Benzopyrans from 2-Bromo-4,6-Diacetyl Resorcinol

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Summary: 6-Acetyl-8-bromo-2-methyl-7-hydroxy-4-oxo-4H-1-benzopyran **Vb**; ethyl-6-acetyl-8-bromo-7-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylate **VIIb**, and 10-bromo-2,8-diphenyl-4,6-dioxo-4H, 6H-benzo[1,2-b:5,6-b']-dipyran **XV** were prepared, from 2-bromo-4,6-diacetylresorcinol **Ib**. The behaviour of the **Vb** towards benzaldehyde, hydroxylamine, hydrazine, and amines was investigated. Also the action of thiourea on the benzodipyran **XV** was investigated, where the dithiopyrimidine derivative **XVI** was obtained.

Introduction

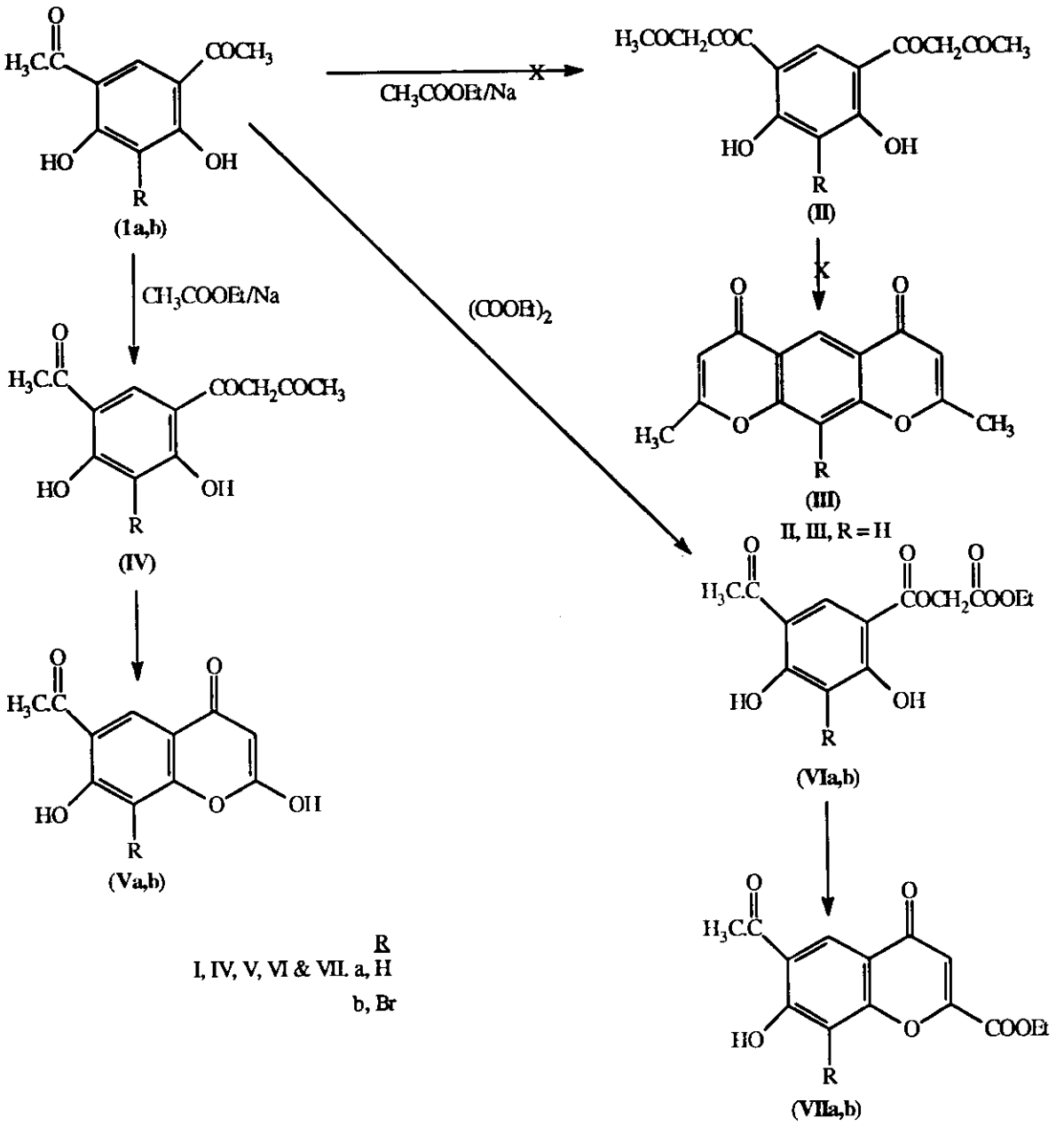
Wide varieties of 4-oxo-4H-1-benzopyrans and their derivatives have been reported to posses biological activities and significant medical importance, *e.g.* as antiplatelet [1], antimicrobial [2], anti-inflamatory and anti-allergy [3]. This prompted us to synthesise several heterocyclic compounds containing the 4-oxo-4H-1-benzopyran moiety and study some of their reactions.

Results and Discussion

B. Veera [4] found that the condensation of 4,6-diacetylresorcinol **Ia** with ethyl acetate under Claisen condensation condition gave a bisdiketone **II**, which upon cyclization, gave the benzodipyran **III**. We tried to synthesize compound **III** according to the same procedure, or even under more drastic conditions, but instead the monoacetoacetyl derivative **IVa** was obtained, which upon cyclization gave the benzopyran **V**. When we start with 2-bromo-4,6-diacetylresorcinol **Ib**, it also gave, under the same conditions, the monoacetoacetyl derivative **IVb**, which upon cyclization gave the benzopyran **Vb**. These observations were confirmed by:

i) Correct elemental analysis.
ii) Compounds **V** are soluble in aqueous alkali and gave colour with ferric chloride.
iii) IR spectra **Va** and **Vb** showed two carbonyl absorption at (1660-1655 cm^{-1}), (1635-1630 cm^{-1}) and a broad band centered at (2950-2850 cm^{-1}) [5] for intramolecular hydrogen bonded OH group.
iv) a- PMR spectrum of **Va** showed signals at δ 14.2 (s, 1H, OH, exchangeable with D_2O); 8.2 (s, 1H, H_5); 7.73 (s, 1H, H_8); 6.69 (s, 1H, H_3); 2.81 (s, 3H, $COCH_3$), and 2.38 ppm (s, 3H, 2-Me).
b - PMR spectrum of **Vb** showed signals at δ 1.40 (br, 1H, OH, exchangeable with D_2O); 8.32 (s, 1H, H_5); 6.52 (s, 1H, H_3); 2.88 (s, 3H, $COCH_3$) and 2.46 ppm (s, 3H, 2-Me).
v) Claisen condensation of **Ia** with ethyl oxalate did not give the dibenzopyran, but instead gave only the mono-β-diketone **VIa**, which upon cyclization gave the benzopyran-carboxylic ester [6] **VIIa**. **Vb** gave the same results with ethyl oxalate, where **VIb** and **VIIb** were obtained.

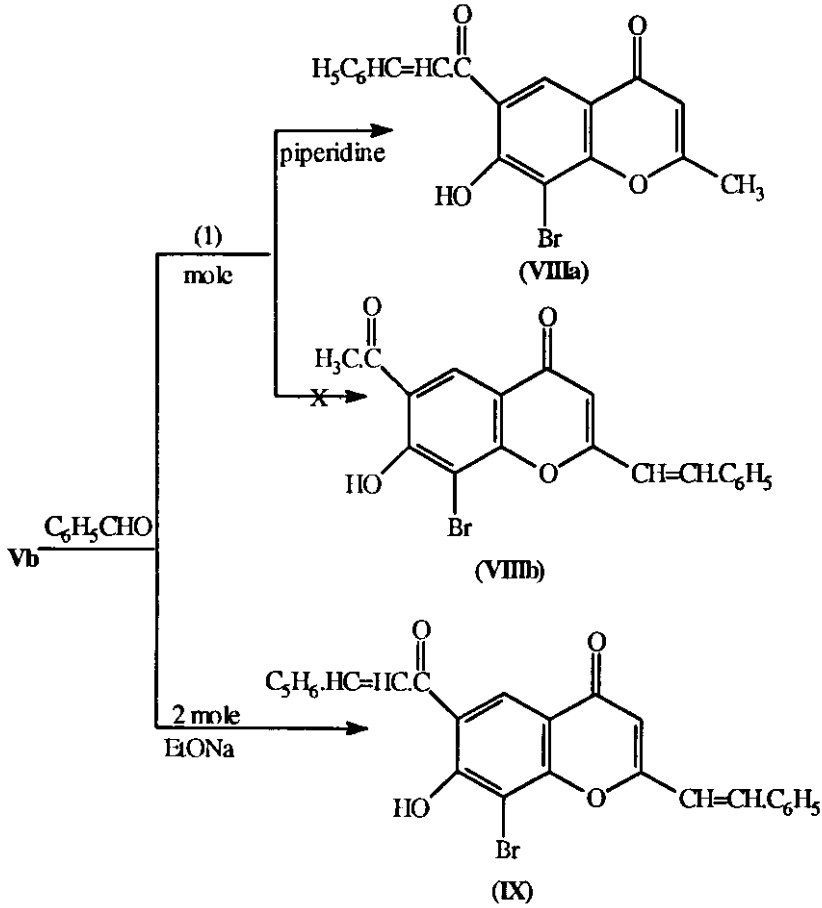
The reactivity of the two active sites; the 2-methyl group [7] and the 6-acetyl group, in compound **Vb** towards aromatic aldehydes was tested, thus on subjecting **Vb** to react with one mole of benzaldehyde in the presence of piperidine as basic catalyst led to the formation of the corresponding 6-cinnamoyl derivative **VIIIa** not the 2-styryl derivatives **VIIIb**. This was confirmed from its PMR spectrum which displayed no signal at δ = 2.88 ppm characteristic for the methyl group of the 6-acetyl moiety, but showed signal at δ = 2.44 characteristic for the 2-methyl group. With two moles of benzaldehyde in ethanolic sodium ethoxide solution, compound **Vb** gave the 2-styryl-6-cinnamoyl derivative **IX**, through the condensation on both sites according to literature, 4-oxo-4H-1-benzopyrans react with hydroxylamine hydrochloride to give isoxazole derivatives [8]. Under the same conditions, compound **Vb** reacted with hydroxylamine hydrochloride, with the opening of the pyrone ring, to give 3-bromo-2,4-dihydroxy-5-(3'-methylisoxazol-5'-yl)acetophenone

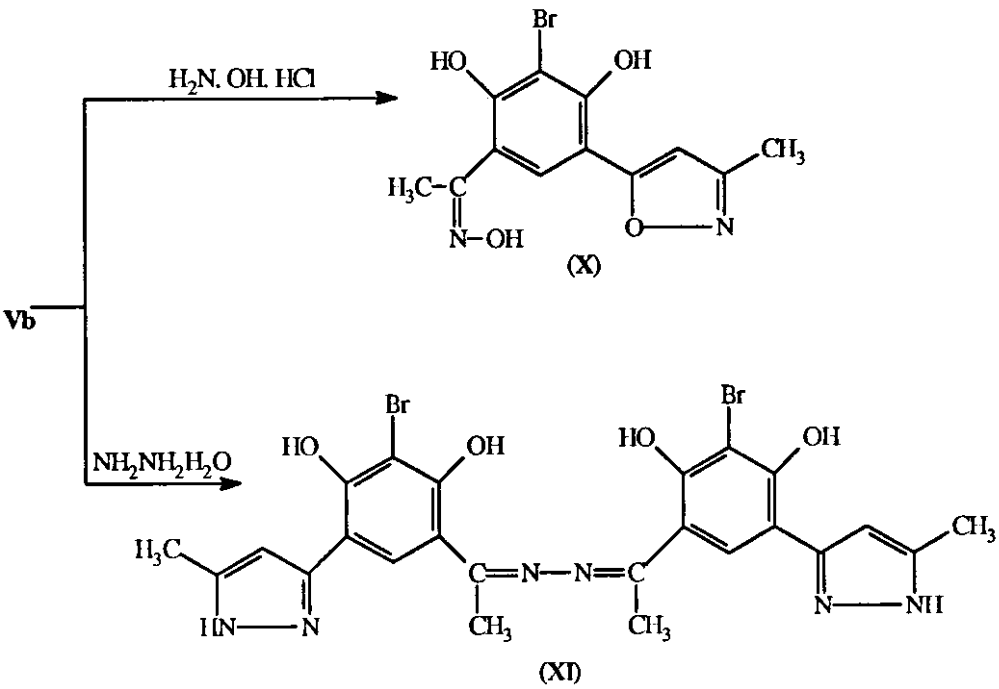


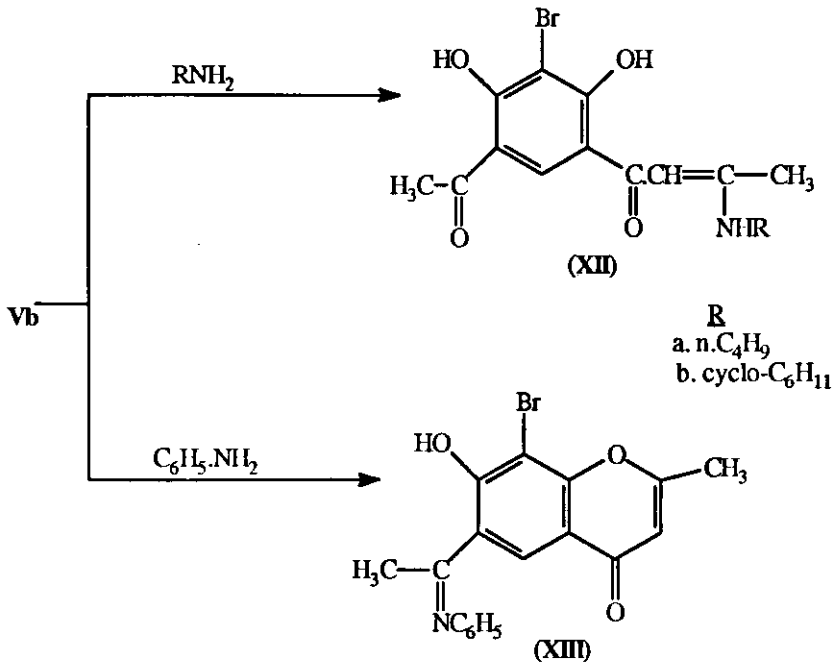
oxime **X**. With hydrazine hydrate, compound **Vb** gave the azine derivative **XI**, as a result of its condensation with the 6-acetyl group and the opening of the ring [9].

The reaction products of compound **Vb** with amines were found to be dependent on the nature of the amine. Thus, when compound **Vb** was allowed to react with two moles of aliphatic amine, namely; *n*-butylamine and cyclohexylamine in boiling ethanol, it behaved like other benzopyrans [10] giving 2-bromo-4-(N-alkylacetimino)-6-(1'-oxo-3'-alkylamino-2'-butenyl) resorcinol **XIIa** and **b**, respectively. On the other hand, with the less basic aniline, it gave the corresponding Schiff's base; 8-bromo-2-methyl-7-hydroxy-6-phenylacetimino-4-oxo-4H-1-benzopyran **XIII**.

The diflavone; [10-bromo-2,8-diphenyl-4,6-dioxo-4H,6H-benzo-(1,2,b:5,4-b')dipyran] **XV** was


piperidine
(1)
mole
(VIIIa)
X
(VIIIb)
C6H5CHO
Vb
2 mole
EtONa
(IX)


H2N. OH. HCl
Vb
(X)
NH2NH2H2O
(XI)



synthesized by using the route of Anjaneyulu *et al* [11]. The required o-hydroxychalcone **XIV** was formed when compound **I** allowed to react with benzaldehyde in alcoholic potassium hydroxide solution.

As 2-thiopyrimidines can be obtained through the action of thiourea on flavones [12], thus, the dipyrimidine derivative **XVI** was also obtained when the diflavone **XV** was allowed to react with thiourea in alcoholic potassium hydroxide solution.

Experimental

All melting points were taken in open capillary tubes and are uncorrected. The structures of the compounds were confirmed by elemental analysis, infrared spectrometry, and NMR spectroscopy. Infrared spectra were recorded on a Perkin-Elmer 598 infrared spectrophotometer using KBr wafer technique, and NMR spectra were obtained on a Varian EM 390 90 MHz spectrometer in DMSO-d_6 with TMS as an internal standard and were consistent with the proposed structures (*c.f.* Table 1).

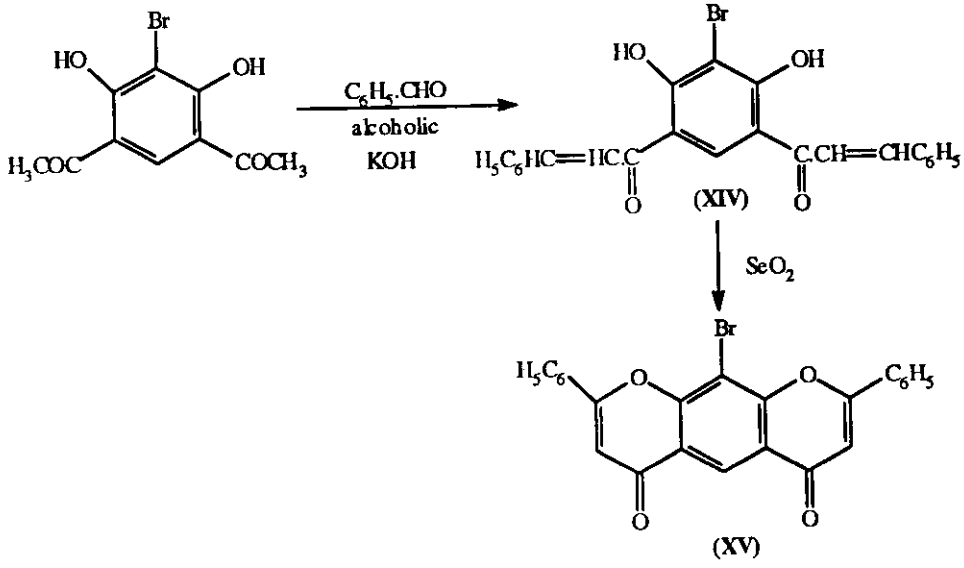
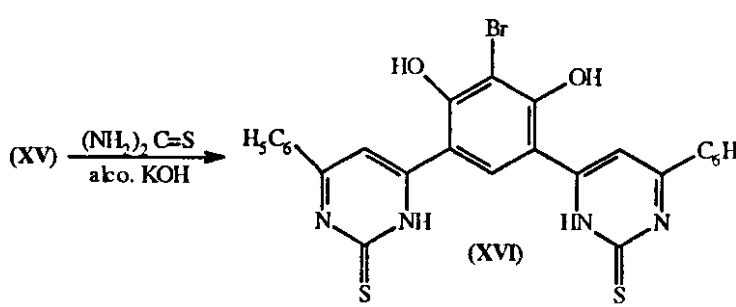


Table-1: Physical and analytical data for the synthesized compounds

Compd. No.	m.p. (°C)	Yield %	Solvent of crysta-llization	Molecular formula (M.wt.)	Elemental analysis (Found/Calcd). C	H	N	S	IR (KBr) νcm^{-1}	^{1}H-NMR [(D_6)DMSO/TMS] δ (ppm)
IVb**	148	87	Benzene-petroleum ether (60-80°)	$C_{12}H_{11}BrO_5$ (315)	45.69 45.71	3.42 3.49			2860 (OH); 1670, 1640, 1630 (C=O of β-diketone and C=O of acetyl group).	1.4 (b, 1H, OH*); 8.64 (s, 1H, H_5); 7.95 (s,1H, one of the CH_2- group present as an enol*); 4.96 (s, 1H, the other proton of the CH_2 group as CH=C); 2.8 (s, 3H, acetyl CH_3); and 1.8 (s, 3H, acetoacetyl CH_3)
Va**	190	85	Ethanol	$C_{12}H_{10}O_4$ (218)	66.00 66.05	4.55 4.58			1645, 1635 (C=O for acetyl and γ-pyrone); 2950 (OH).	14.2 (s, 1H, OH*), 8.2 (s, 1H, H_5); 7.73 (s, 1H, H_8); 6.69 (s, 1H, H_3); 2.81 (s, 3H, $COCH_3$), and 2.38 (s, 3H, 2-Me)
Vb**	232	98	Ethanol	$C_{12}H_9BrO_4$ (297)	48.44 48.48	3.00 3.03			1645, 1635 (C=O for acetyl and γ pyrone).	14,00 (b, 1H, OH*); 8.32 (s, 1H, H_5); 6.52 (s, 1H, H_3), 2.88 (s, 3H, $COCH_3$) and 2.46 (s, 3H, 2-Me).
VIIb**	193	87	Ethanol	$C_{14}H_{11}BrO_6$ (355)					1730, 1655 (C=O ester and γ-pyrone)	14.15 (s, 1H, OH*); 8.86 (s, 1H, H_5); 6.39 (s, 1H, H_3); 4.52 (q, 2H, $-CH_2-$); 2.85 (s, 3H, acetyl CH_3) and 1.64 (t, 3H, CH_3 of ethyl ester).
VIIIa**	240	83	Acetone	$C_{19}H_{13}BrO_4$ (385)	59.18 59.22	3.32 3.37			(1650-1645), 1635 (C=O for cinnamoyl and γ -pyrone).	14.56(b, 1H, OH*), 9.2 (s, 1H, H_5); 8.4-7.84 (s, 7H, cinnamoyl moiety); 6.56 (s, 1H, H_3), and 2.4 (s, 3H, 2-Me).
IX**	217	75	Acetone	$C_{26}H_{17}BrO_4$ (473)	65.74 65.96	3.54 3.59			(1650-1645), 1635 (C=O for cinnamoyl and γ-pyrone).	14.8 (s, 1H,OH*); 9.02 (s, 1H, H_5), 8.2-7.4 (s, 14H, cinnamoyl and styryl moieties), and 6.6 (s, 1H, H_3).
X**	235	82	Acetone	$C_{12}H_{11}BrN_2O_4$ (327)	44.01 44.03	3.30 3.36	8.48 8.56		3460 (OH, oxime); 3160 (phenolic OH), and 1620 (C=N).	13.82 (s, 2H, phenolic OH's*); 12.12 (b, 1H, oxime OH*); 8.14 (s, 1H, H_6); 6.92 (s, 1H, H_4); 2.4 (s, 3H, N=C-CH_3) and 2.23 (s, 3H, isoxazole CH_3).
XI**	>300	80	Acetone	$C_{24}H_{22}Br_2N_6O_4$ (618)					3145, 3120 (NH); 2900 (OH) and 1620 (C=N).	16.08 (s, 2H, 20H*); 13.50 (b, 4H, 20H* and 2 pyrazole NH*); 8.22 (s, 2H, aromatic protons); 7.00 (s, 2H, pyrazole protons), 2.63 (s, 6H, CH_3 CH_3 C=N-N), and 2.2 (s, 6H, 2 pyrazole CH_3).
XIIa**	160	83	Ethanol	$C_{20}H_{19}BrN_2O_3$ (425)	56.50 56.50	6.6 6.8	6.5 6.6		1635 (α,β -unsaturated ketone) and 1515 (C=N).	16.8 (s, 1H, OH*); 14.8 (b, 1H, OH*). 10.91 (s, 1H, NH*); 8.34 (s, 1H, H_5); 6.1 (s, 1H, COCH=C); 3.76 (t, 2H, $-CH_2$-N=); 2.65-2.56 (s, 5H, acetimino CH_3 and H-N-CH_2-CH_2-); and 2.22 (s, 3H, butenyl CH_3); 1.76-1.28 (m, 8H, $(CH_2)_4$ groups) and 1.04-0.88 (s, 6H, two butyl CH_3 groups).
XIIb**	258	78	Ethanol	$C_{24}H_{23}BrN_2O_3$ (477)	60.29 60.37	6.85 6.91	5.70 5.87		1635 (α,β-unsaturated ketone) and 1515 (C=N).	
XIII**	212	83	Ethanol	$C_{18}H_{14}BrNO_3$ (372)	58.02 58.06	3.68 3.76	3.75 3.76		1635 (C=O of γ pyrone) and 1615 (C=N).	1463 (s, 1H, OH*); 8.33 (s, 1H, H_5); 7.91-7.45 (s, 5H, aromatic protons); 6.83 (s, 1H, H_3), 2.61 (s, 3H, acetimino CH_3) and 2.42 (s, 3H, CH_3 at position 2).
XIV**	229	73	Dioxane	$C_{24}H_{17}BrO_4$ (449)	64.05 64.14	3.70 3.78			1645 (α,β -unsaturated ketone) and 1655 (C=O of γ-pyrone).	14.2 (s, 2H, phenolic OH*,s); 8.83 (s, 1H, H_6); 7.95-7.35 (s, 14H, phenyl protons and CH=CH protons).
XV**	>300	80	Dioxane	$C_{24}H_{13}BrO_4$ (445)	64.88 64.71	2.86 2.92			1645 (α,β-unsaturated keton); and 1655 (C=O of γ-pyrone).	9.4 (s, 1H, H_5); 7.47-7.95 (s, 10H, phenyl protons) and 6.76 (s, 2H, $H_{3\&7}$).
XVI**	>300	80	DHF	$C_{16}H_{13}BrN_4S_2O_2$ (437)	43.06 43.93	2.85 2.97	12.74 12.81	7.26 7.32	3200 (-NH); 1620 (C=N, and 1220 (C=S)	

* Exchangeable with D_2O

** Soluble in NaOH 5% and gave violet colour with $FeCl_3$



4-Acetoacetyl-6-acetyl-2-bromoresorcinol IVb

A mixture of 2-bromo-4,6-diacetylresorcinol [13] I (10 g), ethyl acetate (110 ml), and sodium metal (8 g) was refluxed for 4 hr, after that additional weight of sodium metal (4 g) was added and refluxing was continued for further 6 hrs., left overnight at room temperature, and the reaction mixture was then added to crushed ice (300 g) where a yellow solid was separated, filtered, washed with ice-cold water, ether and decomposed with acetic acid. Dilution with water afforded the titled compound which recrystallized from benzene-petroleum ether (60-80°C) as white crystals.

6-Acetyl-8-bromo-2-methyl-7-hydroxy-4-oxo-4H-1-benzopyran (Vb)

4-Acetyl-6-acetoacetyl-2-bromoresorcinol (**IVb**) was dissolved in concentrated sulphuric acid and the mixture was left for 5 min. The dark brown solution that formed was poured on ice-cold water and the solid obtained was filtered off, crystallized from ethanol to give the titled compound (**Vb**) in almost theoretical yield.

7-Acetyl-6-hydroxy-2-methyl-4-oxo-4H-1-benzopyran (Va)

A mixture of 4,6-diacetylresorcinol (10 g), ethyl acetate (110 ml), and sodium metal (8 g) was refluxed for 4 hrs., after that additional weight of sodium metal (4 g) was added and refluxing was continued for further 6 hrs., left overnight at room temperature and the reaction mixture was then added to crushed ice (300 g) where a solid was separated, filtered, washed with ice-cold water, ether and decomposed with acetic acid. Dilution with water afforded the β-diketone **IVa** which was dissolved in concentrated sulphuric acid and left at room temperature for 5 min., poured on ice-cold water and the solid obtained was filtered off, crystallized from ethanol to give **Va**.

6-Acetyl-8-bromo-7-hydroxy-4-oxo-4H-1-benzopyran-2-carboxylic acid ethyl ester (VIIb)

A mixture of **I** (1 g) and diethyl oxalate (3 ml) in sodium ethoxide solution (0.7 g) of sodium in 15 ml of ethanol) was refluxed for 2 hrs. and left overnight. The yellow solid was collected and acidified with dil. acetic acid to give the β-diketone (**VIb**) which was cyclized directly by refluxing its ethanolic solution (0.5 g/10 ml) in presence of few drops of conc., sulphuric acid for 20 min. and left to cool. The solid obtained was filtered off and recrystallized from ethanol to give **VIIb** as white crystals.

8-Bromo-6-cinnamoyl-2-methyl-7-hydroxy-4-oxo-4H-1-benzopyran (VIIIa)

To a solution of **Vb** (0.5 g, 0.0017 mole) in the least volume of ethanol, was added benzaldehyde (0.18 g, 0.0017 mole) and 3 drops of piperidine, the reaction mixture was refluxed for 4 hrs. and left to cool. The yellow crystalline solid that separated was collected and recrystallized from acetone to give compound **VIIIa**.

8-Bromo-6-cinnamoyl-2-styryl-7-hydroxy-4-oxo-4H-1-benzopyran (IX)

To a solution of **Vb** (0.5 g, 0.0017 mole) in ethanolic sodium ethoxide (0.1 g of Na in 10 ml of absolute EtOH), benzaldehyde (0.36 ml, 0.0034 mole) was added, and the mixture was refluxed for 4 hrs. The orange product that formed was filtered off, acidified with dilute acetic acid and recrystallized from acetone to give compound **IX**.

3-Bromo-2,4-dihydroxy-5-(3'-methylisoxazol-5'-yl)-acetophenone oxime (X)

A mixture of **Vb** (0.5 g, 0.0017 mole) in pyridine (10 ml) and aqueous solution of hydroxylamine hydrochloride (1.2 g/10 ml) was refluxed for 4 hrs., cooled, acidified with dilute acetic acid, and the solid that formed was filtered off and crystallized from acetone to give compound **X** as white crystals.

Formation of the azine derivative (XI)

To a solution of **Vb** (0.5 g, 0.0017 mole) in ethanol (10 ml), was added a warm ethanolic solution of hydrazine hydrate (3 ml/10 ml EtOH). The reaction mixture was refluxed for 1 hr., left to cool and diluted with water. The separated solid was filtered and crystallized from acetone as a yellow crystals of **XI**.

Formation of XIIa and b

To a solution of Vb (0.5 g, 0.0017 mole) in ethanol (10 ml), was added the aliphatic amine, namely; *n*-butylamine, and cyclohexylamine (0.0034 mole). The mixture was refluxed for 15 min. and left at room temperature overnight. The solid that formed was filtered off and crystallized from ethanol as a yellow crystals of **XIIa** and **b**.

8-Bromo-2-methyl-7-hydroxy-6-phenylacetimino-4-oxo-4H-1-benzopyran (XIII)

To a solution of **Vb** (0.5 g; 0.0017 mole) in ethanol (20 ml) was added aniline (0.32 ml; 0.0043 mole). The mixture was refluxed for 4 hrs., and kept at room temperature overnight. The separated brown solid was filtered off and recrystallized from ethanol to give **XIII**.

3'-Bromo-2',4'-dihydroxy-5'-cinnamoyl chalcone (XIV)

To a mixture of **I** (5 g) and benzaldehyde (20 ml) in ethanol (100 ml), aqueous solution of potassium hydroxide (50 g./50 ml of H_2O) was added dropwise (ca. 1 hr).. The mixture was kept in the refrigerator for 24 hrs. On acidification with HCl (1:1), a yellow solid was separated, filtered, and recrystallized from dioxane to give **XIV** as a yellow needles.

10-Bromo-2,8-diphenyl-4,6-dioxo-4H,6H-benzo[1,2-b:5,4-b']-dipyran (XV)

A mixture of **XIV** (1 g) and selenium dioxide (6 g) in dry isoamyl alcohol (30 ml) was refluxed for 10 hours in an oil-bath at 140-150°C, filtered hot and the filtrate was kept in the refrigerator overnight where **XV** was separated, filtered, and recrystallized from dioxane as a white crystals.

3-Bromo-2,4-di(4'-methyl-2'(1H)thiopyrimidin-6'-yl) resorcinol (XVI)

A mixture of **XV** (0.5 g; 0.001 mole), thiourea (0.15 g; 0.002 mole) and aqueous potassium hydroxide solution (0.1 g, 0.002 mole. dissolved in the least volume of H_2O), in ethanol (150 ml) was refluxed for 3 hrs., cooled, acidified with dil. HCl, and the separated solid was filtered off and crystallized from DMF to give **XVI**.

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