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Synthetic Studies on Indoles and Related Compounds. XV.[1] An Unusual Acylation of Ethyl Indole-2-carboxylate in the Friedel–Crafts Acylation

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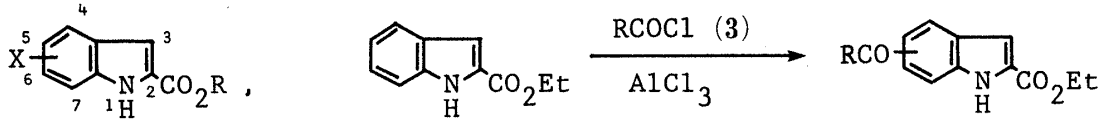
The Friedel–Crafts reaction of ethyl indole-2-carboxylate (**1a**) with acyl chlorides or acid anhydrides in the presence of Lewis acids was investigated in order to establish a preparative procedure for the corresponding ethyl 3-acylindole-2-carboxylates (**4**). Although monoacylation occurred successfully, the products were generally a mixture of ethyl 3-, 5-, and 7-acylindole-2-carboxylates (**4**, **5**, and **6**). The ratio of the yields of these three products varied greatly depending on reaction conditions and reagents used. A tendency that the 3-acylindole (**4**) was obtained as a main product was observed when a Lewis acid other than aluminum chloride was used as a catalyst and/or an acyl chloride derived from a weaker acid was employed, whereas a tendency for formation of the 5- and 7-acylindoles (**5** and **6**) was observed when aluminum chloride and/or an acyl chloride derived from a stronger acid was used. As to the 5- and 7-acylindoles (**5** and **6**), the yields of the former (**5**) were always much higher than those of the latter (**6**). The result indicates that ethyl 3- and 5-acylindole-2-carboxylates can be regioselectively prepared from a common substrate (**1a**) by changing the reaction conditions or reagents.

Keywords——Friedel–Crafts acylation; ethyl indole-2-carboxylate; acyl chloride; acid anhydride; Lewis acid; aluminum chloride; acylindole

Indole-2-carboxylic acids (**1**) can be considered[2] as stable equivalents of corresponding indoles unsubstituted at the 2-position, because they are stable under both acidic and oxidative conditions due to the presence of the electron-attracting carboxyl group, which can be removed by a simple decarboxylation process whenever it becomes unnecessary. In a previous paper,[3] we reported that the acylation at the 3-position of ethyl indole-2-carboxylate (**1a**) occurred successfully with a combination of carboxylic acid, trifluoroacetic anhydride, and phosphoric acid in acetonitrile, which was not applicable to indoles not stabilized by a carboxyl group. However, under the above reaction conditions, some stronger carboxylic acids such as chloroacetic acid and *p*-nitrobenzoic acid did not serve as acylating agents. In order to achieve acylation with stronger carboxylic acids, we attempted the Friedel–Crafts[4] acylation of ethyl indole-2-carboxylate (**1a**), and obtained an unusual result which is described in detail in this paper.[5]



1 : R=H or alkyl　　**1a**　　**2**

Chart 1

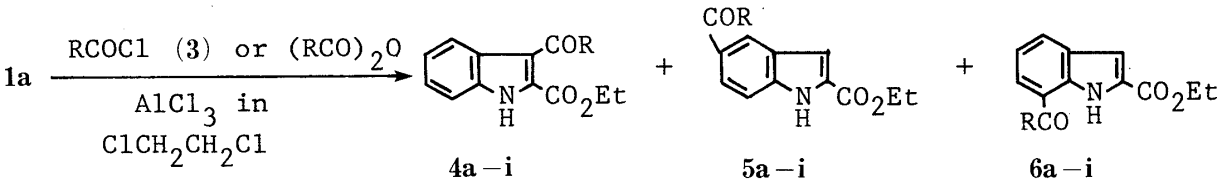


Chart 2

TABLE I. Friedel–Crafts Acylation of Ethyl Indole-2-carboxylate (**1a**) with Acyl Chlorides or Acid Anhydrides

Run	Compound No.	Compound R	Reagent	Reaction conditions: Temperature	Reaction conditions: Time (h)	Product: Total yield (%)	Product: Products ratio 4 : 5 : 6	Recovery of **1a** (%)
1	**3a**	CH_3	A	r.t.	1.0	73.2	55 : 31 : 14	0
2			A[a]	r.t.	1.0	77.6	81 : 15 : 4	0
3			B	Reflux	1.0	72.7	98 : 2 : 0	Trace
4	**3b**	$CH_3(CH_2)_2$	A	0 °C	1.5	72.3	51 : 34 : 15	7.1
5			A[a]	r.t.	1.0	95.3	87 : 10 : 3	Trace
6	**3c**	$(CH_3)_2CH$	A	r.t.	3.5	58.5	57 : 24 : 19	32.6
7	**3d**	$ClCH_2$	A	r.t.	1.0	62.8	1 : 86 : 13	29.1
8			A[a]	r.t.	2.0	37.5	13 : 77 : 10	47.0
9			B	Reflux	1.5	25.8	11 : 76 : 12	70.4
10			B[a]	110 °C	2.0	41.5	23 : 68 : 9	Trace
11	**3e**	*p*-$NO_2C_6H_4$	A	Reflux	1.0	67.7	9 : 72 : 19	19.3
12	**3f**	*p*-ClC_6H_4	A	Reflux	1.0	57.9	63 : 23 : 14	25.6
13	**3g**	C_6H_5	A	Reflux	1.0	78.5	51 : 31 : 18	Trace
14			B	Reflux	1.0	64.5	99 : 1 : 0	25.5
15	**3h**	*p*-$CH_3C_6H_4$	A	Reflux	1.0	72.9	80 : 13 : 7	Trace
16	**3i**	*p*-$CH_3OC_6H_4$	A	Reflux	1.0	69.7	99 : 1 : 0	0

A, acyl chloride (RCOCl); B, acid anhydride [$(RCO)_2O$]; r.t., room temperature. *a*) Nitrobenzene was used as a solvent for the reaction.

First, we undertook the Friedel–Crafts acylation of the indole (**1a**) with various acyl chlorides (**3**), using aluminum chloride as a catalyst in 1,2-dichloroethane (molar ratio; **1a** : **3** : $AlCl_3$ = 1 : 2 : 2, method A in Table I) and found that monoacylation took place in fairly good yields, as shown in Table I.

The results in Table I show that the Friedel–Crafts acylation with aromatic acyl chlorides required more drastic conditions than those with aliphatic ones to complete.

It is interesting to note that monoacylation occurred not only at the most reactive 3-position, but also at the 5- and 7-positions to give 3-, 5-, and 7-acylindoles (**4**, **5**, and **6**). As for the latter two (**5** and **6**), the yields of 5-acylindoles (**5**) were usually much higher than those of 7-acylindoles (**6**). With simple aliphatic acyl chlorides, the ratio of the products acylated at the pyrrole moiety and at the benzene moiety was nearly 1 : 1 (runs 1, 4, and 6), whereas with the acyl chlorides derived from stronger acids, *e.g.*, R = CH_2Cl, the substitution occurred exclusively at the benzene moiety (mainly at the 5-position) (run 7).

This regioselectivity in the acylation of **1a** was clearly confirmed by the experiments using benzoyl (run 13) and *p*-substituted benzoyl chlorides (runs 11, 12, 15, and 16). In Table II, the acidity constants[6] (K_a) of the parent carboxylic acids of acyl chlorides and the ratio of the combined yields of 5- and 7-acylindoles (**5** and **6**) to the total yields of the three acylindoles (**4**, **5**, and **6**) are listed. Table II shows that in general, there is an apparent relationship between the acidity constants and the ratio except for the case of *p*-chlorobenzoyl chloride. It seems

TABLE II. Acidity Constants (K_a) of Carboxylic Acids and the Ratio of the Combined Yields of the 5- and 7-Acylindoles (**5** and **6**) to the Total Yield of the Acylindoles (**4**, **5**, and **6**)

R	K_a[6a] of RCO_2H ($\times 10^5$)	Ratio[a] (%) of **5** and **6**/**4**, **5**, and **6**
$ClCH_2$ (**d**)	136	99
CH_3 (**a**)	1.75	45
$CH_3(CH_2)_2$ (**b**)	1.52	49
$(CH_3)_2CH$ (**c**)	1.38[b]	43
p-$NO_2C_6H_4$ (**e**)	36	91
p-ClC_6H_4 (**f**)	10.3	37
C_6H_5 (**g**)	6.3	49
p-$CH_3C_6H_4$ (**h**)	4.2	20
p-$CH_3OC_6H_4$ (**i**)	3.3	1

a) Calculated by method A in Table I. *b*) Taken from reference 6*b*.

that the effect of bulkiness of reagents does not need to be considered in relation to the regioselectivity (runs 1 and 6).

Indoles are usually attacked by an electrophile exclusively at the 3-position,[7] if it is vacant.[8] The Friedel–Crafts acylation of indoles also takes place[9] at the 3-position, with only a few exceptions.[8b] Ethyl indole-2-carboxylate (**1a**) is in the same situation for formylation,[10a] halogenation,[10b,c] Mannich reaction,[10d] azo-coupling reaction,[10e] and so on. In the case of nitration, Noland and Rush[10f] reported that the nitration of **1a** gave the 4-nitro compound instead of the 3-nitro one due to the steric hindrance of the 2-ethoxycarbonyl group. As the regioselectivity in our reaction markedly depends on the acidity of the parent carboxylic acids of acyl chlorides, it would not be caused by such steric hindrance.

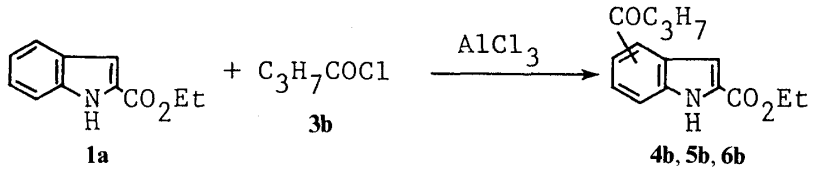
Our procedure may provide a simple method for the selective preparation of 5-acylindoles, though it can be used only for a limited range of compounds at the present time. The previous methods involve a circuitous route *via* acylation of *N*-acylindolines[11] and a non-regioselective route[12] (about equimolar mixture of 5- and 6-acyl compounds, which are hard to separate).

We next focused our attention on other factors which might influence substitution pattern, from both practical and theoretical viewpoints. First, the acylation with acid anhydrides was investigated in several cases ($R = CH_3$, $ClCH_2$, and Ph, Table I), because the acylation with mixed anhydrides has been found to give 3-acylindole derivatives exclusively.[3] The results are summarized in Table I (method B). As expected, the Friedel–Crafts acylation with acid anhydrides greatly increased the regioselectivity for the C-3 acylation except in the case of chloroacetic anhydride.

The effect of the solvent was also examined, because a large solvent effect in the Friedel–Crafts reaction has been reported.[13] The results are also summarized in Table I. Nitrobenzene made the C-3 acylation more favorable than 1,2-dichloroethane did (runs 2 and 5) except in the case of chloroacetic anhydride (run 8).

The effect of molar ratio of an acyl chloride (butyryl chloride) and aluminum chloride to **1a** was examined in two kinds of solvents, 1,2-dichloroethane and nitrobenzene, and the results are summarized in Table III (A and B series). The total acylation yield increased with increasing ratio of butyryl chloride and aluminum chloride to **1a**. The remarkable feature was found that the ratio of the yields of 5-acylindoles increased with increasing molar ratio of aluminum chloride when 1,2-dichloroethane was used (A series). However, the acylation in nitrobenzene occurred almost exclusively at the 3-position irrespective of the molar ratio of

TABLE III. Effect of Molar Ratio of Aluminum Chloride in the Friedel–Crafts Acylation of Ethyl Indole-2-carboxylate (**1a**) with Butyryl Chloride (**3b**) in Two Kinds of Solvents



1a **4b, 5b, 6b**

Molar ratio **1a** : **3b** : $AlCl_3$	Reaction conditions	Product: Total yield (%)	Product: Product ratio **4b** : **5b** : **6b**	Recovery of **1a** (%)
A: In 1,2-dichloroethane				
1 1.2 1.2	r.t., 9 h	58.2	93 5 2	29.4
1 1.2 2	0 °C, 3 h	55.9	65 25 10	34.0
1 1.2 5	r.t., 1 h	47.2	50 38 12	41.9
1 2 1.2	r.t., 2 h	70.0	94 4 2	21.4
1 2 2	0 °C, 1.5 h	72.3	51 34 15	7.1
1 2 5	r.t., 1 h	89.3	35 54 11	0
1 5 1.2	r.t., 1 h	76.4	95 4 1	21.3
1 5 2	r.t., 1 h	90.8	74 18 8	0
B: In nitrobenzene				
1 1.2 1.2	r.t., 1 h	74.4	88 10 2	15.7
1 1.2 5	r.t., 1 h	90.7	88 10 2	0
1 2 2	r.t., 1 h	95.3	87 10 3	Trace
1 5 2	r.t., 1 h	93.5	78 17 5	0

r.t., room temperature.

aluminum chloride (B series).

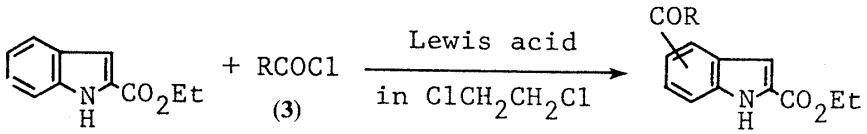
As the molar ratio of aluminum chloride to **1a** was found to affect greatly the regioselectivity of the acylation, various kinds of Lewis acid catalysts were then examined using butyryl chloride and benzoyl chloride in 1,2-dichloroethane. The results are summarized in Table IV (A and B). Run numbers are arranged in the order of mildness of the reaction conditions employed.

From Table IV, we can see that the Lewis acid catalysts other than aluminum chloride have a tendency to give the 3-acylindoles, and that an acyl chloride derived from a weaker acid ($R = n\text{-}C_3H_7$) gave the 3-acylindole (**4**) more regioselectively than the other one ($R = C_6H_5$) did.

Identification of the Structures of the Products

The three isomeric acylindoles formed in the Friedel–Crafts acylation were isolated by column chromatography on silica gel, the order of elution being invariably 7-acylindole (**6**, the fastest moving), 3-acylindole (**4**), and then 5-acylindole (**5**, the slowest moving). In the preliminary short column chromatography, the 3- and 5-acylindoles (**4** and **5**) were obtained as a mixture due to their similar *Rf* values, but the 7-acylindole (**6**) was easily separated in every case. The ratio of the yields of 3- and 5-acylindoles (**4** and **5**) was determined by high-performance liquid chromatography (HPLC). The ratio of the yields of the three acylindoles in each Friedel–Crafts acylation was thus estimated throughout the present study. The 3- and 5-acylindoles (**4** and **5**) were separated by careful column chromatography to obtain authentic samples.

TABLE IV. Effect of Lewis Acids in the Friedel–Crafts Reaction of Ethyl Indole-2-carboxylate (**1a**) with Butyryl (A Series) and Benzoyl (B Series) Chlorides in the Ratio of **1a**: Acyl Chloride (**3**): Lewis Acid = 1 : 2 : 2



1a **4, 5, 6**

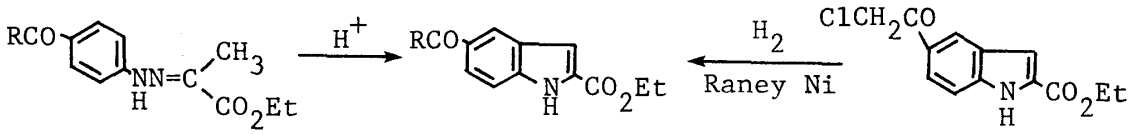
Run	Lewis acid	Reaction conditions	Product: Total yield	Product: Ratio	Recovery of **1a** (%)
A:	$R = n\text{-}C_3H_7$			**4b : 5b : 6b**	
1	$FeCl_3$	0 °C, 10 min	96.1	100 0 0	Trace
2	$SbCl_5$	0 °C, 15 min	86.6	100 0 0	Trace
3	$AlCl_3$[a)]	0 °C, 1.5 h	72.3	51 34 15	7.1
4	$TiCl_4$	r.t., 0.5 h	96.3	100 0 0	Trace
5	$ZnCl_2$	60 °C, 1 h	70.0	94 4 2	24.7
6	$BF_3 \cdot OEt_2$	Reflux, 1 h	80.8	100 0 0	11.0
7	$SnCl_4$	Reflux, 3 h	16.8	100 0 0	79.5
B:	$R = C_6H_5$			**4g : 5g : 6g**	
1	$SbCl_5$	0 °C 15 min	86.7	92 8 0	0
2	$FeCl_3$	r.t., 45 min	90.7	90 10 0	0
3	$SnCl_4$	r.t., 1.5 h	90.9	82 18 0	Trace
4	$TiCl_4$	60 °C, 1 h	85.9	91 9 0	3.8
5	$ZnCl_2$	Reflux, 1 h	79.6	87 13 0	0
6	$AlCl_3$[a)]	Reflux, 1 h	78.5	51 31 18	Trace
7	$BF_3 \cdot OEt_2$	Reflux, 3 h	65.2	88 12 0	Trace

r.t., room temperature. *a*) Data from Table I.

The structures of the acylindoles, especially the position of the acyl group, were determined as follows. Those of the known 3-acylindoles (**4**) were determined by comparison with authentic samples,[3)] whereas those of the new 3-acylindoles (**4**) were determined by inspection of the proton nuclear magnetic resonance (^{1}H-NMR) spectra as described in the previous paper.[3)]

The structures of the 5-acylindoles (**5**) should be determined carefully, because in general, the benzenoid protons of 5- and 6-substituted indoles have similar coupling patterns in the ^{1}H-NMR spectra, and discrimination between them only from the ^{1}H-NMR spectra is not clear-cut. Thus, the key compounds, the 5-acetyl- and the 5-benzoylindoles (**5a**, **g**), were identified by alternative syntheses, by Fischer indole synthesis from *p*-acylphenylhydrazones (**7**) prepared from the corresponding aniline derivatives *via* the Japp–Klingemann reaction,[14)] and the 5-chloroacetylindole (**5d**) was characterized by its conversion to the 5-acetylindole (**5a**) through hydrogenolysis (Chart 3). Other 5-acylindoles (**5**) were characterized by inspection of their ^{1}H-NMR spectra, in which the protons of the 3-position were observed, and the coupling pattern and the chemical shifts of benzenoid protons (that is, the protons of 4, 6, and 7-positions) were very similar to those of the 5-acetyl- (**5a**), the 5-chloroacetyl- (**5d**), and the 5-benzoylindoles (**5g**) (Table V).

The benzenoid protons of 4- and 7-substituted indoles should have similar coupling patterns in the ^{1}H-NMR spectra. Thus, the structures of the 7-acylindoles (**6**) were determined



7a : R=CH_3
7g : R=C_6H_5

5a, g **5d**

Chart 3

TABLE V. ^{1}H-NMR Data for the Aromatic Protons of Ethyl 5-Acylindole-2-carboxylates (**5**)

Compound	R	Solvent	Chemical shift (δ)			
			C_3-H[a]	C_4-H[a]	C_6-H[a]	C_7-H[a]
5a	CH_3	$CDCl_3$	7.33	8.37	7.99	7.46
5b	$CH_3(CH_2)_2$	$CDCl_3$	7.29	8.31	7.96	7.41
5c	$(CH_3)_2CH$	$CDCl_3$	7.33	8.38	8.00	7.47
5d	$ClCH_2$	DMSO-d_6	7.28	8.40	7.84	7.49
5e	*p*-$NO_2C_6H_4$	DMSO-d_6	7.31	8.14	7.81	7.61
5f	*p*-ClC_6H_4	$CDCl_3$	7.28	8.12	7.16—7.99	
5g	C_6H_5	$CDCl_3$	7.31	8.18	7.91	7.51
5h	*p*-$CH_3C_6H_4$	$CDCl_3$	7.28	8.14	7.14—8.00	

a) Coupling pattern and coupling constant (approximately): C_3-H: d, J=2 Hz; C_4-H: d, J=2 Hz; C_6-H: dd, J=2, 8 Hz; C_7-H: d, J=8 Hz.

TABLE VI. ^{1}H-NMR Data for the Aromatic Protons of Ethyl 7-Acylindole-2-carboxylates (**6**) in $CDCl_3$

Compound	R	Chemical shift (δ)			
		C_3-H[a]	C_5-H[a]	C_4,C_6-H[a]	NH
6a	CH_3	7.24	7.18	7.88, 7.90	10.65
6b	$CH_3(CH_2)_2$	7.21	7.14	7.86	10.78
6c	$(CH_3)_2CH$	7.22	7.17	7.88	10.82
6d	$ClCH_2$	7.21	7.16	7.81, 7.91	10.60
6e	*p*-$NO_2C_6H_4$	7.33	7.20	7.62, 8.02	10.65
6f	*p*-ClC_6H_4	7.30	7.18	7.25—8.20	10.70
6g	C_6H_5	7.29	7.14	7.20—8.20	10.64
6h	*p*-$CH_3C_6H_4$		7.00—8.05		10.60

a) Coupling pattern and coupling constant (approximately): C_3-H: d, J=2 Hz; C_5-H: t, J=8 Hz; C_4 and C_6-H: d, J=8 Hz, respectively; NH: br s.

by observing their NH signal in the ^{1}H-NMR spectra (Table VI). The NH signals were observed at lower field by *ca.* 1 ppm in $CDCl_3$ than those of the 3- and 5-acylindoles (**4** and **5**). The lower-field shift of an NH signal can be well interpreted by anisotropy[15] and/or hydrogen bonding with the carbonyl of the acyl group situated on the *peri* position to an NH group. Thus, we concluded that they should be the 7-acylindoles (**6**).

Mechanism for Unusual Substitution

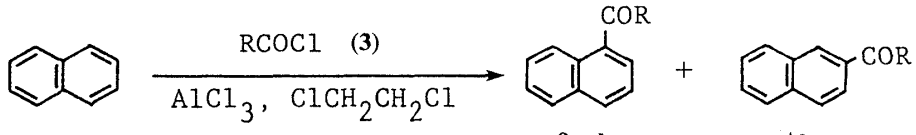
Before discussing the mechanism of the present acylation, it is necessary to clarify whether migration of 3-acylindole (**4**) to 5-acylindole (**5**) and *vice versa* can take place or not,

because the ratio of the yields of the 3- and 5-acylindoles (**4** and **5**) varied with slight changes of reaction conditions. The 3-benzoyl and the 5-benzoylindoles (**4g** and **5g**) were allowed to react under the same Friedel–Crafts acylation conditions, in which **4g** and **5g** were treated with or without benzoyl chloride in the presence of aluminum chloride in 1,2-dichloroethane. As a result, no contamination with the other isomer was found at all when the reaction mixture was checked by thin layer chromatography (TLC) and ^{1}H-NMR spectroscopy. We thus concluded that no migration occurred in the acylation.

In order to examine why the unusual substitution occurred depending on the kind of acyl chloride and the use of aluminum chloride, we carried out the Friedel–Crafts acylation of naphthalene (**8**) with no such functional group as an ethoxycarbonyl group interacting with aluminum chloride. The reactions with acetyl and chloroacetyl chlorides proceeded very smoothly to give the monoacylnaphthalene derivatives in good yields. The results are summarized in Table VII. Although 1- and 2-chloroacetylnaphthalenes (**9d** and **10d**) are known compounds,[16] we converted 1-(chloroacetyl)naphthalene (**9d**) into 1-acetonaphthone (**9a**) by hydrogenolysis with Raney nickel for further confirmation. The hydrogenolysis of **9d** was accompanied with the formation of 1-(1-naphthyl)ethanol as a by-product.

The result revealed that the less electronegative acetyl group tended to substitute at the α-position of naphthalene (**8**) which is the usual reaction center for an electrophile, whereas the more electronegative chloroacetyl group tended to substitute more at the β-position than the acetyl group did, though substitution at the α-position was still predominant. This tendency in naphthalene is the same as that in the indole (**1a**) in that a more electronegative acyl chloride tended to substitute more at the second most reactive center. Although it is known[13] in naphthalene derivatives that a Friedel–Crafts reagent attacks different positions depending on the solvent used, the fact that the substitution position varies depending on the kind of acyl chloride has not been clear. The tendency found in the Friedel–Crafts acylation of ethyl indole-2-carboxylate (**1a**) seems more marked than in that of naphthalene, because the ratio of the yields of the 3-acylindoles (**4**) to the combined yields of the 5- and 7-acylindoles (**5** and

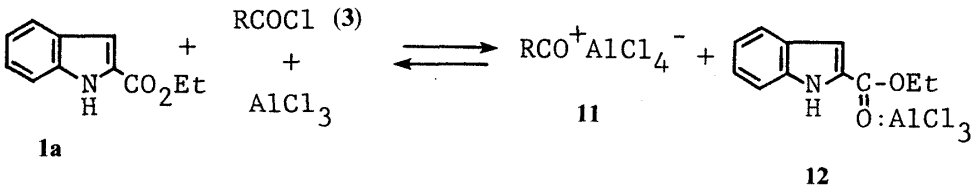
TABLE VII. The Friedel–Crafts Acylation of Naphthalene with Acyl Chlorides



8 **9a, d** **10a, d**

molar ratio; **8**:**3**:$AlCl_3$ = 1:2:2

R	Conditions	Product	
		Total yield (%)	Ratio **9**:**10**
CH_3	0 °C, 15 min	88.6	14 1
$ClCH_2$	0 °C, 10 min	90.4	4 1



1a **11** **12**

Chart 4

6) was reversed in acetyl and chloroacetyl chlorides. For this reason we suppose that the electronegative acyl chloride would coordinate with aluminum chloride more effectively than the more electronegative acyl chloride to give the intermediate complex (**11**), whereas in the case of the more electronegative acyl chloride, aluminum chloride tends to coordinate with the ester carbonyl more than the acyl chloride. The resulting complex (**12**) deactivates the 3-position of the indole (**1a**) due to the increased electronegativity, and thus the second most reactive center, the 5-position, is preferentially attacked. The fact that the carbonyl group of indole-2-carboxylic acids (**1**) coordinates with aluminum chloride has been proven by measurement of the ultraviolet spectrum,[17] supporting the above speculation.

Summary of the Regioselectivity of the Acylation

The following is a summary of the regioselectivity of acylation at the C-3 or C-5 position of ethyl indole-2-carboxylate (**1a**).

1. Reaction conditions for increasing the 3-acylindole (**4**). a) Use of an acyl chloride or an acid anhydride derived from a weaker carboxylic acid as a reagent. b) An acid anhydride is better than an acid chloride as an acylating reagent. c) Use of a Lewis acid other than aluminum chloride as a catalyst and a smaller ratio of equivalents of catalyst to acylating reagent. d) Nitrobenzene is a better solvent than 1,2-dichloroethane.

2. Reaction conditions for increasing the 5-acylindole (**5**). a) Use of an acyl chloride or an acid anhydride derived from a stronger carboxylic acid. b) An acid chloride is better than an acid anhydride as an acylating reagent. c) Aluminum chloride is the best catalyst as a Lewis acid. A greater molar ratio of aluminum chloride gives a better yield. d) 1,2-Dichloroethane is a better solvent than nitrobenzene.

Finally, we wish to note several advantages of using ethyl indole-2-carboxylate (**1a**) as a substrate for acylation. i) 3- and 5-Acylindoles can be prepared from a common substrate, by changing the reaction conditions or reagents. ii) The substrate (**1a**) is so stable under Friedel–Crafts conditions that the unreacted substrate is substantially recovered, when reaction does not proceed completely. iii) With respect to acylation on the benzene moiety, **1a** seems to be superior to others, because **1a** gives the 5-acylindole as a main product, although accompanied with the easily separable 7-acylindole in a small ratio, whereas other substrates, 3-carbonylindole derivatives,[12,18] give hardly separable mixtures of 5- and 6-acylindoles in a comparable ratio.

Experimental

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-400 spectrometer (in Nujol, unless otherwise stated). ^{1}H-NMR spectra were measured on Hitachi R-24B (60 MHz) and JEOL GX-400 (400 MHz) spectrometers in deuteriochloroform, unless otherwise stated, with tetramethylsilane as an internal reference. ^{1}H-NMR spectra were recorded at 60 MHz, unless otherwise stated. The assignment of NH signals was confirmed by disappearance of the signals after addition of deuterium oxide, and the protons of the 3-position were identified at the same time, by observing that the broad singlet or doublet signals changed to sharp singlet signals. Mass spectra (MS) were measured on JEOL JMS-01-SG-2 and JEOL JMS-D300 spectrometers with a direct inlet system. For column chromatography, Silica gel 60 (70—230 mesh ASTM, Merck, unless otherwise stated), and for TLC, Silica gel 60 F_{254} (Merck) were used. All identification of products was done by comparisons of melting points, IR spectra, ^{1}H-NMR spectra, and *Rf* values in TLC with those of authentic samples. The ratios of the yields of the 3- and 5-acylindoles (**4** and **5**) were measured on a Hitachi 635A liquid chromatograph (HPLC) [column, Waters Radial Pack Silica (5 μm) (8 × 100 mm); wavelength, 295 nm; solvent, methylene chloride: ethyl acetate = 50 : 1]. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; q, quartet; sep, septet; m, multiplet; br, broad; dif, diffused; arom, aromatic; BP, base peak.

General Procedure of Friedel–Crafts Acylation of Ethyl Indole-2-carboxylate (1a) (see Table I)——An acid chloride (**3**) or an acid anhydride (1.6 mmol) was added to an ice-cooled suspension of aluminum chloride (213 mg, 1.6 mmol) in 1,2-dichloroethane or nitrobenzene (3 ml), and the whole was stirred for 5 min under an argon atmosphere. A solution of ethyl indole-2-carboxylate[19] (**1a**) (151 mg, 0.8 mmol) in 1,2-dichloroethane (3 ml) was

TABLE VIII. Physical and Analytical Data for Ethyl 3-, 5-, and 7-Acylindole-2-carboxylate (**4**, **5**, and **6**)

Compound No.	R	Melting point (°C)	Recrystallization solvent (Crystal form)	Formula	Analysis (%) Calcd (Found) C	H	N
4c	$(CH_3)_2CH$	75.0—76.0	Hexane–ethyl acetate (Colorless needles)	$C_{15}H_{17}NO_3$	69.48 (69.48	6.61 6.68	5.40 5.39)
4f	*p*-ClC_6H_4	150—151.5	Benzene (Colorless needles)	$C_{18}H_{14}ClNO_3$	65.96 (66.12	4.31 4.25	4.27 4.28)
4h	*p*-$CH_3C_6H_4$	177—179	Benzene–hexane (Colorless plates)	$C_{19}H_{17}NO_3$	74.25 (74.00	5.57 5.45	4.56 4.46)
5a	CH_3	136.5—138	Ethyl acetate–hexane (Colorless prisms)	$C_{13}H_{13}NO_3$	67.52 (67.53	5.66 5.56	6.06 5.96)
5b	$CH_3(CH_2)_2$	127—129.5	CH_2Cl_2–hexane (Colorless needles)	$C_{15}H_{17}NO_3$	69.48 (69.48	6.61 6.71	5.40 5.40)
5c	$(CH_3)_2CH$	206—207	CH_2Cl_2–hexane (Colorless prisms)	$C_{15}H_{17}NO_3$	69.48 (69.31	6.61 6.49	5.40 5.28)
5d	$ClCH_2$	185—187	Ethyl acetate (Colorless needles)	$C_{13}H_{12}ClNO_3$	58.77 (58.51	4.55 4.41	5.27 5.01)
5e	*p*-$NO_2C_6H_4$	228—229.5	Ethyl acetate–hexane (Pale yellow needles)	$C_{18}H_{14}N_2O_5$	63.90 (63.82	4.17 4.09	8.28 8.12)
5f	*p*-ClC_6H_4	191.5—192.5	Benzene (Colorless needles)	$C_{18}H_{14}ClNO_3$	65.96 (65.67	4.31 4.16	4.27 4.15)
5g	C_6H_5	164—166	Ethyl acetate–hexane (Colorless needles)	$C_{18}H_{15}NO_3$	73.71 (73.71	5.15 5.28	4.78 4.76)
5h	*p*-$CH_3C_6H_4$	169—170.5	Ethyl acetate–hexane (Colorless needles)	$C_{19}H_{17}NO_3$	74.25 (73.85	5.57 5.65	4.56 4.61)
6a	CH_3	51—52	Hexane (Colorless needles)	$C_{13}H_{13}NO_3$	67.52 (67.69	5.66 5.68	6.06 6.16)
6b	$CH_3(CH_2)_2$	64—65	Hexane–benzene (Colorless prisms)	$C_{15}H_{17}NO_3$	69.48 (69.45	6.61 6.72	5.40 5.31)
6c	$(CH_3)_2CH$	—	— (Colorless oil)	$C_{15}H_{17}NO_3$	259.1211[a] (259.1228)		
6d	$ClCH_2$	103.5—105	Hexane–benzene (Colorless needles)	$C_{13}H_{12}ClNO_3$	58.77 (58.83	4.55 4.59	5.27 5.28)
6e	*p*-$NO_2C_6H_4$	145—147	Hexane–benzene (Colorless needles)	$C_{18}H_{14}N_2O_5$	63.90 (64.01	4.17 4.06	8.28 8.32)
6f	*p*-ClC_6H_4	122.5—124.5	Ethyl acetate–hexane (Colorless prisms)	$C_{18}H_{14}ClNO_3$	65.96 (65.80	4.31 4.16	4.27 4.15)
6g	C_6H_5	72—74	Hexane (Colorless needles)	$C_{18}H_{15}NO_3$	73.71 (73.69	5.15 5.23	4.78 4.66)
6h	*p*-$CH_3C_6H_4$	116—118.5	Hexane–ether (Colorless needles)	$C_{19}H_{17}NO_3$	74.25 (74.19	5.57 5.62	4.56 4.59)

a) High-resolution mass spectral data.

added dropwise, and the whole mixture was stirred under the conditions shown in Table I, until the formation of products was found to have ceased by TLC monitoring. The reaction mixture was poured into ice-water (50 ml) and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give the residue. The residue was subjected to column chromatography on silica gel; gradient elution with benzene–ethyl acetate or ethyl acetate–hexane gave the 7-acylindole (**6**), the starting material (**1a**), and a mixture of the 3- and 5-acylindoles in order of elution. The ratio of the yields of the 3- and 5-acylindoles (**4** and **5**) was estimated by measuring the areas of the peaks on the HPLC chart, with reference to those of previously isolated authentic samples. The ratio of the yields of the three acylindoles was estimated from a combination of the isolated yields for **6** and HPLC determination for **4** and **5**. The mixture of the 3- and 5-acylindoles (**4** and **5**) was separated by careful column chromatography on silica gel using methylene chloride or methylene chloride–ethyl acetate by gradient elution. The experiments for Tables III and IV were performed similarly.

Spectral Data for Ethyl Acylindole-2-carboxylate (4, 5, and 6)——Ethyl 3-Isobutyrylindole-2-carboxylate (**4c**): IR ν_{max} cm^{-1}: 3290 (NH), 1690, 1679 (C=O). ^{1}H-NMR δ: 1.21 [6H, d, J=7.5 Hz, CH(C$\underline{H}_3$)$_2$], 1.40 (3H, t, J=7.0 Hz, CH$_2$C$\underline{H}_3$), 3.51 [1H, sep, J=7.5 Hz, C$\underline{H}$(CH$_3$)$_2$], 4.41 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 6.99—7.50 (3H, m, C$_{5,6,7}$-H), 7.59—7.87 (1H, m, C$_4$-H), 9.21 (1H, brs, NH). MS m/z: 259 (M$^+$, 23% of BP), 216 (BP).

Ethyl 3-(4-Chlorobenzoyl)indole-2-carboxylate (**4f**): IR ν_{max} cm^{-1}: 3300 (NH), 1692 (C=O). ^{1}H-NMR δ: 0.93 (3H, t, J=8.0 Hz, CH$_2$C$\underline{H}_3$), 4.09 (2H, q, J=8.0 Hz, OC$\underline{H}_2$CH$_3$), 6.90—8.00 (4H, m, arom H), 7.38 (2H, d, J=9.0 Hz, C$_{3',5'}$-H), 7.81 (2H, d, J=9.0 Hz, C$_{2',6'}$-H), 9.68 (1H, brs, NH). MS m/z: 329 (M$^+$+2, 34% of M$^+$), 327 (M$^+$, BP).

Ethyl 3-(4-Methylbenzoyl)indole-2-carboxylate (**4h**): IR ν_{max} cm^{-1}: 3310 (NH), 1692, 1645 (C=O). ^{1}H-NMR δ: 0.92 (3H, t, J=7.0 Hz, CH$_2$C$\underline{H}_3$), 2.40 (3H, s, arom CH$_3$), 4.09 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 7.09—7.95 (8H, m, arom H), 9.58 (1H, brs, NH). MS m/z: 307 (M$^+$, BP).

Other 3-acylindoles (**4**) obtained in the present study were identified by comparison with the samples reported in the previous paper.[3]

Ethyl 5-Acetylindole-2-carboxylate (**5a**)[20]: IR ν_{max} cm^{-1}: 3280 (NH), 1660 (C=O). ^{1}H-NMR (400 MHz) δ: 1.43 (3H, t, J=7.0 Hz, CH$_2$C$\underline{H}_3$), 2.67 (3H, s, COCH$_3$), 4.44 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 7.33 (1H, m, C$_3$-H), 7.46 (1H, d, J=8.5 Hz, C$_7$-H), 7.99 (1H, dd, J=8.5, 2.0 Hz, C$_6$-H), 8.37 (1H, m, C$_4$-H), 9.15 (1H, brs, NH). MS m/z: 231 (M$^+$, 63% of BP), 170 (BP).

Ethyl 5-Butyrylindole-2-carboxylate (**5b**): IR ν_{max} cm^{-1}: 3300 (NH), 1680, 1670 (C=O). ^{1}H-NMR δ: 1.03 (3H, t, J=7.5 Hz, CH$_2$CH$_2$C$\underline{H}_3$), 1.44 (3H, t, J=7.5 Hz, OCH$_2$C$\underline{H}_3$), 1.80 (2H, m, CH$_2$C$\underline{H}_2$CH$_3$), 3.02 (2H, t, J=7.5 Hz, COC$\underline{H}_2$CH$_2$), 4.44 (2H, q, J=7.5 Hz, OC$\underline{H}_2$CH$_3$), 7.29 (1H, difs, C$_3$-H), 7.41 (1H, d, J=9.0 Hz, C$_7$-H), 7.96 (1H, dd, J=8.5, 1.5 Hz, C$_6$-H), 8.31 (1H, difs, C$_4$-H), 9.45 (1H, brs, NH). MS m/z: 259 (M$^+$, 44% of BP), 170 (BP).

Ethyl 5-Isobutyrylindole-2-carboxylate (**5c**): IR ν_{max} cm^{-1}: 3320 (NH), 1713 (C=O). ^{1}H-NMR (400 MHz) δ: 1.26 [6H, d, J=7.0 Hz, CH(C$\underline{H}_3$)$_2$], 1.43 (3H, t, J=7.0 Hz, CH$_2$C$\underline{H}_3$), 3.67 [1H, sep, J=7.0 Hz, C$\underline{H}$(CH$_3$)$_2$], 4.44 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 7.33 (1H, m, C$_3$-H), 7.47 (1H, d, J=9.0 Hz, C$_7$-H), 8.00 (1H, dd, J=9.0, 1.5 Hz, C$_6$-H), 8.38 (1H, difs, C$_4$-H), 9.16 (1H, brs, NH). MS m/z: 259 (M$^+$, 26% of BP), 216 (BP).

Ethyl 5-(Chloroacetyl)indole-2-carboxylate (**5d**): IR ν_{max} cm^{-1}: 3290 (NH), 1700, 1670 (C=O). ^{1}H-NMR [(CD$_3$)$_2$SO] δ: 1.37 (3H, t, J=7.0 Hz, CH$_2$C$\underline{H}_3$), 4.35 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 5.14 (2H, s, C$\underline{H}_2$Cl), 7.28 (1H, d, J=2.5 Hz, C$_3$-H), 7.49 (1H, d, J=9.0 Hz, C$_7$-H), 7.84 (1H, dd, J=9.0, 2.0 Hz, C$_6$-H), 8.40 (1H, difs, C$_4$-H), 12.19 (1H, brs, NH). MS m/z: 267 (M$^+$+2, 46% of M$^+$), 265 (M$^+$), 217 (BP).

Ethyl 5-(4-Nitrobenzoyl)indole-2-carboxylate (**5e**): IR ν_{max} cm^{-1}: 3290 (NH), 1685 (C=O). ^{1}H-NMR [(CD$_3$)$_2$SO] δ: 1.37 (3H, t, J=8.0 Hz, CH$_2$C$\underline{H}_3$), 4.39 (2H, q, J=8.0 Hz, OC$\underline{H}_2$CH$_3$), 7.31 (1H, s, C$_3$-H), 7.61 (1H, d, J=9.0 Hz, C$_7$-H), 7.81 (1H, dd, J=9.0, 2.0 Hz, C$_6$-H), 7.92 (2H, d, J=8.5 Hz, C$_{2',6'}$-H), 8.14 (1H, difs, C$_4$-H), 8.37 (2H, d, J=8.5 Hz, C$_{3',5'}$-H), 12.25 (1H, brs, NH). MS m/z: 338 (M$^+$, BP).

Ethyl 5-(4-Chlorobenzoyl)indole-2-carboxylate (**5f**): IR ν_{max} cm^{-1}: 3290 (NH), 1685 (C=O). ^{1}H-NMR δ: 1.41 (3H, t, J=7.0 Hz, CH$_2$C$\underline{H}_3$), 4.43 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 7.16—7.62 (3H, m, arom H), 7.28 (1H, difs, C$_3$-H), 7.63—7.99 (3H, m, arom H), 8.12 (1H, difs, C$_4$-H), 9.46 (1H, brs, NH). MS m/z: 329 (M$^+$+2, 36% of M$^+$), 327 (M$^+$, 89% of BP), 170 (BP).

Ethyl 5-Benzoylindole-2-carboxylate (**5g**): IR ν_{max} cm^{-1}: 3300 (NH), 1690 (C=O). ^{1}H-NMR (400 MHz) δ: 1.43 (3H, t, J=7.0 Hz, CH$_2$C$\underline{H}_3$), 4.44 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 7.31 (1H, m, C$_3$-H), 7.50 (2H, dift, J=7.5 Hz, C$_{3',5'}$-H), 7.51 (1H, difd, J=8.5 Hz, C$_7$-H), 7.60 (1H, dift, J=7.5 Hz, C$_{4'}$-H), 7.80 (2H, difd, J=7.0 Hz, C$_{2',6'}$-H), 7.91 (1H, dd, J=8.5, 1.5 Hz, C$_6$-H), 8.18 (1H, m, C$_4$-H), 9.22 (1H, brs, NH). MS m/z: 293 (M$^+$, 91% of BP), 170 (BP).

Ethyl 5-(4-Methylbenzoyl)indole-2-carboxylate (**5h**): IR ν_{max} cm^{-1}: 3300 (NH), 1700, 1647 (C=O). ^{1}H-NMR δ: 1.40 (3H, t, J=7.5 Hz, CH$_2$C$\underline{H}_3$), 2.43 (3H, s, arom C$\underline{H}_3$), 4.42 (2H, q, J=7.5 Hz, OC$\underline{H}_2$CH$_3$), 7.10—7.49 (3H, m, C$_{3,6,7}$-H), 7.58 (2H, d, J=7.0 Hz, C$_{3',5'}$-H), 7.88 (2H, dd, J=7.0, 2.0 Hz, C$_{2',6'}$-H), 8.14 (1H, difs, C$_4$-H), 9.24 (1H, brs, NH). MS m/z: 307 (M$^+$, BP).

Ethyl 5-(4-Methoxybenzoyl)indole-2-carboxylate (**5i**): Obtained in too small an amount to be characterized.

Ethyl 7-Acetylindole-2-carboxylate (**6a**): IR ν_{max} cm^{-1}: 3225 (NH), 1721 (C=O). ^{1}H-NMR δ: 1.41 (3H, t, J=7.5 Hz, CH$_2$C$\underline{H}_3$), 2.69 (3H, s, COCH$_3$), 4.42 (2H, q, J=7.5 Hz, OC$\underline{H}_2$CH$_3$), 7.18 (1H, t, J=8.0 Hz, C$_5$-H), 7.24 (1H, d, J=3.0 Hz, C$_3$-H), 7.88 (1H, d, J=8.0 Hz, C$_4$ or C$_6$-H), 7.90 (1H, d, J=8.0 Hz, C$_6$ or C$_4$-H), 10.65 (1H, brs, NH). MS m/z: 231 (M$^+$, BP).

Ethyl 7-Butyrylindole-2-carboxylate (**6b**): IR ν_{max} cm^{-1}: 3430 (NH), 1700, 1658 (C=O). ^{1}H-NMR δ: 1.04 (3H, t, J=7.0 Hz, CH$_2$CH$_2$C$\underline{H}_3$), 1.41 (3H, t, J=7.0 Hz, OCH$_2$C$\underline{H}_3$), 1.84 (2H, m, CH$_2$C$\underline{H}_2$CH$_3$), 3.06 (2H, t, J=7.0 Hz, COC$\underline{H}_2$CH$_2$), 4.40 (2H, q, J=7.0 Hz, OC$\underline{H}_2$CH$_3$), 7.14 (1H, dift, J=8.0 Hz, C$_5$-H), 7.21 (1H, d, J=2.5 Hz, C$_3$-H), 7.86 (2H, d, J=8 Hz, C$_{4,6}$-H), 10.78 (1H, brs, NH). MS m/z: 259 (M$^+$, 85% of BP), 170 (BP).

Ethyl 7-Isobutyrylindole-2-carboxylate (**6c**): IR ν_{max} cm^{-1}: 3430 (NH), 1720, 1712 (C=O). ^{1}H-NMR δ: 1.30 [6H, d, J=8.0 Hz, CH(C$\underline{H}_3$)$_2$], 1.43 (3H, t, J=7.5 Hz, CH$_2$C$\underline{H}_3$), 3.74 [1H, sep, J=8.0 Hz, C$\underline{H}$(CH$_3$)$_2$], 4.42 (2H, q, J=7.5 Hz, OC$\underline{H}_2$CH$_3$), 7.17 (1H, t, J=8.0 Hz, C$_5$-H), 7.22 (1H, d, J=2.5 Hz, C$_3$-H), 7.88 (2H, d, J=8.0 Hz, C$_{4,6}$-H), 10.82 (1H, brs, NH). MS m/z: 259 (M$^+$, 31% of BP), 170 (BP).

Ethyl 7-(Chloroacetyl)indole-2-carboxylate (**6d**): IR ν_{max} cm^{-1}: 3435 (NH), 1700, 1665 (C=O). ^{1}H-NMR δ: 1.40 (3H, t, J=8.0 Hz, CH$_2$C$\underline{H}_3$), 4.40 (2H, q, J=8.0 Hz, OC$\underline{H}_2$CH$_3$), 4.78 (2H, s, C$\underline{H}_2$Cl), 7.16 (1H, t, J=8.0 Hz, C$_5$-H),

7.21 (1H, d, J=2.5 Hz, C_3-H), 7.81 (1H, dd, J=8.0, 1.0 Hz, C_4 or C_6-H), 7.91 (1H, dd, J=8.0, 1.0 Hz, C_6 or C_4-H), 10.60 (1H, br s, NH). MS m/z: 267 (M^++2, 37% of M^+), 265 (M^+, 48% of BP), 170 (BP).

Ethyl 7-(4-Nitrobenzoyl)indole-2-carboxylate (**6e**): IR ν_{max} cm^{-1}: 3430 (NH), 1705 (C=O). ^{1}H-NMR δ: 1.44 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 4.46 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 7.20 (1H, t, J=8.0 Hz, C_5-H), 7.33 (1H, d, J=2.5 Hz, C_3-H), 7.62 (1H, dd, J=8.0, 1.5 Hz, C_4 or C_6-H), 7.89 (2H, d, J=9.0 Hz, $C_{3',5'}$-H), 8.02 (1H, dd, J=8.0, 1.5 Hz, C_6 or C_4-H), 8.37 (2H, d, J=9.0 Hz, $C_{2',6'}$-H), 10.65 (1H, br s, NH). MS m/z: 338 (M^+, BP).

Ethyl 7-(4(Chlorobenzoyl)indole-2-carboxylate (**6f**): IR ν_{max} cm^{-1}: 3370 (NH), 1695 (C=O). ^{1}H-NMR δ: 1.42 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 4.43 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 7.00—8.20 (7H, m, arom H), 7.30 (1H, d, J=2.5 Hz, C_3-H), 10.70 (1H, br s, NH). MS m/z: 329 (M^++2, 35% of M^+), 327 (M^+, BP).

Ethyl 7-Benzoylindole-2-carboxylate (**6g**): IR ν_{max} cm^{-1}: 3425 (NH), 1695, 1640 (C=O). ^{1}H-NMR δ: 1.42 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 4.44 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 7.01—8.02 (8H, m, arom H), 7.29 (1H, d, J=2.0 Hz, C_3-H), 10.65 (1H, br s, NH). MS m/z: 293 (M^+, BP).

Ethyl 7-(4-Methylbenzoyl)indole-2-carboxylate (**6h**): IR ν_{max} cm^{-1}: 3410 (NH), 1692, 1640 (C=O). ^{1}H-NMR δ: 1.41 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.45 (3H, s, arom $C\underline{H}_3$), 4.42 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.00—8.05 (8H, m, arom H), 10.60 (1H, br s, NH). MS m/z: 307 (M^+, BP).

Alternative Synthesis of Ethyl 5-Acetyl- and 5-Benzoylindole-2-carboxylates (5a, g) by Fischer Indole Synthesis——Ethyl 5-Acetylindole-2-carboxylate (**5a**): A solution of $NaNO_2$ (3.81 g, 54 mmol) was added portionwise to a solution of *p*-aminoacetophenone (6.76 g, 50 mmol) in a mixture of 35% HCl (10.5 ml) and water (40 ml) at 4 °C. The process yielded a diazonium salt solution. A 50% aqueous KOH solution (13.5 ml) was added dropwise to another solution of ethyl α-methylacetoacetate (7.31 g, 51 mmol) in ethanol (50 ml) at below 7 °C. The above diazonium solution was then added dropwise to the latter alkaline solution at below 7 °C. The resulting mixture was stirred for a further 10 min under ice-cooling, poured into water, and extracted with ether. The organic layer was washed with saturated NaCl and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave the crude phenylhydrazone (**7a**), which was, without purification, heated with polyphosphoric acid (13.1 g) at 85 °C (bath temperature). The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using hexane–ethyl acetate to give a solid (489 mg, 4.2% from *p*-aminoacetophenone). The solid was recrystallized from ethyl acetate–hexane to give colorless prisms, mp 134.5—136.5 °C. (lit.,[20] mp 138—139 °C). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.51; H, 5.65; N, 6.13. This sample was identical with the sample (**5a**) obtained by the Friedel–Crafts acylation of **1a**.

Ethyl 5-Benzoylindole-2-carboxylate (**5g**): The phenylhydrazone (**7g**) was prepared, in the same way as above, by mixing the diazonium salt solution [prepared from *p*-aminobenzophenone (983 mg, 4.9 mmol), 35% HCl (0.97 ml) and $NaNO_2$ (411 mg, 5.9 mmol)], and a 50% KOH solution (11.4 ml) of ethyl α-methylacetoacetate (743 mg, 5.2 mmol). A solution of the crude phenylhydrazone (1.42 g) (**7g**) in acetic acid (10 ml) was treated with anhydrous $ZnCl_2$ (1.88 g, 13.8 mmol), and the whole was refluxed for 8.5 h, poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo* to give a residue. The residue was chromatographed on silica gel using benzene–ethyl acetate to give a solid (179 mg). Recrystallization from ethyl acetate–hexane gave colorless needles (124 mg, 8.5% from *p*-aminobenzophenone), mp 163.5—165.5 °C. *Anal.* Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.81; H, 5.09; N, 4.73. This sample was identical with the sample (**5g**) obtained by the Friedel–Crafts acylation of **1a**.

Ethyl 5-Acetylindole-2-carboxylate (5a) from Ethyl 5-(Chloroacetyl)indole-2-carboxylate (5d)——Raney Ni W-4 (2 ml of wet volume) was added to a solution of ethyl 5-(chloroacetyl)indole-2-carboxylate (**5d**) (97 mg, 0.4 mmol) in ethanol (45 ml). The mixture was stirred at 0 °C for 17 min. The Raney Ni was filtered off, and the filtrate was evaporated to dryness *in vacuo* to leave a residue (81 mg). The residue was chromatographed on silica gel with methylene chloride–ethyl acetate (40 : 1) to give a solid (51 mg). Recrystallization from ethyl acetate–hexane gave colorless prisms (33 mg, 39%), mp 136.0—137.5 °C. *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.66; N, 6.06. Found: C, 67.57; H, 5.68; N, 6.04. This compound was identical with the sample obtained by the alternative synthesis described above.

Experiments to Examine Rearrangement of the Acyl Group in the Acylindoles (4g and 5g)——a) The Reaction of Ethyl 3-Benzoylindole-2-carboxylate (**4g**) with $AlCl_3$ in the Absence of Benzoyl Chloride: A solution of ethyl 3-benzoylindole-2-carboxylate (**4g**) (100 mg, 0.34 mmol) in 1,2-dichloroethane (3.0 ml) was added to an ice-cooled suspension of $AlCl_3$ (92 mg, 0.69 mmol) in 1,2-dichloroethane (2.5 ml) under an argon atmosphere. The whole was refluxed for 1 h, then poured into ice-water, and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (76 mg, 76%) was found to be pure starting material (**4g**); no contamination with the isomer (**5g**) was detectable by TLC and ^{1}H-NMR spectroscopy.

b) The Reaction of Ethyl 3-Benzoylindole-2-carboxylate (**4g**) with $AlCl_3$ in the Presence of Benzoyl Chloride: Benzoyl chloride (0.16 mg, 1.36 mmol) was added to an ice-cooled suspension of $AlCl_3$ (92 mg, 0.69 mmol) in 1,2-dichloroethane (2.5 ml) under ice-cooling in an argon atmosphere, and the mixture was stirred for 5 min. To this mixture was added a solution of ethyl 3-benzoylindole-2-carboxylate (**4g**) (100 mg, 0.34 mmol) in 1,2-dichloroethane

(3.0 ml). The whole mixture was refluxed for 1 h and worked up in the same way as in a). The extracted residue (69 mg, 69%) contained only the starting material (**4g**), and was not contaminated with ethyl 5-benzoylindole-2-carboxylate (**5g**) at all, as checked by TLC and ^{1}H-NMR spectroscopy.

c) The Reaction of Ethyl 5-Benzoylindole-2-carboxylate (**5g**) with $AlCl_3$ in the Absence of Benzoyl Chloride: A mixture of ethyl 5-benzoylindole-2-carboxylate (**5g**) (45 mg, 0.15 mmol) and $AlCl_3$ (77 mg, 0.58 mmol) in 1,2-dichloroethane (2 ml) was refluxed for 5.5 h under an argon atmosphere. The same work-up as in a) gave the recovered starting material (**5g**) (44 mg, 98%), which was not contaminated with the isomer (**4g**) at all as checked by TLC and ^{1}H-NMR spectroscopy.

Friedel–Crafts Acylation of Naphthalene (8)——a) With Acetyl Chloride (**3a**): A solution of naphthalene (**8**) (192 mg, 1.5 mmol) in 1,2-dichloroethane (3 ml) was added to a mixture of $AlCl_3$ (404 mg, 3 mmol) and acetyl chloride (**3a**) (0.216 ml, 3 mmol) in 1,2-dichloroethane (3 ml) under an argon atmosphere. The whole mixture was stirred at 0 °C for 15 min, then poured into ice-water, and extracted with ethyl acetate. The extract was washed with saturated $NaHCO_3$ and saturated NaCl, dried over $MgSO_4$, and evaporated to dryness *in vacuo*. The residue (241 mg) was chromatographed on silica gel (silicic acid, Mallinckrodt, 100 mesh) using methylene chloride–hexane (1 : 2) to give 1-acetonaphthone (**9a**) (211 mg, 83%) as a colorless oil and 2-acetonaphthone (**10a**) (15 mg, 6%), mp 50—52 °C (from hexane–benzene) in order of elution. They were identified by comparison with commercially available samples.

b) With Chloroacetyl Chloride (**3d**): A solution of naphthalene (**8**) (193 mg, 1.5 mmol) in 1,2-dichloroethane (3 ml) was added to a mixture of $AlCl_3$ (407 mg, 3.0 mmol) and chloroacetyl chloride (0.245 ml, 3 mmol) in 1,2-dichloroethane (3 ml) under an argon atmosphere. The whole mixture was stirred at 0 °C for 10 min. The reaction mixture was worked-up in the same way as in a) to give 1-(chloroacetyl)naphthalene (**9d**) (220 mg, 71%) and 2-(chloroacetyl)naphthalene (**10d**) (58 mg, 19%).

1-(Chloroacetyl)naphthalene (**9d**): Colorless oil, (lit.,[16] mp 34—36 °C). High-resolution MS: Calcd for $C_{12}H_9ClO$: 204.0342. Found: 204.0349. IR ν_{max}^{neat} cm^{-1}: 1698 (C=O). ^{1}H-NMR δ: 4.69 (2H, s, $COC\underline{H}_2Cl$), 7.15—8.10 (6H, m, arom H), 8.35—8.80 (1H, m, arom H). MS *m/z*: 206 (M^++2, 35% of M^+), 204 (M^+, 16% of BP), 155 (BP).

2-(Chloroacetyl)naphthalene (**10d**): Colorless needles from hexane–ethyl acetate, mp 63.5—64.5 °C, (lit.,[16] mp 62—63 °C). *Anal.* Calcd for $C_{12}H_9ClO$; C, 70.43; H, 4.43. Found: C, 70.30; H, 4.38. IR ν_{max} cm^{-1} 1687 (C=O). ^{1}H-NMR δ: 4.76 (2H, s, $COC\underline{H}_2Cl$), 7.35—8.10 (6H, m, arom H), 8.38 (1H, difs, C_1-H). MS *m/z*: 206 (M^++2, 32% of M^+), 204 (M^+, 26% of BP), 155 (BP).

1-Acetonaphthone (9a) from 1-(Chloroacetyl)naphthalene (9d)——Raney Ni W-4 (3 ml of wet volume) was added to a solution of 1-(chloroacetyl)naphthalene (**9d**) (87 mg, 0.43 mmol) in ethanol (30 ml), and the mixture was stirred for 40 min at room temperature. After removal of the catalyst, the filtrate was evaporated to dryness *in vacuo*. The residue (64 mg) was chromatographed on silica gel with hexane–ethyl acetate to give 1-acetonaphthone (**9a**) as a colorless oil, which was identical with a commercially available authentic sample. Further elution gave 1-(1-naphthyl)ethanol as a colorless oil, (lit.,[21] mp 62—64 °C). High-resolution MS: Calcd for $C_{12}H_{12}O$: 172.0888. Found: 172.0887. IR ν_{max}^{neat} cm^{-1}: 3350 (OH). ^{1}H-NMR δ: 1.62 (3H, d, J=7.0 Hz, $CHC\underline{H}_3$), 1.97 (1H, s, $CHO\underline{H}$), 5.59 [1H, q, J=7.0 Hz, $C\underline{H}(OH)CH_3$], 7.15—8.20 (7H, m, arom H).

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