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Search for New Antiviral Agents Part V : Synthesis of Some 1, 2 Disubstituted Benzimidazole Derivatives

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A few 1-oxo-styryl-2-alkyl-N-phthaloyl benzimidazole derivatives have been synthesized with a view to test their antiviral activity.

THE wide range of pharmacological and biochemical significance of benzimidazole derivatives is well established. A survey of literature reveals that benzimidazole derivatives exhibit significant analgesic[1], radioprotective[2], musclerelaxant[3], anticonvulsant[4], central nervous system depressant[5] and antiparkinsonian[6] properties. Further, the efficacy of this class of compounds in combating diseases caused by viruses is well known[7-11]. Harshball *et al*[9] reported pronounced effectiveness of these derivatives in various ailments caused by viruses. They also demonstrated that with low doses the results were highly promising and these derivatives had less side effects than other antiviral agents. In view to these observations, the authors were prompted to undertake the synthesis of some newer benzimidazole derivatives for testing their antiviral activity.

Experimental

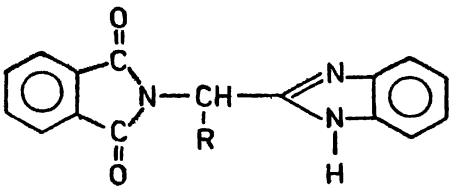
All melting points were taken in open capillaries in sulphuric acid melting point bath and are uncorrected.

1. *2-Alkyl-amino-benzimidazoles :* As reported earlier[12].

2. *2-Alkyl-N-phthaloyl benzimidazoles :* Equimolecular amounts of 2-alkyl-amino-benzimidazole and phthalic anhydride were heated on an oil bath at 190-200° for about 1/2 hr with occasional stirring. Heating was further continued for 15 minutes. The solid product obtained on cooling was treated with 5% sodium bicarbonate solution. It was filtered and recrystallised from ethanol. Various compounds thus synthesized are listed in Table 1.

3. *1-Acetyl-2-alkyl-N-phthaloyl-benzimidazoles :* A mixture of 2-alkyl-N-phthaloyl-benzimidazole (0.2 mole) and acetic anhydride (0.81 mole) was heated under reflux on a free flame with constant stirring for 4½ hrs. The mixture was allowed to cool slowly to room temperature with stirring and then to 5-10° rapidly. A solid mass separated out which was filtered, triturated with petroleum ether and recrystallized from ethanol. Various compounds thus synthesized are listed in Table 2.

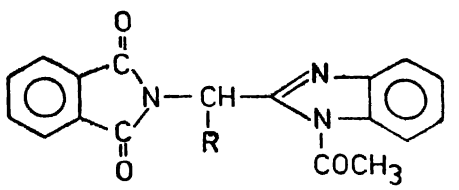
TABLE 1—2-ALKYL-N-PHTHALOYL-BENZIMIDAZOLES



Sl. No.	R	m.p.	Mol. For.	Nitrogen Analysis% Calcd.	Found
1.	H	244°	$C_{16}H_{11}N_3O_2$	15.16	14.84
2.	CH_3	219-20°	$C_{17}H_{13}N_3O_2$	14.43	14.02

Note : The present yield ranged from 60-65%. The ir spectrum for compound 1 exhibited a strong absorption band at 1710 cm^{-1} (C=O stretching in five membered ring) and 3400 cm^{-1} (N−H stretching) thus supporting the formation of the compounds.

TABLE 2—1-ACETYL-2-ALKYL-N-PHTHALOYL-BENZIMIDAZOLES



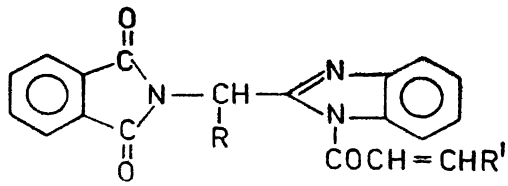
Sl. No.	R	m.p.	Mol. For.	Nitrogen Analysis% Calcd.	Found
1.	H	165-66°	$C_{18}H_{13}N_3O_3$	13.16	13.57
2.	CH_3	176-77°	$C_{19}H_{15}N_3O_3$	12.64	12.79

Note : The yield ranged from 50-60%. The ir spectrum for compound 1 showed an additional strong band at 1778 cm^{-1} (for C=O of $-COCH_3$) confirming the acetylation step.

4. *1-Oxo-styryl-2-alkyl-N-phthaloyl-benzimidazoles :* A mixture of 1-acetyl-2-alkyl-N-phthaloyl-benzimidazole (0.01 mole) and appropriate aromatic aldehyde (0.012 mole) in 40 ml ethanol and 2 ml 2% NaOH solution was heated under reflux for 1-2 hrs. The reaction mixture was poured into ice cold water. The precipitate was filtered and

recrystallization was effected with ethanol. Various compounds thus synthesized are listed in Table 3.

TABLE 3—1-OXO-STYRYL-2-ALKYL-N-PHTHALOYL-BENZIMIDAZOLES



Sl. No.	R	R'	m.p.	Mol. For.	Nitrogen Analysis% Calcd.	Found
1.	H	$-C_6H_5$	92°	$C_{25}H_{17}N_3O_3$	10.31	10.62
2.	H	p-$(CH_3)_2NC_6O_4$	76-77°	$C_{27}H_{22}N_4O_3$	12.44	12.09
3.	H	p-OH-m-$OCH_3C_6H_3$	123°	$C_{26}H_{19}N_3O_5$	9.27	0.46
4.	H	p-$OCH_3C_6H_4$	142-43°	$C_{26}H_{19}N_3O_4$	9.61	9.89
5.	H	o-OH$-C_6H_4$	113-14°	$C_{25}H_{17}N_3O_4$	9.93	9.61
6.	CH_3	$-C_6H_5$	138°	$C_{26}H_{19}N_3O_3$	9.98	10.25
7.	CH_3	p-$(CH_3)_2NC_6H_4$	66-7°	$C_{28}H_{24}N_4O_3$	12.07	12.37
8.	CH_3	p-OH-m-$OCH_3C_6H_3$	72-73°	$C_{27}H_{21}N_3O_5$	8.99	9.26
9.	CH_3	p-$OCH_3-C_6H_4$	164-65°	$C_{27}H_{21}N_3O_4$	9.31	9.01
10.	CH_3	o-OH$-C_6H_4$	103-04°	$C_{26}H_{19}N_3O_4$	9.61	10.02

Note : The present yield ranged from 50-55%. The ir spectra for compounds 1 and 8 exhibited characteristic bands at 1710 cm^{-1} (C=O in ring) and 1780 cm^{-1} (N-CO-CH=CH grouping) thereby confirming the validity of these compounds.

Antiviral activity :

Materials and Methods : Five compounds (Compound Nos. 2, 5, 6, 7 and 9 of table 3) were screened for their antiviral activity against Semliki forest virus (S. F. V) on Swiss albino mice. Each test compound (100 mg/kg body weight) was added to carboxymethyl cellulose (CMC) solution and injected in test mouse through intraperitoneal route in two divided doses at 24 and 48 hrs after virus infection. Ten mice were used for each test compound and ten were kept as control. The mice were then observed for 15 days for the appearance of symptoms (paralysis) and death. Protection rate (survival percentage) and mean survival time (M. S. T) were calculated as follows :

$$\text{Survival Percentage} = \frac{\text{Survival number of animals}}{\text{Initial number of animals}} \times 100$$

$$\text{M. S. T} = \frac{\text{Summation of time taken for each animal to die} + \text{Summation of survival time of animals not dying}}{\text{Number of animals dying} + \text{Number of animals surviving.}}$$

Results : The compounds 5 and 9 were found to possess 10% antiviral activity (net protection of mice) while the others were found inactive. Further, the mice treated with compound 5 showed a lengthening in mean survival time by 2.0 days but the rest showed no significant change.

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