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Chemoselective reactions of 3,6-diacetylindoles towards araldehydes, hydrazine hydrate and bromine: Synthesis and antimicrobial activity of novel 6-pyridyl/6-hydrazinoacetyl/6-bromoacetyl-3-acetylindole derivatives‡

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The exclusive formation of 6-pyridyl/6-hydrazinoacetyl/6-bromoacetylindoles **5a-f**, **7a,b** and **9a** from 3,6-diacetylindole derivatives **1a,b** reveal the chemoselective reaction of C_6-acetyl over C_3-acetyl function towards araldehydes, hydrazine hydrate and bromine, respectively. Indol-6-yl-propen-1-ones **4a-f** when treated with malononitrile and ammonium acetate furnish 1-substituted-3-acetyl-6-(2-amino-3-cyano-4-arylpyrid-6-yl)-5-methoxy-2-methylindoles **5a-f**. Similarly, 3,6-diacetylindole derivatives **1a,b** on reaction with hydrazine hydrate (99%) in ethanol and bromine in chloroform afford 1-substituted-3-acetyl-6-hydrazinoacetyl-5-hydroxy-2-methylindoles **7a,b** and 3-acetyl-6-bromoacetyl-1-(4-chlorophenyl)-5-hydroxy-2-methylindole **9a**, respectively. The newly synthesised compounds are screened for their antibacterial and antifungal activities.

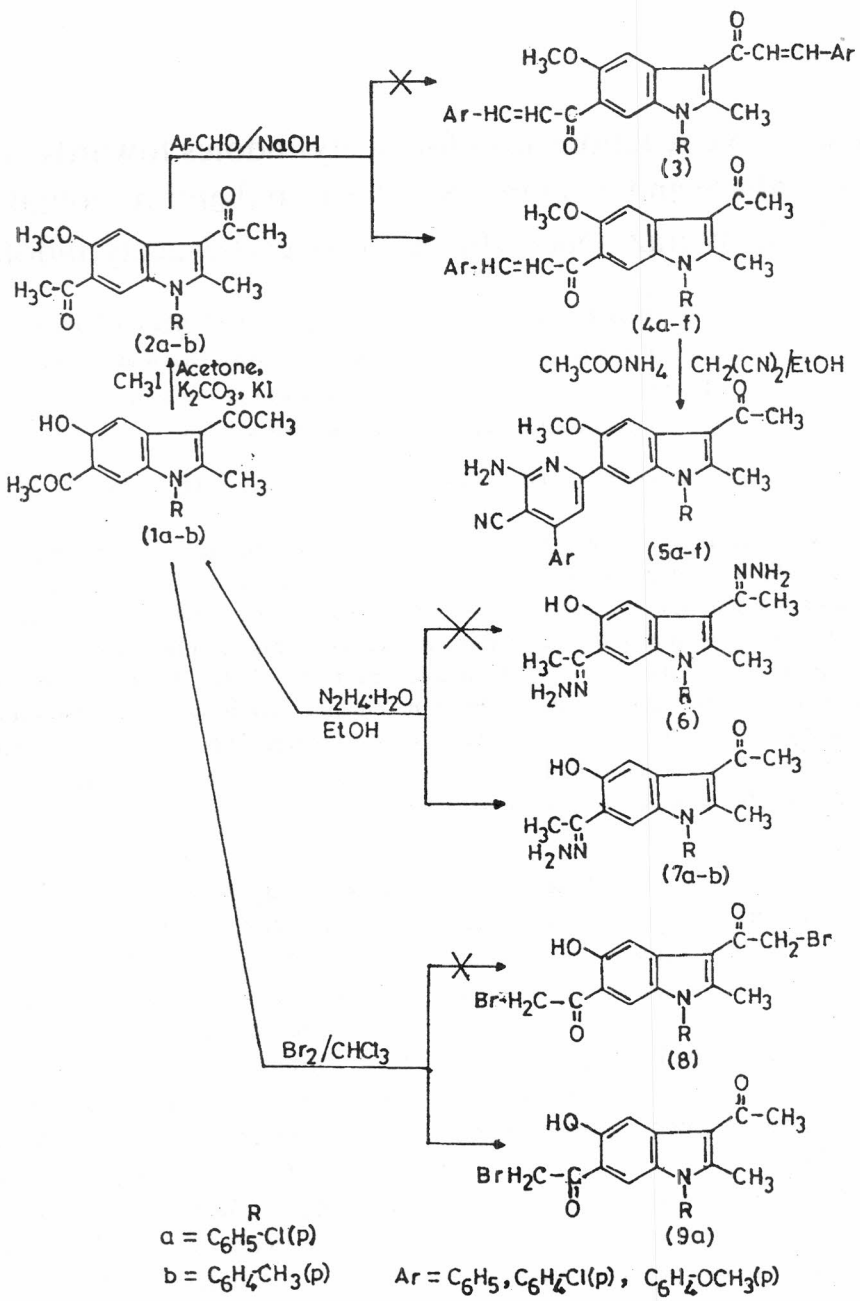
A large number of heterocyclic compounds have displayed valuable properties as chemotherapeutic agents. Similarly, various cinnamoyl indoles exhibited good antiinflammatory, analgesic, nonulcerogenic, sedative, antihypertensive, vasodilator, diuretic, bronchodilator, hypotensive, antihypertensive activity[1-4]. Various cyanopyridyl derivatives have been documented for their variety of biological activities[5-8].

In the light of above reports and also in continuation of our work on the chemoselective reactions of indole derivatives[9], we have embarked upon the chemoselective reactions of 3,6-diacetylindoles towards araldehydes, hydrazine hydrate and bromine leading to the synthesis of hitherto unknown novel indole derivatives having antimicrobial activities.

The required 3,6-diacetyl-5-hydroxyindoles **1a,b** were prepared as reported by us[10], which were reacted with methyl iodide in the presence of K_2CO_3 and dry acetone to yield the desired 3,6-diacetyl-5-methoxyindoles **2a,b**. **2a,b** were then reacted with different araldehydes in 1:2 molar ratio to secure only 1-(1-substituted- 3-acetyl-5-methoxy-2-methylindol-6-yl)-3-aryl-2-propen-1-ones **4a-f** (monochalcones) instead of the expected dichalcone derivatives **3**. The monochalcones **4a-f** were further reacted with malononitrile (in 1:1 molar ratio) in the presence of NH_4OAc in refluxing ethanol to give 1-substituted-3-acetyl-6-(2-amino-3-cyano-4-arylpyrid-6-yl)-5-methoxy-2-methylindoles **5a-f** in good yields. Similarly, when **1a,b** were treated with hydrazine hydrate (99%) in refluxing ethanol, only the C_6-acetyl underwent reaction with hydrazine to produce 1-substituted-3-acetyl-6-hydrazinoacetyl-5-hydroxy-2-methylindoles **7a,b**. Further, when 3, 6-diacetyl-1-(4-chlorophenyl)-5-hydroxy-2-methylindole **1a** was reacted with bromine in chloroform, the bromination occurred preferentially at C_6-acetyl group to produce 3-acetyl-6-bromoacetyl-1-(4-chlorophenyl)-5-hydroxy-2-methylindole **9a** (**Scheme I**).

In all the above three reactions of 3,6-diacetylindole derivatives, the C_3-acetyl group remained unaffected which revealed the chemoselectivity of C_6-acetyl group over C_3-acetyl

‡Part of this work was presented at the 32nd Annual Convention of Chemists held at Jaipur, December 1995.



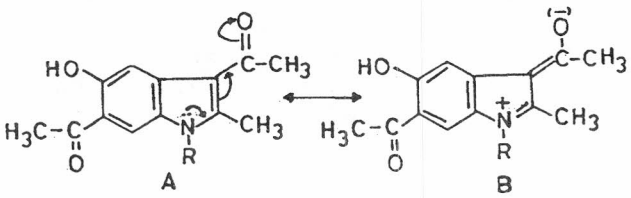
Scheme I

function towards araldehydes, hydrazine hydrate and bromine.

The nonreactivity of C_3-acetyl function of diacetylindoles **2a,b** and **1a,b** towards araldehydes, hydrazine hydrate and bromine could be related to the reduced double bond character of C_3-acetyl group due to the canonical structure **B** of 3,6-diacetylindole derivatives **A** wherein the π-electrons of indole nitrogen are delocalised on the oxygen of C_3-acetyl group (**Scheme II**). The structure of all the newly synthesised compounds were confirmed on the basis of their spectral and analytical data (**Table I**).

Antimicrobial activity

All the newly synthesised compounds (doses of 100 μg in 0.1 mL of DMF) were screened for their antibacterial activity *in vitro* against Gram



Scheme II

negative bacterium *Escherichia coli*, Gram positive bacterium *Bacillus cirroflagellosus* using Norfloxocin as standard and for their antifungal activity *in vitro* against fungi *Aspergillus niger* and *Candida albicans* using Griseofulvin as standard. Dimethyl formamide was used as solvent control. The culture media was nutrient agar and the method employed was cup-plate method[11,12]. The zones of inhibition formed were measured in mm and are represented by (-), (+), (++) and (+++) depending upon the diameter and clarity. Norfloxocin showed a zone of inhibition of 28 mm against *Escherichia coli* and 25 mm against *Bacillus cirroflagellosus*. Griseofulvin exhibited a zone of inhibition of 30 mm against both fungi *Aspergillus niger* and *Candida albicans*. Results of

Table I—Analytical and physical data of compounds **2a,b, 4a-f, 5a-f, 7a,b** and **9a**

Compd	R	Ar	m.p °C	Yield (%)	Nature (Solvent)	Mol. formula	Found (%) (Calc.) C	H	N
2a	C_6H_4-Cl(*p*)	–	200-01	91	Pale Yellow needles (Ethanol)	$C_{20}H_{18}ClNO_3$	67.70 (67.51	5.31 5.10	3.80 3.94)
2b	C_6H_4-CH_3(*p*)	–	181-82	88	Yellow needles (Ethanol)	$C_{21}H_{21}NO_3$	75.11 (75.20	6.43 6.31	4.32 4.18)
4a	C_6H_4-Cl(*p*)	C_6H_5	180-81	60	Yellow granules (Benz. Pet ether)	$C_{27}H_{22}ClNO_3$	73.43 (73.05	5.08 5.00	3.01 3.16)
4b	C_6H_4-Cl(*p*)	C_6H_4-Cl(*p*)	136-37	53	Yellow needles (aq. Ethanol)	$C_{27}H_{22}Cl_2NO_3$	67.89 (67.65	4.51 4.63	3.00 2.92)
4c	C_6H_4-Cl(*p*)	C_6H_4-OCH_3(*p*)	170-71	55	Bright yellow needles (Benzene)	$C_{28}H_{24}ClNO_4$	73.20 (73.44	4.99 5.28	2.83 3.06)
4d	C_6H_4-CH_3(*p*)	C_6H_5	152-53	48	Yellow granules (Benz. Pet ether)	$C_{28}H_{25}NO_3$	79.29 (79.41	5.89 5.95	3.42 3.31)
4e	C_6H_4-CH_3(*p*)	C_6H_4-Cl(*p*)	110-11	57	Yellow granules (Benz. Pet ether)	$C_{29}H_{24}ClNO_3$	73.98 (74.12	5.44 5.15	3.03 2.98)
4f	C_6H_4-CH_3(*p*)	C_6H_4-OCH_3(*p*)	122-23	44	Yellow granules (Benz. Pet ether)	$C_{29}H_{24}NO_4$	77.51 (77.32	5.56 5.37	3.01 3.11)
5a	C_6H_4-Cl(*p*)	C_6H_5	150-51	45	Yellow amarphous (Benz. Pet ether)	$C_{30}H_{23}ClN_4O_2$	71.23 (71.01	4.32 4.57	10.89 11.05)
5b	C_6H_4-Cl(*p*)	C_6H_4-Cl(*p*)	155-56	59	Yellow powder (Benz. Pet ether)	$C_{30}H_{22}Cl_2N_4O_2$	66.65 (66.55	4.00 4.10	10.02 10.35)
5c	C_6H_4-Cl(*p*)	C_6H_4-OCH_3(*p*)	120-21	61	Yellow powder (Benz. Pet ether)	$C_{31}H_{25}ClN_4O_3$	69.58 (69.33	4.80 4.69	10.11 10.43)
5d	C_6H_4-CH_3(*p*)	C_6H_5	141-42	60	Yellow powder (Benz. Pet ether)	$C_{31}H_{26}N_4O_2$	76.82 (76.52	5.61 5.39	11.28 11.51)
5e	C_6H_4-CH_3(*p*)	C_6H_4-Cl(*p*)	158-59	51	Yellow powder (Benzene)	$C_{31}H_{25}ClN_4O_2$	71.58 (71.46	4.69 4.84	10.63 10.75)
5f	C_6H_4-CH_3(*p*)	C_6H_4-OCH_3(*p*)	140-41	50	Yellow granules (Ethanol)	$C_{32}H_{28}N_4O_3$	74.51 (74.40	5.29 5.46	10.90 10.85)
7a	C_6H_4-Cl(*p*)	–	149-50	50	Yellow granules (Ethanol)	$C_{19}H_{20}ClN_3O_2$	63.53 (63.77	5.39 5.63	11.60 11.74)
7b	C_6H_4-CH_3(*p*)	–	141-42	59	Yellow granules (Ethanol)	$C_{20}H_{21}N_3O_2$	71.69 (71.62	6.40 6.31	12.39 12.53)
9a	C_6H_4-Cl(*p*)	–	183-84	62	Yellow needles (Ethanol)	$C_{19}H_{15}ClBrNO_2$	52.92 (52.74	3.63 3.49	9.87 9.71)

antibacterial screening showed that most of the compounds showed weak (zone of inhibition 12-16mm) to moderate activities (17-21mm) against both bacteria. Compounds **4f, 5b** and **5e** showed high order of activity (22-30 mm) against *Aspergillus niger* and compound **5c** exhibited high order of antifungal activity against *Candida albicans* and the remaining compounds exhibited weak (12-17mm) to moderate (17-21mm) anti-fungal activity against both fungi (**Table II**).

Table II—Antibacterial and antifungal activities of compounds **2-9**

Compd	Zone of Inhibition			
	E. coli	*B. cirro-flagellosus*	*A. niger*	*C. albicans*
2a	+	+	+	+
2b	+	+	++	++
4a	-	++	+	++
4b	+	-	++	++
4c	-	+	++	+
4d	-	+	+	+
4e	+	+	++	+
4f	+	+	+++	+
5a	+	+	++	+
5b	-	+	+++	++
5c	-	-	+	+++
5d	-	-	++	+
5e	-	+	+++	-
5f	+	+	++	+
7a	+	+	++	+
7b	+	+	++	+
9a	-	++	++	++

(-)= inactive, (+) = weakly active (12-16 mm), (++) = moderately active (17-21 mm) and (+++) = highly active (22-30 mm).

Experimental Section

Melting points were determined in open capillary tubes and are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on Perkin Elmer 881 spectrophotometer and ^1H NMR spectra in $CDCl_3$ or DMSO-d_6 on 300 MHz NMR spectrometer (chemical shifts in δ, ppm with TMS as internal reference). Elemental analysis were carried out on Heraus CHN-rapid analyser.

1-Substituted-3, 6-diacetyl-5-methoxy-2-methylindoles 2a,b. To a solution of 3,6-diacetyl-5-hydroxyindoles **1a,b** (0.005 mole) in dry acetone (200 mL) were added methyl iodide (0.02 mole), anhydrous K_2CO_3 (6.0 g) and KI (0.1 g). The reaction mixture was heated at reflux for 40 hr and then it was filtered while hot. The solvent was removed under reduced pressure and the residue was recrystallised from suitable solvent.

Compound **2a**: IR (KBr): 1670 (C_3-acetyl >C=O), 1719 (C_6-acetyl >C=O); ^1H NMR ($CDCl_3$, TMS): δ2.55 (s, 3H, C_3-COC*H*$_3$), 2.62 (s, 3H, C_6-COC*H*$_3$), 2.66 (s, C_2-C*H*$_3$), 4.00 (s, 3H, -OCH$_3$), 7.22 (d, *J*=8.7Hz, 2H, C_3- and C_5-H of C_6H_4-Cl(*p*)), 7.42 (s, 1H, C_7-H), 7.53 (d, *J*=8.7Hz, 2H, C_2- and C_6-H of -C_6H_4-Cl(*p*)), 7.70 (s, 1H, C_4-H).

1-(1-Substituted-3-acetyl-5-methoxy-2-methylindol-6-yl)-3-aryl-2-propen-1-ones 4a-f. Appropriate 1-substituted-5-methoxy-3, 6-diacetyl-2-methylindoles **2a,b** (0.002 mole) in ethanol (20 mL) were stirred with sodium hydroxide (0.5 g) in water (10 mL) for 30 min at room temperature. Then, appropriate aromatic aldehyde (0.002 mole) was added to it and stirring was continued for 12 hr at room temperature. The separated yellow solid was filtered, washed with water till the washings are neutral, washed with little ethanol, dried and recrystallised from appropriate solvent.

Compound **4b**: IR (KBr): 1610, 1650 (C_3- and C_6-acetyl >C=O); ^1H NMR ($CDCl_3$, TMS): δ1.58 (3H, 1-C_6H_4-C*H*$_3$), 2.45 (s, 3H, C_3-COC*H*$_3$), 2.60 (s, 3H, C_2-C*H*$_3$), 3.98 (s, 3H. C_5-OC*H*$_3$), 7.10-7.90 (m, 13H, 11ArH and 2 vinyl H).

1-Substituted-3-acetyl-6-(2-amino-3-cyano-4-arylpyrid-6-yl)-5-methoxy-2-methylindoles 5a-f. A mixture of chalcone **4a-f** (0.001 mole), malononitrile (0.001 mole) and ammonium acetate (0.008 mole) in ethanol (20 mL) was refluxed for 8-10 hr on hot water-bath. The cooled contents were then poured on crushed ice (50 g) with constant stirring and the separated yellow solid was filtered, washed with water, dried and recrystallised from suitable solvent.

Compound **5a:** IR (KBr) 3345/3400 (-NH_2), 2900 (-CH), 2175 (-C≡N), 1615 (C_3-acetyl >C=O); ^1H NMR ($CDCl_3$, TMS): δ2.55 (s, 3H, C_3-COC*H*$_3$), 3.89 (s, 3H, C_5-OC*H*$_3$), 4.01 (*s*, 2H, -NH_2 disappeared on D_2O exchange), 6.78-7.77 (m, 12H, ArH).

1-Substituted-3-acetyl-6-hydrazinoacetyl-5-hydroxy-2-methylindoles 7a,b. To a suspension of appropriate diacetylindole **1a,b** (0.001 mole) in ethanol (50 mL) was added hydrazine hydrate (0.62 mL, 0.01 mole, 99%) and the mixture was refluxed on a steam-bath for about 20 hr. The solution was concentrated and the separated yellow solid on cooling was collected by filtration and recrystallised from suitable solvent.

Compound **7a:** IR (KBr): 3200 and 3380 (-OH/ -NH_2), 1630 (C_3-acetyl >C=O); ^{1}H NMR ($CDCl_3$, TMS): δ1.59 (br, 2H, -NH_2, vanished on D_2O exchange), 2.12 (s, 3H, C_6-C(CH_3)=N-NH_2), 2.28 (s, 3H, C_3-COCH_3,), 2.33 (s, 3H, C_2-CH_3), 5.19 (br, 1H, C_5-OH, disappeared on D_2O exchange), 6.99-7.53 (m, 6H, ArH).

3-Acetyl-6-bromoacetyl-1-(4-chlorophenyl)-5-hydroxy-2-methylindole 9a. To a well stirred solution of 3,6-diacetylindole **2a** (0.005 mole) in chloroform (50 mL) was added bromine (0.005 mole) in chloroform (5 mL) during 10 min. The mixture was stirred further for half an hr. The solvent was evaporated and the residue was recrystallised from benzene-pet. ether to give **9a**. IR (KBr): 2950 (C_5-OH, intramolecular H-bonded), 1635 (C_3-acetyl >C=O), 1719 (C_6-CO-CH_2Br); ^{1}H NMR ($CDCl_3$, TMS): δ2.55 (s, 6H, C_3-COCH_3 and C_2-CH_3), 4.90 (s, 2H, C_6-COCH_2-Br), 6.99-7.70 (m, 6H, ArH), 12.7 (br, 1H, C_5-OH; vanished on D_2O exchange).

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