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The Acetylation of 3-Acylindoles

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Acetylation of 3-acetylindole (**9**) with acetyl chloride–aluminum chloride in nitrobenzene or methylene chloride gave 3,5-diacetylindole (**10**) as the major product, together with 3,6- and 3,7-diacetylindole (**11**, **12**) as minor products. The similar acetylation of ethyl 3-indolecarboxylate (**16**) also gave the 5-acetyl derivative (**17a**) as the major product, together with the 6- and 7-acetyl derivatives (**18a**, **19**) as minor products. Oxidation of 1,3-diacetylindole (**15**) with lead tetratrifluoroacetate gave 3-indolinones (**22**, **23**) and a dimeric product (**24**).

Keywords——acetylation; 3-acylindole; acetylindole; oxidation; lead tetratrifluoroacetate; 3-indolinone

Electrophilic substitution of 3-alkylindoles (**1**) is generally known to give the corresponding 2-substituted derivatives (**3**) *via* 3-substituted indolenine (**2**) formed by the initial attack at the 3-position.[1] 3-Alkylindoles which have a substituent at the benzene ring have usually been prepared from the benzene derivatives which are already carrying the substituent. Recently, we have developed a new route to introduce a substituent such as halogen, hydroxy, or nitro group into the benzene ring of tryptophan derivatives by utilizing their cyclic tautomers.[2] On the other hand, electrophilic substitution of 3-acylindoles (**4**), whose reactivity at the 3-position is diminished, has been reported to give 5- and 6-substituted derivatives (**5**), although

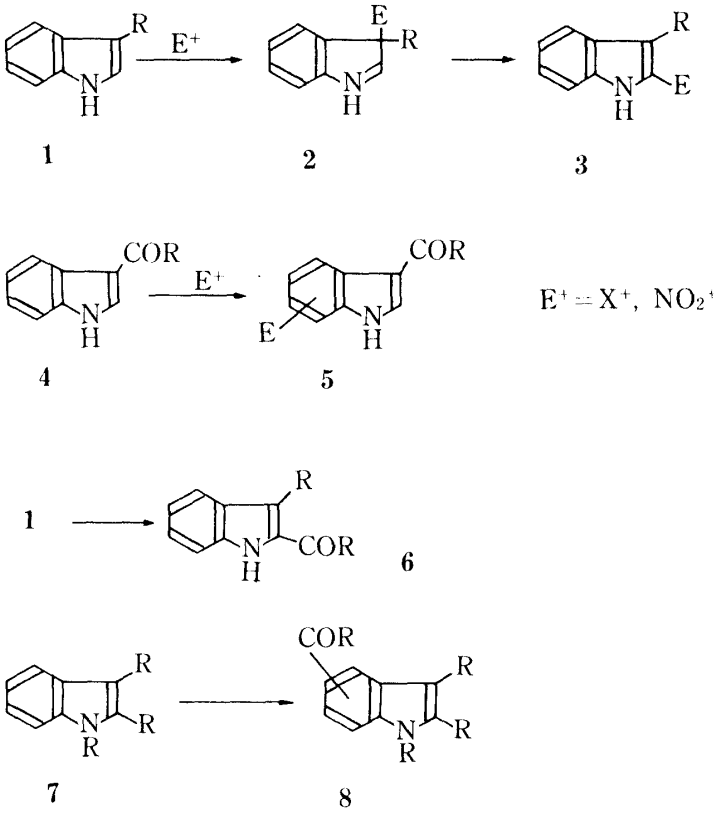


Chart 1

known examples are limited to halogenation[3] and nitration.[4]

In this paper we describe the acetylation of 3-acetylindole and ethyl 3-indolecarboxylate to obtain indole derivatives having an acetyl group at the benzene ring.

The acylation of 3-alkylindoles has been reported to give 2-acyl derivatives (**6**),[5] while 5- or 6-acyl derivatives (**8**) were obtained[6] by the acetylation of 1,2,3-trisubstituted indoles (**7**) under various conditions. However, acetylation of 3-acylindoles has not been described.

3-Acetylindole (**9**) was found to be inert to mild acetylation conditions such as acetic anhydride–acetic acid–boron trifluoride etherate,[5d,f] acetic anhydride–boron trifluoride etherate,[5e]

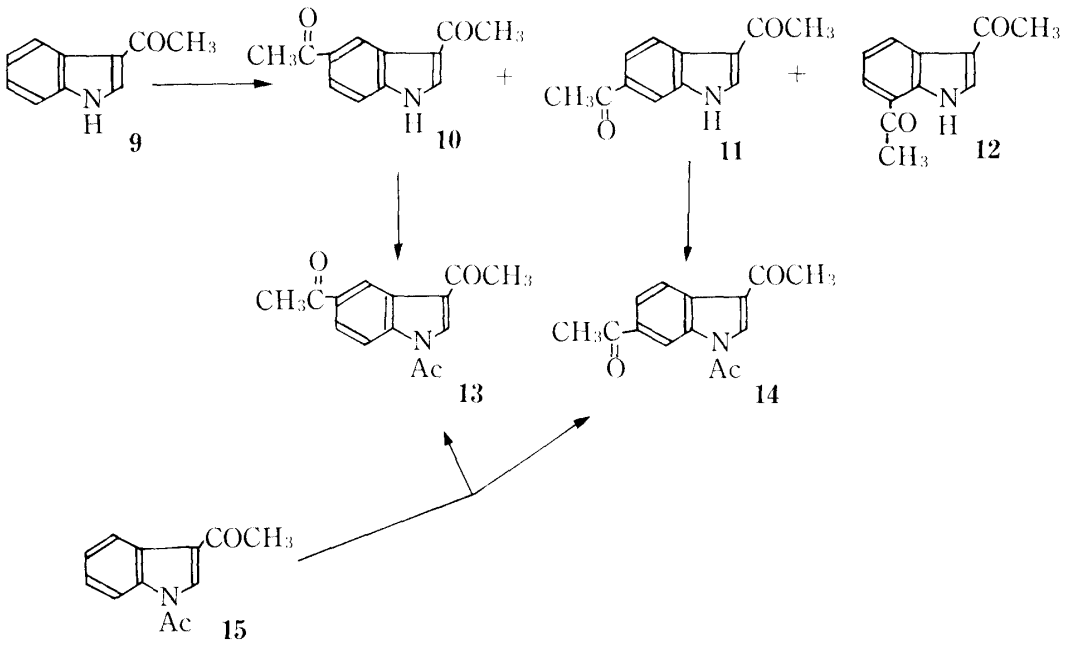


Chart 2

Table I. Analytical Data for Acetylindoles

Compd. No.	R^1	R^2	X	mp °C	Formula	Analysis (%) Calcd (Found) C	H	N
10	H	CH_3	5-	263—264 (dec.)	$C_{12}H_{11}NO_2$	71.62 (71.48	5.51 5.48	6.96 6.99)
11	H	CH_3	6-	278—279 (dec.)	$C_{12}H_{11}NO_2$	71.62 (71.23	5.51 5.45	6.96 6.82)
12	H	CH_3	7-	162—163	$C_{12}H_{11}NO_2$	71.62 (71.68	5.51 5.54	6.96 7.02)
13	Ac	CH_3	5-	219—221	$C_{14}H_{13}NO_3$	69.12 (68.72	5.39 5.43	5.72 5.56)
14	Ac	CH_3	6-	212—214	$C_{14}H_{13}NO_3$	69.12 (68.73	5.39 5.30	5.76 5.68)
17a	H	OEt	5-	170—173	$C_{13}H_{13}NO_3$	67.52 (67.62	5.67 5.69	6.06 6.02)
18a	H	OEt	6-	168—169.5	$C_{13}H_{13}NO_3$	67.52 (67.76	5.67 5.67	6.06 6.03)
19	H	OEt	7-	125—126	$C_{13}H_{13}NO_3$	67.52 (67.72	5.67 5.69	6.06 6.01)
17b	Ac	OEt	5-	164—165	$C_{15}H_{15}NO_4$	65.92 (66.02	5.53 5.49	5.13 5.09)
18b	Ac	OEt	6-	151—152	$C_{15}H_{15}NO_4$	65.92 (65.81	5.53 5.48	5.13 5.07)

Table II. Spectral Data for Diacylindoles

Compd. No.	R^1	R^2	x	UV λ_{max}^{EtOH} nm ($\varepsilon \times 10^{-3}$)	IR ν_{max}^{KBr} cm^{-1}	MS m/e (rel. %)
10	H	CH_3	5	245(39.7), 255 sh(23.3) 297.5(2.0)	3150 (NH) 1670, 1630 (CO)	201 (41, M^+), 186 (100, M–Me), 158 (14, M–Ac) 143 (12, M–Ac–Me)
11	H	CH_3	6	233(9.3), 274(33.6) 293 sh(15.3)	3150 (NH) 1680, 1640 (CO)	201 (40, M^+), 186 (100, M–Me), 143 (20, M–Ac–Me)
12	H	CH_3	7	226(21.6), 269(10.8) 321(14.1)	3340 (NH) 1650 (CO)	201 (53, M^+), 186 (100, M–Me), 168 (35, M–Me–H_2O) 158 (5, M–Ac)
13	Ac	CH_3	5	241.5, 261, 285 sh	1730, 1715, 1665 (CO)	243 (35, M^+) 201 (22, M–CH_2CO), 186 (100, M–Ac–Me) 158 (7)
14	Ac	CH_3	6	228, 263, 310, 317	1720, 1665 (CO)	
17a	H	OEt	5	244(42.2), 294(11.9)	3225 (NH) 1665 (CO)	231 (61, M^+), 216 (100, M–Me) 188 (30, M–Ac) 186 (35, M–OEt)
18a	H	OEt	6	236(13.8), 264(36.3) 296(11.1)	3200 (NH) 1680 (CO)	231 (75, M^+), 216 (100, M–Me) 188 (27, M–Ac) 186 (43, M–OEt)
19	H	OEt	7	220(24.0), 234 sh(14.4) 248 sh(10.4), 320(12.2)	3225 (NH) 1690, 1655 (CO)	231 (69, M^+), 216 (23, M–Me), 186 (100, M–OEt), 168 (16, M–OEt–H_2O)
17b	Ac	OEt	5	220 sh, 236, 258	1700, 1650 (CO)	273 (57, M^+), 231 (47, M–Ac), 216 (100, M–Ac–Me)
18b	Ac	OEt	6	223, 243, 277 sh, 289, 310, 319	1735, 1710, 1670 (CO)	273 (44, M^+), 231 (54, M–Ac), 216 (100, M–Ac–Me)

Table III. NMR Data for Diacylindoles
(δ in ppm in DMSO-d_6)

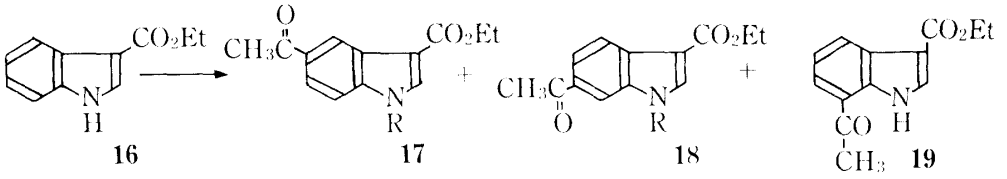
Compd. No.	CH_3CO	NH	2-H	4-H	5-H	6-H	7-H
10	2.50, 2.65	12.20 br s[a]	8.50 br s[b]	8.90 d (J=2.0)	—	7.90 dd (J=8.0, 2.0)	7.60 d (J=8.0)
11	2.45, 2.60	12.10 br s[a]	8.40 br s[b]	8.15 d (J=8.0)	7.70 dd (J=8.0, 2.0)	—	8.00 d (J=2.0)
12	2.45, 2.70	11.95 br s[a]	8.20 d[b]	8.50 d (J=8.0)	7.30 t (J=8.0)	7.95 d (J=8.0)	—
13	2.55, 2.60, 2.75	—	8.75 s	8.65 d (J=2.0)	—	7.95 dd (J=8.0, 2.0)	8.35 d (J=8.0)
14	2.55, 2.60, 2.75	—	8.80 s	8.20 d (J=2.0)	7.90 dd (J=8.0, 2.0)	—	8.75 d (J=8.0)
17a	2.60	12.15 br s[a]	8.15 s[b]	8.65 d (J=2.0)	—	7.85 dd (J=8.0, 2.0)	7.55 d (J=8.0)
18a	2.65	12.20 br s[a]	8.25 s	8.05 d (J=8.0)	7.80 dd (J=8.0, 2.0)	—	8.10 d (J=2.0)
19	2.65	11.90 br s[a]	7.95 br s[b]	8.30 d (J=8.0)	7.30 t (J=8.0)	7.90 d (J=8.0)	—
17b	2.60, 2.75	—	8.45 s	8.55 d (J=2.0)	—	7.95 dd (J=8.0, 2.0)	8.35 d (J=8.0)
18b	2.60, 2.75	—	8.50 s	7.8—8.1 m		—	8.80 bs

a) Disappeared on the addition of D_2O.
b) Became a sharp singlet on the addition of D_2O.

or acetyl chloride–zinc chloride[5c] by which 3-alkylindoles are acetylated at the 2-position. However, the acetylation of 3-acetylindole (**9**) with acetyl chloride (an excess) and aluminum chloride (3 mol eq.) in nitrobenzene at room temperature gave a mixture of 3,5- and 3,6-diacetylindoles (**10**, **11**), and 3,7-diacetylindole (**12**) in 66% and 8% yields, respectively. Separation of 3,5- and 3,6-diacetylindoles by column chromatography was unsuccessful, but 3,5-diacetylindole (**10**), mp 278—279°C, and 3,6-diacetylindole (**11**), mp 263—264°C, were separated by recrystallization from ethyl acetate and acetone. The reaction in methylene chloride at room temperature conveniently gave a mixture of 3,5- and 3,6-diacetylindoles (**10**, **11**) in 75% yield and 3,7-diacetylindole (**12**) in 15% yield. The total yield and the yield of **12** were higher than those obtained in nitrobenzene. The increased ratio of 3,7-diacetylindole in methylene chloride is probably due to the smaller bulk of the reactive species in methylene chloride than in nitrobenzene. The ratio of 3,5- and 3,6-diacetylindole was estimated as 6.5 : 1 from the NMR spectrum of the mixture.

The structures of these diacetylindoles were confirmed by the spectral data shown in Tables II and III. The position of the newly introduced acetyl group was determined mainly from the NMR spectrum in dimethyl sulfoxide-d_6. In 3,5-diacetylindole (**10**) a fine doublet due to the proton at the 4-position between the 3-and 5-acetyl groups appeared at 8.90 ppm. A broad singlet due to the proton at the 2-position appeared at 8.50 ppm, which became a sharp singlet on the addition of D_2O and shifted to 8.75 ppm upon *N*-acetylation. A doublet due to the proton at the 7-position appeared at 7.60 ppm and shifted to 8.35 ppm on *N*-acetylation, while a double doublet due to the proton at the 6-position appeared at 7.90 ppm and shifted slightly to 7.95 ppm on *N*-acetylation. On the other hand, in 3,6-diacetylindole (**11**) a doublet due to the proton at the 4-position appeared at 8.15 ppm and a double doublet due to the proton at the 5-position appeared at 7.70 ppm, which was slightly shifted to 7.90 ppm on *N*-acetylation. A fine doublet due to the proton at the 7-position appeared at 8.00 ppm, which was shifted to 8.78 ppm on *N*-acetylation. The NMR spectrum of 3,7-diacetylindole (**12**) did not permit discrimination of **12** from 3,4-diacetylindole. However, strong evidence for the 7-acetyl derivative was obtained on *N*-acetylation with acetic acid and sodium acetate. Under these conditions the 3,7-diacetyl derivative did not afford an *N*-acetyl derivative, though the 3,5- and 3,6-diacetylindoles both gave the corresponding *N*-acetyl derivatives in good yields. Further evidence for the 3,7-diacetyl derivative was obtained from its IR spectrum which showed a hydrogen bond between the 7-acetyl and NH groups.

The acetylation of 3-acetylindole thus gave the 5-acetyl derivative as the main product and the 6- and 7-acetyl derivatives as minor products. In contrast to the bromination of 3-alkyl- and 3-phenylindoles[8] where the 2,6-dibromide was obtained as the major product



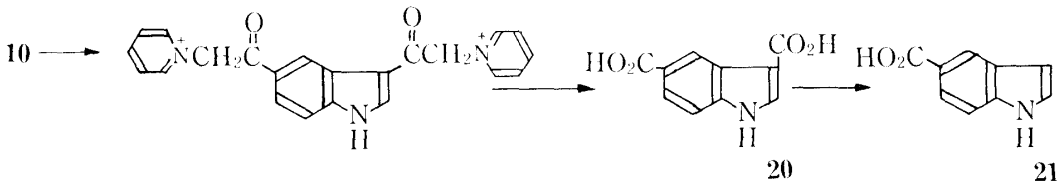


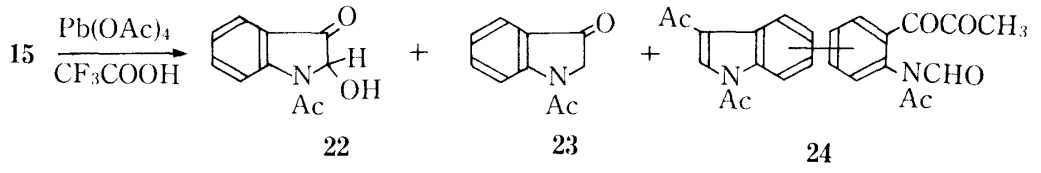
Chart 3

and the 2,5-dibromide as a minor product, the 3-acetyl group prevents not only 2-substitution, but also affects the attacking position at the benzene ring. Direct substitution at the 7-position by electrophilic substitution of indole derivatives has not been reported previously.

To examine the effect of the *N*-acetyl group on the acetylation, we next carried out the acetylation of 1,3-diacetylindole. The reaction of 1,3-diacetylindole with acetyl chloride–aluminum chloride in methylene chloride did not proceed, while the reaction in nitrobenzene gave a mixture of 5- and 6-acetyl derivatives in 9% yield. *N*-Acetylation retards the reaction, as expected. Elevation of the reaction temperature simply resulted in more resinous products.

We next carried out the acetylation of ethyl 3-indolecarboxylate (**16**) to investigate the effect of the 3-substituent. When a mixture of ethyl 3-indolecarboxylate (**16**), acetyl chloride, and aluminum chloride in the same ratio as above in methylene chloride was stirred for 3 h at room temperature, the 5-acetyl (**17a**), mp 170—173°C, 6-acetyl (**18a**), mp 168—169°C, and 7-acetyl (**19**), mp 125—126°C, derivatives were obtained in 40%, 20%, and 20% yields, respectively. Separation of the 5- and 6-acetyl derivatives was achieved by column chromatography in contrast to the case of 3-acetylindole. The structures of these products were confirmed by their spectral data and those for the *N*-acetylated derivatives (**17b**, **18b**) as in the case of the 3-acetyl derivatives. The ratio of the products obtained from 3-acetyl and 3-ethoxycarbonylindoles was different and the selectivity was decreased in the latter case. This indicates that the acetyl group has a stronger 5-position-directing power which might be correlated to the σ_p-values for the acetyl (0.508) and the ester (0.31).[9]

As an aromatic methylketone can be converted to a carboxylic acid *via* a pyridinium salt, 3,5-diacetylindole (**10**) was treated with pyridine and iodine followed by alkaline hydrolysis to give indole-3,5-dicarboxylic acid (**20**), mp 266—267°C. This dicarboxylic acid was decarboxylated by heating in 10% hydrochloric acid–ethanol for 1 h to give 5-indolecarboxylic acid (**21**),[10] mp 209—213°C (identical with the reported value), confirming the position of the newly introduced acetyl group. The acetyl group at the 3-position of indole has been reported to be removed under alkaline or acidic conditions.[4,11] Selective deacetylation of 3,5- and 3,6-diacetylindoles by refluxing in conc. hydrochloric acid gave unsatisfactory results. Baeyer–Villiger oxidation of ethyl 5-acetyl-3-indole carboxylate with *m*-chloroperbenzoic acid under various conditions failed to give the 5-hydroxy derivative.



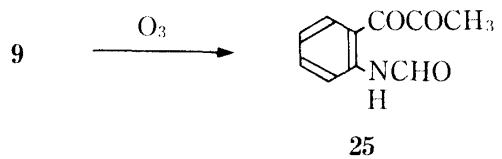


Chart 4

Thus, we examined the direct acetoxylation of 3-acylindoles. As lead tetratrifluoroacetate has been reported[12] to trifluoroacetoxylate less reactive aromatics such as benzene and chlorobenzene, in contrast with lead tetraacetate, the reaction of 3-acylindoles with lead tetraacetate in trifluoroacetic acid (which is equivalent to lead tetratrifluoroacetate) was carried out. 3-Acetylindole and ethyl 3-indolecarboxylate gave small amounts of dimeric compounds (struc-

ture unknown) besides polymeric compounds, and no hydroxylated compound was isolated. The reaction of 1,3-diacetylindole with lead tetraacetate in trifluoroacetic acid at room temperature gave 1-acetyl-2-hydroxy-3-indolinone (**22**), mp 146—147°C, 1-acetyl-3-indolinone (**23**), mp 130—132°C, and a dimeric compound, mp 244—247°C, in 15%, 5%, and 5% yields, respectively. The structures of 3-indolinones were established by their spectral data (see "Experimental"). Alkaline hydrolysis of **22** and **23** gave anthranilic acid, which was formed by autoxidation and hydrolysis. The structure of the dimeric compound was assigned as **24** from the spectral data, but the position of the bond between the two benzene rings was not established. As the UV spectra of 1-acetyl-3-indolinones (**22**, **23**) were similar to that of diketoamide (**25**), a standard sample of **25** was prepared by the ozonolysis of 3-acetylindole, and it was found to be not identical with 1-acetyl-3-indolinones. Although the mechanism of formation of these 3-indolinones is not clear, lead tetratrifluoroacetate may attack at the deactivated 3-position of 1,3-diacetylindole in preference to the benzene ring.

Experimental

All melting points are uncorrected. The UV spectra were taken with a Hitachi 323 spectrophotometer, and IR spectra with Hitachi EPI-G-3 and IR-215 spectrometers. The NMR spectra were recorded on a JEOL MH-100 spectrometer and MS on a Hitachi RMU-6 instrument.

Acetylation of 3-Acetylindole (**9**)——i) In Nitrobenzene: Acetyl chloride (10 ml, 0.17 mol) was added dropwise to a solution of 3-acetylindole (**9**, 5.0 g, 0.03 mol) in nitrobenzene (50 ml) at room temperature. Anhydrous $AlCl_3$ (10.0 g, 0.075 mol) was added to the reddish-orange mixture under cooling. The resulting dark red mixture was stirred at room temperature for 3.5 h then poured into cold water (500 ml). The separated solid (A) was collected and washed with H_2O. The mother liquor was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with sat. $NaHCO_3$ solution, H_2O, and dried. Removal of CH_2Cl_2 and nitrobenzene by evaporation *in vacuo* gave a dark brown oil (B). The solid (A) was purified by passage through a short silica gel column to give pale brown crystals (3.31 g, A') which were shown to be a mixture of **10** and **11** in a ratio of 5.5 : 1 by its NMR spectrum. The dark brown oil (B) was chromatographed on a silica gel (200 g) column. Elution with CH_2Cl_2–AcOEt (10: 1) gave 3,7-diacetylindole (**12**, 536 mg, 8.5%), which yielded pale brown crystals, mp 162—163°C, on recrystallizations from benzene–hexane. Further elution with the same solvent gave an unknown compound (466 mg), mp 170—180°C, which showed the presence of chlorine in its mass spectrum, but it was not investigated further. Elution with CH_2Cl_2–AcOEt (3: 1) gave a mixture of **10** and **11** (886 mg, total yield of the mixture, 4.196 g, 66.4%). Recrystallizations of the mixture from AcOEt gave 3,5-diacetylindole (**10**), mp 263—264°C (dec.), as pale brown crystals. Recrystallizations of the residue obtained from the mother liquor from acetone gave 3,6-diacetylindole (**11**), mp 278—279°C (dec.). Both compounds showed an identical spot on TLC (silica gel) in several solvent systems. The melting point of a mixture of the two compounds was depressed to mp 238—243°C.

When the same reaction was carried out at 80—100°C (bath temperature) for 5 h, a mixture of **10** and **11** was isolated in 10% yield along with a small amount of **12**.

ii) In CH_2Cl_2: Acetyl chloride (2 ml, 33.3 mmol) and anhydrous $AlCl_3$ (2.0 g, 15 mmol) were added to a solution of 3-acetylindole (**9**, 1.0 g, 6.3 mmol) in CH_2Cl_2 (20 ml) at room temperature. The dark red mixture was stirred at room temperature for 4 h and poured into cold water (200 ml). The separated solid (884 mg, A), a mixture of **10** and **11** (7: 1), was collected and the filtrate was extracted with CH_2Cl_2. The extracts were washed with $NaHCO_3$ and H_2O, and dried. Removal of the solvent by evaporation gave a dark red residue (250 mg) which was chromatographed on silica gel. Elution with CH_2Cl_2–AcOEt (10: 1) gave **12** (179 mg, 14.2%), mp 160—163°C. Elution with CH_2Cl_2–AcOEt (10: 1—1: 1) gave a mixture of **10** and **11** (3: 1) (54 mg(B), total 938 mg, 75%). From the NMR spectra of the mixture of A and B, 3,5-diacetylindole (**10**) was the major product (65%) and 3,6-diacetylindole (**11**) was the minor product (10%).

1-Acetylation of 10 and 11——Diacetylindole (**10** or **11**) was heated at 100°C (bath temperature) with Ac_2O and AcONa (catalytic amount) for 1 h. The mixture was concentrated *in vacuo* and the residue was added to cold water. The separated crystals were collected and recrystallized. 1,3,5-Triacetylindole (**13**, 87%), mp 219—221°C (from AcOEt). 1,3,6-Triacetylindole (**14**, 91%), mp 212—214°C (from benzene). Under similar conditions, 3,7-diacetylindole (**12**) did not give the 1-acetyl derivative and **12** was recovered in 68% yield.

Acetylation of 1,3-Diacetylindole——1,3-Diacetylindole (**15**, 500 mg, 3.14 mmol) was added to a mixture of nitrobenzene (10 ml), acetyl chloride (2 ml) and anhydrous $AlCl_3$ (1.0 g) at room temperature. The mixture was stirred at room temperature for 16 h then poured into cold water (300 ml). The mixture was extracted with CH_2Cl_2. The extracts were washed with aq. $NaHCO_3$ and H_2O and dried. Removal of the solvents *in vacuo* gave a dark brown residue which was chromatographed on a silica gel column. Elution

with CH_2Cl_2 gave the starting material (226 mg). Further elution gave a mixture of **13** and **14** (54 mg, 9.0%).

Acetylation of Ethyl 3-Indolecarboxylate (16)——Acetyl chloride (4 ml, 70 mmol) and then anhydrous $AlCl_3$ (4.0 g, 30 mmol) were added gradually to a solution of 3-indolecarboxylate (**16**, 2.0 g, 10 mmol) in CH_2Cl_2 (50 ml) at room temperature. The mixture was stirred at room temperature for 3 h, poured into cold water (400 ml), and extracted with CH_2Cl_2. The extracts were washed with $NaHCO_3$ and H_2O, and dried. Removal of the solvent by evaporation gave a residue (2.3 g) which was chromatographed on silica gel column (150 g). Elution with CH_2Cl_2–AcOEt (15: 1) gave 7-acetyl derivative (**19**, 513 mg, 21%), which was obtained as pale brown crystals, mp 125—126°C, on recrystallization from benzene–hexane. Elution with CH_2Cl_2–AcOEt (10: 1) gave a mixture of **17a** and **18a** (2.1 g) which was separated by repeated alumina column chromatography to yield the 5-acetyl derivative (**17a**, 832 mg, 34%) and the 6-acetyl derivative (**18a**, 521 mg, 21%). Recrystallization of **17a** from AcOEt–hexane gave colorless crystals, mp 170—173°C. Acetylation of **17a** with Ac_2O–AcONa gave the 1-acetyl derivative (**17b**, mp 164—165°C (from benzene–hexane)) in 83% yield. Recrystallization of **18a** from AcOEt–hexane gave colorless crystals, mp 168—169.5 °C. 1-Acetyl derivative (**18b**), mp 151—152°C (from benzene–hexane).

Preparation of 5-Indolecarboxylic Acid from 3,5-Diacetylindole——Iodine (2.5 g, 10 mmol) was added to a solution of **10** (827 mg, 4 mmol) in pyridine (15 ml) at room temperature. The mixture was heated at 100°C (bath temperature) for 1 h then concentrated to leave a black residue. The residue was poured into H_2O and the insoluble solid was collected. The solid was dissolved in hot water and the solution was treated with charcoal, then concentrated to give a pyridinium salt (1.65 g). UV λ_{max}^{EtOH}: 229, 241, 256, and 304 nm. IR (KBr) cm^{-1}: 3400—3000, 1670, and 1640. The crude pyridinium salt was dissolved in EtOH–H_2O (1: 1, 60 ml), and NaOH pellets (1.20 g) were added to the solution. The mixture was heated at 80—90°C (bath temperature) for 1 h with stirring. The mixture was acidified with 10% HCl to pH 1—2, concentrated *in vacuo* to remove EtOH, and extracted with AcOEt. The extracts were washed with aq. NaCl solution and dried. Removal of the solvent by evaporation gave 3,5-indoledicarboxylic acid (**20**, 400 mg), mp 266—267°C. UV λ_{max}^{EtOH} m: 235, 286, and 293. IR (KBr) cm^{-1}: 3340, 3000—2500, 1670, and 1610. MS *m/e* 205 (M^+, 95), 188 (100, M–OH). A solution of the above dicarboxylic acid (350 mg) in 10% HCl (60 ml) and EtOH (20 ml) was refluxed for 1 h. The mixture was concentrated to remove EtOH and extracted with AcOEt. The extracts were washed with sat. NaCl solution and dried. Removal of the solvent gave a residue which was chromatographed on a silica gel column. Elution with CH_2Cl_2–AcOEt (10: 1) gave indole-5-carboxylic acid (50 mg, 18%), which was recrystallized from H_2O to give pale yellow crystals, mp 213—214°C (reported mp[10] 208°C). UV λ_{max}^{EtOH} nm: 237 and 267. IR (Nujol) cm^{-1}: 3325, 1660, 1300, 990, 745, and 715. MS *m/e*: 161 (100, M^+), 144 (93, M–OH).

Reaction of 1,3-Diacetylindole (15) with Lead Tetraacetate in CF_3COOH——A solution of $Pb(OAc)_4$ (90%, 3.88 g, 7.88 mmol) in CF_3COOH (15 ml) was added to a solution of **15** (1.58 g, 7.86 mmol) in CF_3COOH (50 ml) at 0°C during 15 min. The mixture was stirred at room temperature for 1 h then concentrated The residue was extracted with AcOEt–H_2O. The extracts were washed with sat. $NaHCO_3$ and H_2O, and dried. Removal of the solvent by evaporation gave a residue (1.84 g) which was chromatographed on a silica gel column (70 g). Elution with CH_2Cl_2 resulted in recovery of the starting material (396 mg, 25%). Elution with CH_2Cl_2–AcOEt (10: 1) gave a mixture(A) of a dimer (**24**) and 1-acetyl-3-indolinone (**23**, 252 mg). Elution with CH_2Cl_2–AcOEt (15: 2) gave 1-acetyl-2-hydroxy-3-indolinone (**22**, 110 mg, 6.6%) which was recrystallized from benzene–hexane as pale brown crystals, mp 146—147°C. Fraction A was recrystallized from benzene–isopropyl ether to give a dimer (**24**, 60 mg) as pale brown crystals. Recrystallizations from benzene gave pure **24**, mp 255—257°C. The mother liquor was further separated by preparative TLC (silica gel/CH_2Cl_2–AcOEt (1: 1)) to give the dimer 15 mg, total 75 mg, 4.4%) and **23** (75 mg, 5.5%). Recrystallization of **23** from isopropyl ether gave pale pink crystals, mp 130—132°C (reported mp 136°C).[13]

1-Acetyl-2-hydroxy-3-indolinone (**22**): UV λ_{max}^{EtOH} (ε) nm: 233 sh (25000), 238.5 (27000), 260 (10300), 265 sh (9500), 342 (3000). IR (KBr): cm^{-1}: 3240 (OH), 1715, 1660 (CO), 760. MS *m/e*: 191 (52, M^+), 149 (100, M–CH_2=C=O), 148 (100, M–Ac), 132 (10, M–Ac-16). NMR δ (DMSO-d_6): 2.30 (s, 3H, $COCH_3$), 5.40 (d, 1H, 2-H, changed to a singlet on the addition of D_2O), 7.20—7.40 (m, 2H, aromatic H + OH, OH signal disappeared on the addition of D_2O), 7.60—7.80 (m, 2H, aromatic H), 8.30 (dd, 1H, aromatic H). *Anal.* Calcd for $C_{10}H_9NO_3$: C, 62.86; H, 4.75; N, 7.33. Found: C, 62.85; H, 4.73; N, 7.42.

1-Acetyl-3-indolinone (**23**): UV λ_{max}^{EtOH} nm (ε): 232.5 sh (26500), 238 (31300), 257.5 (13000), 265 (11500), 337 (4500). IR (KBr) cm^{-1}: 1710, 1675, 1600, 1280, 760. MS *m/e*: 175 (69, M^+), 133 (100, M–CH_2=C=O), 132 (22, M–Ac), 105 (73, M–CH_2CO–CO), 104 (49, M–Ac–CO). NMR δ ($CDCl_3$); 2.30 (s, 3H, $COCH_3$), 4.30 (s, 2H, CH_2), 7.25 (m, 1H, aromatic H), 7.70 (m, 2H, aromatic H), 8.55 (m, 1H, aromatic H). *Anal.* Calcd for $C_{10}H_9NO_2$; C, 68.56; H, 5.18; N, 8.00. Found: C, 68.49; H, 5.09; N, 7.99.

Dimer (**24**): UV λ_{max}^{EtOH} nm (ε): 263 (21600), 290 sh (16000). IR (KBr) cm^{-1}: 1760, 1705, 1665. MS *m/e*: 432 (19, M^+), 390 (17, M–CH_2=C=O), 374 (14), 347 (42), 290 (42), 146 (100). NMR δ (DMSO-d_6): 2.20 (s, 3H, $COCH_3$), 2.50 (s, 3H, $COCH_3$), 2.55 (s, 3H, $COCH_3$), 2.70 (s, 3H, $COCH_3$), 7.20—7.60 (m, 3H, aromatic H), 8.20—8.30 (m, 3H, aromatic H), 8.75 (s, 1H, CHO). *Anal.* Calcd for $C_{24}H_{20}N_2O_6$: C, 66.66; H, 4.66; N, 6.48. Found: C, 66.96; H, 4.65; N, 6.24.

Ozonolysis of 3-Acetylindole——Ozone in oxygen obtained by means of an ozone generator was introduced into a chilled solution of 3-acetylindole (500 mg, 2.49 mmol) in MeOH (150 ml) during 20 min at

−70°C (dry ice–acetone). Nitrogen gas was introduced into the mixture to remove excess ozone. Dimethyl sulfide was added to the mixture and the cooling bath was removed. The mixture was stirred at room temperature for 90 min until the KI-starch test became negative. The dark orange mixture was concentrated to leave a residue (946 mg) which was chromatographed on a silica gel column. Elution with CH_2Cl_2 gave the ketoamide (**25**, 210 mg, 35%), which was recrystallized from benzene–hexane as pale yellow prisms, mp 168—169°C. UV λ_{max}^{EtOH} nm (ε): 235 sh ((24000), 240 (26600), 261 (11700), 336 (3100). IR (KBr) cm^{-1}: 3200 (NH), 1725, 1660 (CO). MS *m/e*; 191 (51, M^+), 162 (15, M–CHO), 149 (100, M–CH_2=C=O), 148 (47, M–Ac). NMR δ (DMSO-d_6); 1.60 (s, 3H, $COCH_3$), 7.20—7.30 (m, 2H, NH and aromatic H), 7.60—7.90 (m, 2H, aromatic H), 8.30 (d, 1H, aromatic H), 8.80 (s, 1H, CHO). *Anal.* Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.93; H, 4.67; N, 7.30.

Alkaline Hydrolysis of 1-Acetyl-3-indolinones——A solution of 1-acetyl-2-hydroxy-3-indolinone (**22**, 23 mg) in NaOH–EtOH was stirred at room temperature for 15 h. The mixture was concentrated *in vacuo* to remove EtOH then extracted with AcOEt. The aqueous layer was acidified with 10% HCl to pH 2 and extracted with AcOEt. Usual work-up gave anthranilic acid (11 mg), mp 140—142°C. Under similar conditions, 1-acetyl-3-indolinone (**23**) also gave anthranilic acid.

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