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Note

Synthesis of 1-arylamido-2-oxo-4-methylpyrido[*b*]phenothiazines

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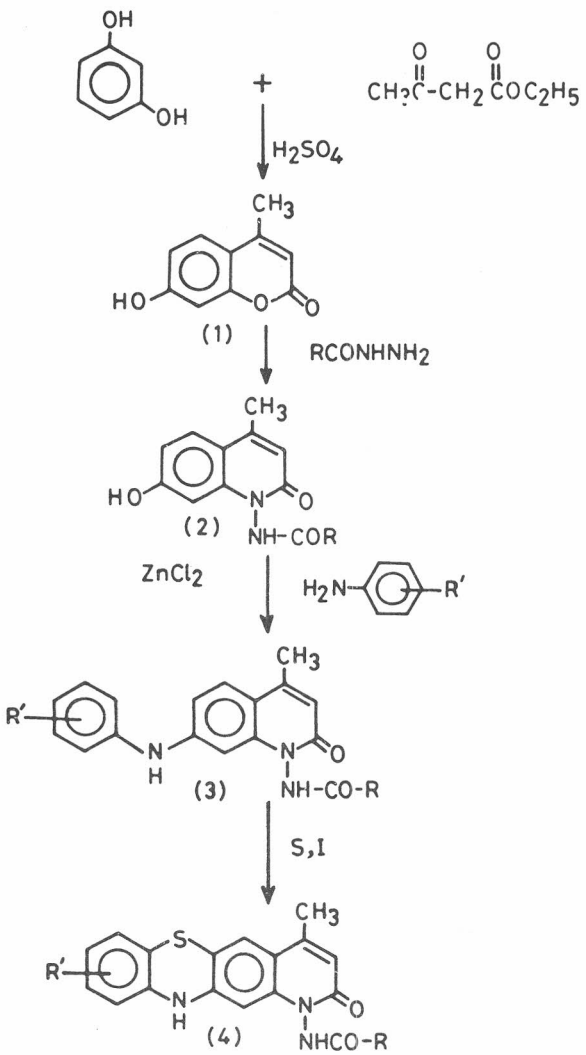
Resorcinol on treatment with ethyl acetoacetate (EAA) in the presence of conc. H_2SO_4 gives 7-hydroxy-4-methylcoumarin **1** which reacts with aromatic acid hydrazides affording 1-arylamido-7-hydroxy-2-oxo-4-methylquinolines (carbostyrils) **2**. Interaction of **2** with aromatic amines in the presence of anhydrous $ZnCl_2$ results in the formation of 1-arylamido-7-arylamino-2-oxo-4-methylquinolines **3**. Compounds **3** undergo cyclisation with sulphur and iodine giving 1-arylamido-2-oxo-4-methylpyrido[*b*]phenothiazines **4**. The CNS activity of **4** has been reported.

Phenothiazine derivatives constitute an important class of compounds possessing diverse types of biological properties including antiparkinsonian, anticonvulsant and antihistaminic activities[1-7]. Further, several pyrido[**b**]phenothiazines have been reported to possess antiviral and antiparasitic properties[8-9]. In continuation of our on-going research programme on newer phenothiazine derivatives of biological significance, it was considered of interest to synthesize some 1-arylamido-2-oxo-4-methylpyrido[*b*]phenothiazines and evaluate their CNS activity.

1-Arylamido-2-oxo-4-methylpyrido[*b*]phenothiazines **4** were prepared by heating a mixture of 1-arylamido-7-arylamino-2-oxo-4-methylquinolines **3** (cf. Table I) powdered sulphur and iodine (cf. Scheme I) at 215-220°C in an oil-bath. THe synthesized compounds wre characterized with the help of elemental analysis, IR and ^{1}H NMR spectral data. IR spectra of the above compounds showed absorption bands at 3400 ± 10 cm^{-1} due to secondary amino group and 1680 cm^{-1} due to carbonyl of amide. The ^{1}H NMR spectra of compounds **4a-c** (Table I) showed signals at δ6.5-8.0 for aromatic protons, two singlets at 2.50 and 2.54 due to C-CH_3 protons at position-4 and Ar—CH_3 protons, respectively. The singlet at δ3.14 was due to Ar-OCH_3 protons. The broad singlet at δ8.7-11.2 was due to NH protons. Methine protons at position-3 in all the three compounds appeared at δ6.25.



Scheme I

Pharmacological activity. Compounds **4** were screened to ascertain various pharmacological effects in relation to CNS in albino mice of either sex weighing 15-25 g each. The method of Weil[10] was followed for the determination of approximate lethal dose (ALD_{50}). The compounds were found to be both CNS stimulants as well as depressants in nature. Compounds **4b** and **4c** exhibited stimulant activity while compounds **4a** and **4b** showed tremorigenic effect (cf.Table II). In addition, compounds **4a** and **4d** were found to be depressants in nature. Except compound **4a**, all other compounds were found without any writhing effect (Table II).

Table I—Characterization data of 1-arylamido-7-arylamino-2-oxo-4-methylquinolines **3** and 1-arylamido-2-oxo-4-methylpyrido[*b*]phenothiazines **4**

Compd	R	R′	m.p. °C	Yield (%)	Mol. formula	N(%) Found	N(%) Calcd.
3a	C_6H_5	7-CH_3	170-72	52	$C_{24}H_{21}N_3O_2$	10.94	10.96
3b	C_6H_5	9-CH_3	146	54	$C_{24}H_{21}N_3O_2$	10.95	10.96
3c	C_6H_5	7-OCH_3	162	51	$C_{24}H_{21}N_3O_3$	10.50	10.52
3d	$C_6H_5CH=CH$	7-CH_3	179-80	53	$C_{26}H_{23}N_3O_2$	10.24	10.26
3e	$C_6H_5CH=CH$	9-CH_3	166	52	$C_{26}H_{23}N_3O_2$	10.23	10.26
3f	$C_6H_5CH=CH$	7-OCH_3	181	53	$C_{26}H_{23}N_3O_3$	9.86	9.88
4a*	C_6H_5	7-CH_3	230	47	$C_{24}H_{19}N_3O_2S$	10.14	10.16
4b*	C_6H_5	9-CH_3	240	45	$C_{24}H_{19}N_3O_2S$	10.13	10.16
4c*	C_6H_5	7-OCH_3	80-81	44	$C_{24}H_{19}N_3O_3S$	9.77	9.79
4d	$C_6H_5CH=CH$	7-CH_3	195-98	43	$C_{26}H_{21}N_3O_2S$	9.53	9.56
4e	$C_6H_5CH=CH$	9-CH_3	208-9	42	$C_{26}H_{21}N_3O_2S$	9.54	9.56
4f	$C_6H_5CH=CH$	7-OCH_3	174-75	46	$C_{26}H_{21}N_3O_3S$	9.20	9.23

Compounds **4** showed IR (KBr) absorption bands at 3400 ± 10 (NH), 1680 (C=O), 3300 (Aromatic C—H) and 1620 ± 10 cm^{-1} (N – H bending).

*^{1}H NMR ($CDCl_3$ + DMSO-d_6) : δ6.5-8.0 (m, 10H, Ar-H), 2.50(s, 3H, CH_3 at position-4), 2.54 (s, 3-H, Ar-CH_3), 3.14 (s, 3H, Ar-OCH_3), 8.7 (br s, 1H, NH) and 11.2 (br, s, 1H, NHCOR, D_2O exchangeable).

Table II—CNS activity data of 1-Arylamido-2-oxo-4-methylpyrido[*b*]phenothiazines **4**

Compd	R	R′	Dose (mg/kg) i.p.	Mortality	Gross Central Nervous System Activity: Body temp. (°C)	SMA	Other gross effects	ALD_{50} (mg/kg)
4a	C_6H_5	7-CH_3	464	0/4	—	↓	Writhing (+) Ataxia (+) Tremor (+)	316
			215	0/4	—	↓	React ↓	
			63.2	0/5	—		—	
4b	C_6H_5	9-CH_3	464	0/4	—	↑	React↑ React↑	681
			1000	4/4	—	↑	Tremor (+)	
			136.2	0/5	↓1.2	↑	↑	
4c	C_2H_5	7-OCH_3	464	0/4	—	↑	Resp. ↑	681
			1000	4/4	—	↑↑	React.↑ Resp. ↑ Anoxia (+) React ↑	
			136	0/5	↑0.1	↑↑	React ↑ Resp. ↑	
4d	$C_6H_5-CH=CH$	7-CH_3	464	4/4	—	↓	Resp. ↓ React. ↓	100
			215	4/4	—	↓	Resp. ↓ React. ↓	
			100	2/4	—	↓	React. ↓	
			46.4	0/4	—	↓	React. ↓	
			20	0/5	—	—	No effect	
4e	$C_6H_5CH=CH$	9-CH_3	464	4/4	—	—	Resp. ↑ React. ↑	316
			215	0/4	—	—	Resp. ↑ React. ↑	
			63.2	0/5	—	—	Resp. ↑ React. ↑	
4f	$C_6H_5CH=CH$	7-OCH_3	464	0/4	—	—	Resp. ↑ React. ↑	> 1000
			1000	0/4	—	—	Resp. ↑ React. ↑	
			200	0/5	—	—	Resp. ↑ React. ↑	

Experimental Section

Melting points were determined in open capillaries using a Toshniwal melting point apparatus and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 157 spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR spectra in a mixture of DMSO-d_6 and $CDCl_3$ on a Varian $A_{60}D$ instrument using TMS as internal standard (chemical shift in δ, ppm).

4-Methyl-7-hydroxycoumarin 1. The method of Pechmann and Duisberg[11] was followed for the preparation of 4-methyl-7-hydroxycoumarin.

Aromatic acid hydrazides. Aromatic acid hydrazides required in the present synthesis were prepared following the method of Vogel[12].

1-Arylamido-7-hydroxy-2- oxo-4-methylquinolines 2[13]. A mixture of 4-methyl-7-hydroxycoumarin **1** (0.1 mole) and an appropriate aromatic acid hydrazide (0.1 mole) in anhydrous pyridine (100 mL) was refluxed for 6 hr on a sand-bath under anhydrous conditions. The reaction mixture was allowed to stand at room temperature for 1 hr and poured into ice-cold water containing conc. HCL (10 mL). The solid which separated out, was allowed to settle. It was filtered and washed repeatedly with water, dried in a vacuum desiccator and crystallized from ethanol. Following compounds were prepared:

1-Benzamido-7- hydroxy-2-oxo-4-methylquinoline (2; $R = C_6H_5$): m.p. 160-162°, yield 60% (Found: N, 9.49. $C_{17}H_{14}N_2O_3$ requires N 9.52%).

1-Styrylamido-7-hydroxy-2-oxo-4-methylquinoline (2: $R = C_6H_5-CH=CH-$): m.p. 170-72°, yield 60% (Found: N, 8.71. $C_{19}H_{16}N_2O_3$ requires N 8.75%).

1-Arylamido-7-arylamino-2-oxo-4-methylquinolines 3[14]. A mixture of 1-arylamido-7-hydroxy-2-oxo-4-methylquinoline (**2**; 0.05 mole) and an aromatic primary amine (0.05 mole) in absolute ethanol (50 mL) was heated under reflux in the presence of anhydrous $ZnCl_2$ (0.5 gm) for 5 hr on a steam-bath. The contents were cooled when a crude solid mass separated out which was washed repeatedly with acidified water to remove inorganic materials. It was filtered, dried and crystallised from ethanol. The compounds thus, synthesised, are recorded in Table I.

1-Arylamido-2-oxo-4-methylpyrido[*b*]phenothiazines 4[14]. A mixture of **3** (0.01 mole), sulphur (0.1 mole) and iodine (0.5 g) was rapidly heated at 215-220°C in an oil-bath and maintained at this temperature for 1 hr. The hot melt was rapidly poured into a mortor and crushed to a fine powder. It was washed with water, dried and crystallised from ethanol containing animal charcoal. The compounds thus prepared are given in Table I.

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