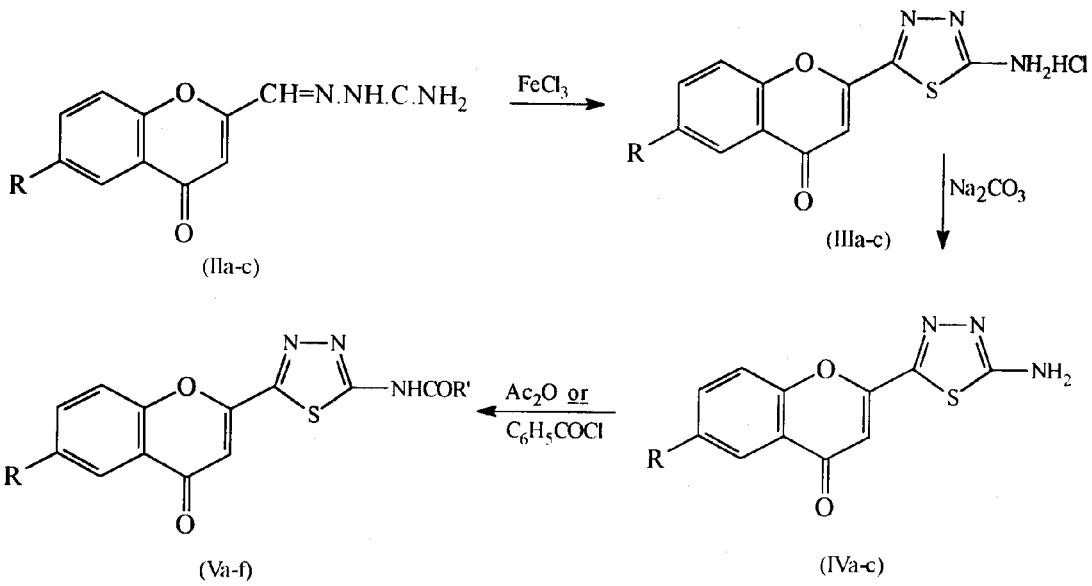
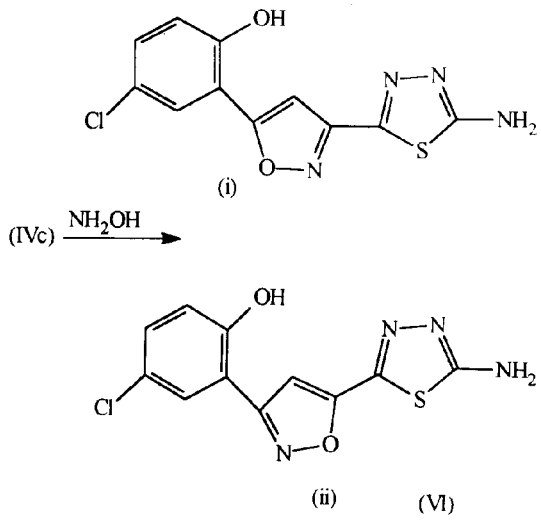


II, III, IV, V, R,	a	b	c	d	e	f
	H	CH_3	Cl			
V, R'	CH_3	CH_3	CH_3	C_6H_5	C_6H_5	C_6H_5

The structure of compounds (**IVa-c**) were confirmed by IR spectra which indicated bands at 3400-3340, 3280-3270, 3140-3100 (NH_2), 1636-1630 (CO pyrone) and 1610-1595 cm^{-1} (C=N). The PMR spectrum of compound (IVb) taken as an example showed the following signals at 7.97-7.62 (3H, m, ArH), 6.34 (1H, s, H-3) and 2.44 (3H, s, Ar-CH_3). The IR spectra of compunds (**Va-f**) indicated the following bands at 3150 (NH), 1710-1670 (CO amide), 1660-1645 (CO pyrone) and 1620-1605 cm^{-1} (C=N). The PMR spectrum of compound (Vb) taken as an example showed the following signals at 7.69-7.46 (3H, m, H-5, H-7 and H-8), 8.63 (1H, s, H-3), 2.38 (3H, s, Ar-CH_3) and 2.2 (3H, s, $COCH_3$).

It is known that when 4-oxo-4H-1-benzopyrans were treated with hydroxylamine, they gave isoxazole derivatives [6,7]. We have found that compound (IVc) reacted similarly with hydroxylamine hydrochloride in boiling pyridine to give the isoxazole derivative VI (i or ii).



Compound VI is soluble in aqueous sodium hydroxide and gives a deep violet colour with ferric chloride confirming the presence of phenolic

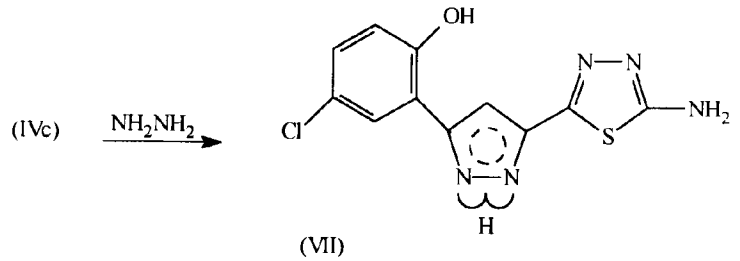
hydroxy group. Its IR spectrum showed bands at 3400, 3280, 3180 (NH_2), broad centered at 2900 (hydrogen bonded OH) and 1625 cm^{-1} (C=N).

The heterocyclic oxygen ring in 4-oxo-4H-1-benzopyrans is cleaved with hydrazine to give pyrazole derivative [7,8]. Compound (**IVc**) reacted successfully with hydrazine hydrate in alcohol and gave the pyrazole derivative (**VII**).

The pyrazole **VII** gives green colour with alcoholic ferric chloride and is soluble in aqueous sodium hydroxide confirming the presence of phenolic hydroxy group. Its IR spectrum showed absorption bands at 3485, 3380, 3300 (NH_2), 3180 (br., OH) and 1615 cm^{-1} (C=N).

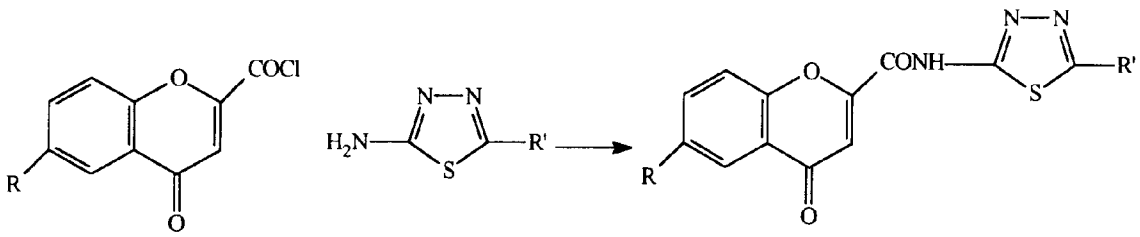
Some N-(1,3,4-thiazolyl)benzopyran-2-carboxamides

It is reported that chromone derivatives carrying acidic group at C-2 possess interersting pharmacological activities e.g., chromone-2-carboxamides [6,7]. We succeeded in preparing new carboxamides containing both the chromone and thiadiazole moieties. The N-(5'-methyl (or phenyl)-1,3,4-thiadiazol-2'-yl)-4-oxo-4H-1-benzopyran-2-carboxamides (**Xa-h**) were prepared by reacting the acid chloride (**VIII-d**) with 2-amino-5-methyl (or phenyl)1,3,4-thiadiazole (**XIa,b**) in benzene.



(VII)

The structures of compounds **Xa-h** were established by their correct analytical data and their IR spectra which showed bands at 1700-1670 (CO amide) and 1680-1640 (CO pyrone). The structures



R
a H
b CH_3
c Cl
d NO_2

R'
a CH_3
b C_6H_5

R	R'
a H	CH_3
b CH_3	CH_3
c Cl	CH_3
d NO_2	CH_3
e H	C_6H_5
f CH_3	C_6H_5
g Cl	C_6H_5
h NO_2	C_6H_5

Table-1: Characterization data of compound II, IV V and X

Compd.	M.P oC	Yield (%)	Solvent of crysta.	Mol.formula Mol.Wt.	Found % (Calc.)					IR (Kbr) cm			
					C	H	Cl	N	S	NH	CO (Pyrone)	CO (Amide)	C=N
IIa	258 d	58	butanol-pyridine	$C_{11}H_9N_3O_2S$	53.23	3.90	–	17.15	12.65	3360	1640	–	1605
			(247)	(247)	(53.44	3.64		17.00	12.96)	3280			
										3180			
IIb	254 d	90	DMF	$C_{12}H_{11}N_3O_2S$	55.35	4.16	–	16.40	12.15	3360	1640	–	1620
				(261)	(55.17	4.21		16.09	12.26)	3270			
										3160			
IIc	267 d	88	DMF	$C_{11}H_8ClN_3O_2S$	46.75	2.63	12.17	14.62	11.15	3480	1640	–	1620
				(281.5)	(46.89	2.84	12.61	14.92	11.37)	3320			
										3160			
IVa	322 d	83	DMF	$C_{11}H_7N_3O_2S$	53.65	3.10	–	17.10	13.23	3400	1630	–	1610
				(245)	(53.88	2.86	–	17.14	13.06)	3270			
										3140			
IVb	330 d	96	DMF	$C_{12}H_9N_3O_2S$	55.37	3.76	–	16.15	12.20	3320	1630	–	1600
				(259)	(55.60	3.47	–	16.22	12.35)	3270			
										3095			
IVc	331 d	96	DMF	$C_{11}H_6ClN_3O_2S$	47.55	2.25	12.55	14.85	11.23	3340	1635	–	1595
				(279.8)	(47.23	2.15	12.70	15.03	11.45)	3280			
										3100			
Va	340 d	85	DMF	$C_{13}H_9N_3O_3S$	54.15	3.30	–	1 .22	10.45	3160	1650	1710	1610
				(287)	(54.35	3.40	–	14.63	11.15)				
Vb	>350	92	DMF	$C_{14}H_{11}N_3O_3S$	55.45	3.59	–	13.65	10.42	3150	1640	1700	1610
				(301)	(55.81	3.65	–	13.95	10.63)				
Vc	>350	84	DMF	$C_{13}H_8ClN_3O_3S$	48.45	2.60	10.55	12.75	9.85	3140	1650	1715	1610
				(321.5)	(48.52	2.49	11.04	13.06	9.75)				
Vd	335 d	57	DMF	$C_{19}H_{11}N_3O_3S$	62.00	3.40	–	11.80	9.00	3140	1646	1670	1600
				(349)	(61.89	3.15	–	12.03	9.17)				
Ve	>350	79	DMF	$C_{16}H_{13}N_3O_3S$	62.91	3.76	–	11.55	8.65	3150	1645	1665	1610
				(363)	(62.81	3.58	–	11.57	8.81)				
Vf	343 d	68	DMF	$C_{18}H_{10}ClN_3O_3S$	56.20	2.90	9.10	10.65	8.23	3060	1660	1670	1605
				(383.5)	(56.32	2.61	9.26	10.95	8.34)				
Xa	282 d	90	DMF	$C_{13}H_8N_3O_3S$	54.75	3.40	–	14.35	11.10	3140	1650	1660	1615
				(287)	(54.35	3.14	–	14.63	11.15)				
Xb	295 d	63	DMF	$C_{13}H_9ClN_3O_3S$	48.00	2.70	11.20	13.21	9.50	3080	1650	1695	1610
				(321.5)	(48.52	2.45	11.40	13.06	9.95)				
Xc	348 d	77	DMF	$C_{13}H_8N_4O_5S$	46.80	2.55	–	16.70	9.50	3100	1650	1670	1630
				(332)	(46.99	2.41	–	16.87	9.64)				
Xe	314 d	89	DMF	$C_{19}H_{11}N_3O_3S$	62.10	3.20	–	12.30	9.20	3110	1650	1690	1625
				(349)	(61.89	3.15	–	12.03	9.13)				
Xf	>350	91	DMF	$C_{18}H_{13}N_3O_3S$	62.60	3.20	–	11.40	8.50	3080	1650	1680	1610
				(363)	(62.81	3.58	–	11.57	8.81)				
Xg	>350	92	DMF	$C_{18}H_{10}ClN_3O_3S$	56.15	2.80	9.42	10.90	8.20	3080	1650	1690	1695
				(383.5)	(56.32)	2.61	9.62	10.95	8.34)				
Xh	>350	96	DMF	$C_{18}H_{10}N_4O_5S$	55.20	2.65	–	14.70	8.15	3080	1650	1670	1620
				(394)	(54.82)	2.54	–	14.21	8.12)				

were also supported by the PMR spectra of Xc and Xg.

Experimental

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded in potassium bromide discs on a Perkin-Elmer 137 and 298 spectrophotometer. PMR spectra were recorded on a Varian Em-360 instrument (60 MHz) using TMS as an internal standard and DMSO-d_6 as a solvent.

4-Oxo-4H-1-benzopyran-2-carboxaldehyde thiosemicarbazones (IIa-c)

To a solution of Ia-c (100 mmole) in the least amount of ethanol, a solution of thio-semicarbazide (9.1 g, 100 mmole) in water (120 ml) was added and the mixture was left at room temperature for 1 hr. The yellow crystals that separated out were filtered, washed with ethanol and crystallized from suitable solvent (Table 1). The PMR spectrum of (IIc) showed the following signals: 12.3 (1H, s, N-NH-C=S, exchangeable with D_2O), 8.5 (2H, d, S=C-NH_2, exchangeable with D_2O), 7.97-7.79 (4H, m, Ar-H + -CH=N-) and 7.12 (1H, s, H-3).

2(2'-Amino-1,3,4-thiadiazol-5'-yl)-4-oxo-4H-1-benzopyrans (IVa-c)

To suspensions of the thiosemicarbazones IIa-c (10 mmole) in aqueous dioxane (37%, 55 ml), $FeCl_3$. $6H_2O$ (5.4 g, 20 mmol) was added. The mixture was heated at 90-92°C for 1 hr. and left to cool. The hydrochlorides (III) which separated out were filtered. The hydrochlorides (III) when stirred with 10% aqueous sodium carbonate solution for 1 hr. gave (IVa-e) as pale yellow to orange crystals from DMF (Table 1). The PMR spectrum of (IVb) showed the following signals 7.97-7.62 (3H, m, Ar-H), 6.84 (1H, s, H-3) and 2.44 (3H, s, CH_3).

2-(2'-Acetamino-1,3,4-thiadiazol-5'-yl)-4-oxo-4H-1-benzopyrans (Va-c)

A miture of **IVa-c** (22 mmole), acetic anhydride (2 ml) and acetic acid (2 ml) was refluxed for 30 min and left to cool. The mixture was diluted with water (50 ml) and the solid thereby formed was collected and recrystallized from DMF to give (**Va-c**) as pale yellow crystals (Table-1). The PMR spectra of (**Vb**) showed the following signals 7.69-7.46 (3H, m, Ar-H), 6.83 (1H, s, H-3), 2.38 (3H, s, Ar-CH_3) and 2.20 (3H, s, $COCH_3$).

2-(2'-Benzamido-1,3,4-thiadiazol-5'-yl)-4-oxo-4H-1-benzopyrans (Vd-f)

A mixture of **IVa-c** (10 mmole), dry pyridine (30 ml) and benzoyl chloride (1.55 g, 11 mmole) was heated at 100°C for 1 hr. The cooled mixture was diluted with water and the solid which separated out was filtered, washed successively with water and ethanol and recrystallised from DMF to give (**Vd-f**) (Table 1). The PMR spectra of Vf showed the following signals: 8.08-7.43 (8H, m, Ar-H) and 6.97 (1H, s, H-3).

5-(5'-Chloro-2'-hydroxyphenyl)-3-(2'-amino-1,3,4-thiadiazol-5'-yl)isoxazole (VI)

A mixture of **IVc** (0.73 g, 2.5 mmole) in pyridine (10 ml) and excess of hydroxylamine hydrochloride (0.6 g) in water (5 ml) was refluxed for 4 hr. The cooled mixture was acidified with dilute acetic acid. The solid deposited was filtered. On crystallization from water, it formed white crystals (**VI**, 86%), m.p. 281°C (Found: C, 44.55; H, 2.25; Cl, 12.20; N, 19.40; S, 10.63 $C_{11}H_7ClN_4O_2S$ requires c, 44.82; H, 2.38; Cl, 12.05, N, 19.01; S, 10.87%); IR: 3400, 3280, 3180, (NH_2), 2900 (br., OH) and 1625 cm^{-1} (C=N).

3-(5'-Chloro-2'-hydroxyphenyl)-5-(2'-amino-1,3,4-thiadiazol-5'-yl)pyrazole (VII)

To suspension of **IVc** (0.73 g, 2.5 mmole) in ethanol (20 ml), a solution of hydrazine hydrate (2.5 g) in ethanol (5 ml) was added. The reaction mixture was heated for 15 min. cooled and diluted with water when a solid separated out. It on crystallization from aqueous DMF formed white crystals (**VII**, 95%), m.p. above 350°C; (Found: C, 44.75; H, 2.60; Cl, 12.50; N, 23.55; S, 10.50 $C_{11}H_8ClN_5OS$ requires C, 44.97; H, 2.73; Cl, 12.09; N, 23.85; S, 10.90%); IR 3485, 3380, 3300 (NH_2), 3180 (br., OH) and 1615 cm^{-1} (C=N).

N(5'-Methyl(or phenyl)-1,3,4-thiadiazol-2'-yl]-4-oxo-4H-1-benzopyran-2-carbozamides (Xa-b)

To a solution of the acid chlorides **VIIIa-d** (10 mmole) in the least amount of dry benzene, 2-amino-5-methyl (or phenyl)-1,3,4-thiadiazole **IXa** and **IXb** (10 mmole) was added. The mixture was refluxed for 3 hr. cooled, the solid formed was filtered off and recrystallized from DMF to give **Xa-h** as pale yellow crystals (cf. Table 1).

References

1. K. Shagius and B. Zetterberg, *Chemotherapy* **9**, 37 (1961).
2. E. Hoggarth, *J. Chem. Soc.*, 1163 (1949).
3. G. Werber, F. Buccheri, M. Gentile and L. Librici, *J. Heterocycl. Chem.*, **14**, 853 (1977).
4. T. Vacula, R. Rao, V. Ranga and V.R. Srinivasan, *Indian J. Chem.*, **7**, 577 (1969).
5. Y. George and E. Wilium, *J. Chem. Soc.*, **79**, 546 (1901).
6. V.P. Khilya, L. G. Grishko and T.L. Davidkova, *Khim. Getertosikl. Soedin.*, 892 (1980); *C.A.* **94**, 15496 (1981).
7. S.B. Nair ad K.N. Wadolkar, *Indian J. Chem., Sect. B*, **21B** (6), 273 (1982); *C.A.* **98**, 89239 d (1983)