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Synthetic Studies on Indoles and Related Compounds. XII.[1,2] A Simple General Method for the C-3 Acylation of Ethyl Indole-2-carboxylates[3]

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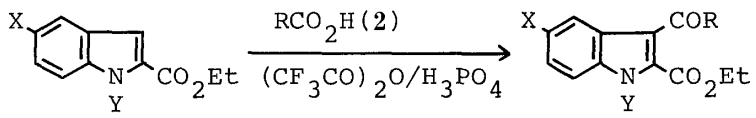
Ethyl indole-2-carboxylate (**1a**) and its derivatives were reacted with various carboxylic acids by using trifluoroacetic anhydride and phosphoric acid (or polyphosphoric acid) to yield effectively the corresponding ethyl 3-acylindole-2-carboxylates (**3**). However, strongly acidic carboxylic acids and nitrogen-containing carboxylic acids were poor acylating agents. Ethyl 3-acylindole-2-carboxylate (**3**) could easily be converted to 3-acylindole (**5**).

Keywords——acylation; indole; ethyl indole-2-carboxylate; carboxylic acid; trifluoroacetic anhydride; phosphoric acid; polyphosphoric acid

Acylation of indoles at their C-3 position is one of the most important and fundamental reactions of indole chemistry, and many methods have been reported,[4] of which the most important are the Vilsmeier–Haack reaction and acylation *via* the indolic magnesium salt with acyl chloride. In these methods, however, acylation under strongly acidic conditions is difficult, because simple indoles which are not stabilized by an electron-attracting substituent are labile under those conditions. On the other hand, ethyl indole-2-carboxylates (**1**) are known[5] to serve as stable equivalents of simple indoles, as they are stable under acidic conditions and to air oxidation. However, acylation of these compounds (**1**) has been little investigated except for formylation,[6] because their reactivity at the C-3 position is decreased by the electron-attracting carbonyl group at the C-2 position. Since we required some 3-acylindole-2-carboxylic acid esters during the course of our program of studies on synthetic indole chemistry, we became interested in developing a method for acylation of **1**. In this paper we report a simple general method for acylation of ethyl indole-2-carboxylates (**1**) using various carboxylic acids as acylating reagents.

Trifluoroacetic anhydride (TFAA) is known to be a good activating reagent of carboxylic acids for the preparation of esters,[7] lactones,[8] and ketones.[9] The last method[9] [carboxylic acid/TFAA/phosphoric acid (H_3PO_4)] is convenient for ketone synthesis, but was not used for acylation of indoles, probably because the reagent (TFAA) liberates strongly acidic trifluoroacetic acid (TFA) in the reaction media, and this would attack unreacted indoles. Therefore, ethyl indole-2-carboxylates (**1**) might be useful as substrates for acylation with this reagent.

We report here that the treatment of ethyl indole-2-carboxylates (**1**) with various carboxylic acids successfully provided 3-acylindole derivatives (**3**) after the establishment of suitable reaction conditions. Yields are collected in Table I. With regard to NH-indoles (**1a**—**c**), the yields are in the range of 0—93.2%, and are dependent on the kind of carboxylic acid used as reagent. Weaker acids tended to give better yields than stronger acids, namely, butyric



1 3

Chart 1

acid and pivalic acid (runs 2 and 3) gave 3-acyl derivatives (**3**) in good yields, while *p*-nitrobenzoic acid and chloroacetic acid (runs 7 and 8) gave **3** in very poor yields. Nitrogen-containing acids, α-picolinic acid and glycine derivatives (runs 9 and 10), gave no acylated compounds. This result shows that the electronic effect in the carboxylic acid is critical for this reaction, while steric hindrance is not a factor (runs 3 and 6). It is noteworthy that sterically hindered pivaloyl and mesitoyl groups could easily be introduced. The 5-substituted indoles (**1b** and **1c**) gave low acylation yields. Chlorine at the C-5 position would lower the electron density at the C-3 position. However, the reason why the 5-methoxyindole (**1b**) gave 3-acylindole derivatives (**3i**, **j**) in low yields is not clear.

Next, the *N*-benzylindole derivative (**1d**) was tried as a substrate, since it was expected that **1d** would give a better result than the corresponding NH-indole (**1a**), and a novel debenzylation process[2k] has recently been developed. As shown in Table I, somewhat better yields resulted.

The main by-product in the acylation was the anhydride of the starting carboxylic acid, $(RCO)_2O$, which was actually obtained in the cases of the aromatic carboxylic acids (runs 4, 5, 12, and 14), while no *N*-acylindole was obtained. A positional isomer was obtained when **1b** was used as a substrate (run 12). Trifluoroacetylation was found not to occur, and this might be related to the low reactivity of **1** with strong acids, such as chloroacetic and *p*-nitrobenzoic acids.

The present acylation reaction should occur *via* the mixed anhydride[10] between the carboxylic acid used and TFA. However, as a carboxylic anhydride was obtained in some reactions with an aromatic acid, we wanted to rule out the possibility that the reaction occurred with carboxylic anhydride formed in the reaction media. Thus, the reaction of **1a** with benzoic anhydride in the presence of TFA was attempted, but did not proceed. During this investigation, trifluoromethanesulfonic anhydride[11] was tried as a reagent instead of TFAA, but gave worse results.

The C-3 position of acylation was proved as follows. 3-Acetyl- and 3-benzoyl-indole-2-carboxylates (**3a** and **3d**) were hydrolyzed, followed by decarboxylation, to give known 3-acetyl- and 3-benzoyl-indoles (**5a** and **5d**), respectively, which were identified by comparison with authentic samples prepared from indole (**6**) according to the reported method (see Experimental) (Chart 2).

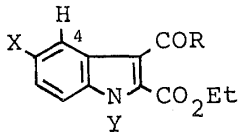
The position of the acyl group in other acylindoles (**3**) was determined as follows. The ^{1}H-nuclear magnetic resonance (^{1}H-NMR) spectrum of the structurally confirmed ethyl 3-benzoylindole-2-carboxylate (**3d**) shows a high field shift of methyl (Δ value, 0.50 ppm) and methylene (Δ value, 0.34 ppm) protons in the ethoxy group, compared with the chemical shifts of corresponding protons in the reference compound (**1a**) (Table II). This shift must be due to the benzene moiety of the C-3 benzoyl group, since no such shift is observed in the ^{1}H-NMR spectra of 3-acetyl and other aliphatic acylindole derivatives (**3**). As the ^{1}H-NMR spectra of other aroylindoles show similar high-field shifts of the ethyl group protons (Table II), the position of the introduced acyl group of the aroylindoles must be C-3. On the other hand, the C-4 proton of the 3-acetylindole derivative (**3a**) shows a low-field shift (Δ value, −0.42 ppm) in the ^{1}H-NMR spectrum, as compared with that of **1a**. This shift must be due to the anisotropic effect of the acetyl carbonyl at the C-3 position, *i.e.* the peri-position to C-4. As

TABLE I. Acylation of Ethyl Indole-2-carboxylates (**1**) with $RCO_2H/(CF_3CO)_2O/H_3PO_4$ to Ethyl 3-Acylindole-2-carboxylates (**3**)

Run	Starting indole (**1**)		Carboxylic acid (**2**) R	Reaction conditions		3-Acylindole[a] derivatives (**3**)		Recovered indole (**1**) (%)	By-product
	X	Y		Time (h)	Temperature[b]	Compound	Yield (%)		
1	H	H (**1a**)	CH_3 (**2a**)	5	r.t.	**3a**	64.0	3.8	
2	H	H (**1a**)	$CH_3(CH_2)_2$ (**2b**)	5	r.t.	**3b**	84.4	0	
3	H	H (**1a**)	$(CH_3)_3C$ (**2c**)	1	r.t.	**3c**	93.2	0	
4	H	H (**1a**)	C_6H_5 (**2d**)	5	r.t.	**3d**	62.2	27.5	$(RCO)_2O$
5	H	H (**1a**)	*p*-$CH_3OC_6H_4$ (**2e**)	6.5	r.t.	**3e**	73.9	6.5	$(RCO)_2O$
6	H	H (**1a**)	2,4,6-Trimethylphenyl (**2f**)	Over night	r.t.	**3f**	82.1	Trace	
7	H	H (**1a**)	*p*-$NO_2C_6H_4$ (**2g**)	5.5	50 °C	**3g**	21.4	31.1	
8	H	H (**1a**)	$ClCH_2$ (**2h**)	9.5	60 °C	**3h**	2.9	41.7	
9	H	H (**1a**)	 (**2p**)	5	r.t.	—	0	Not try	
10	H	H (**1a**)	$PhCONHCH_2$ (**2q**)[c]	4	r.t.	—	0	92.6	
11	CH_3O	H (**1b**)	$CH_3(CH_2)_2$ (**2b**)	6.5	r.t.	**3i**	34.8	12.7	
12	CH_3O	H (**1b**)	C_6H_5 (**2d**)	5.5	r.t.	**3j**	44.0	28.2	Acylindole[d] (9.7%), $(RCO)_2O$
13	Cl	H (**1c**)	$CH_3(CH_2)_2$ (**2b**)	5.5	r.t.	**3k**	65.8	22.7	
14	Cl	H (**1c**)	C_6H_5 (**2d**)	5.2	r.t.	**3l**	16.2	76.5	$(RCO)_2O$
15	H	$PhCH_2$ (**1d**)	CH_3 (**2a**)	5	r.t.	**3m**	86.5	4.4	
16	H	$PhCH_2$ (**1d**)	$(CH_3)_3C$ (**2c**)	1	r.t.	**3n**	88.7	6.9	
17	H	$PhCH_2$ (**1d**)	C_6H_5 (**2d**)	2	r.t.	**3o**	63.7	30.8	
18	H	$PhCH_2$ (**1d**)	$ClCH_2$ (**2h**)	1	60 °C	—	0	70.0	
19[e]	H	H (**1a**)	CH_3 (**2a**)	1	r.t.	**3a**	87.7	0	
20[e]	H	H (**1a**)	C_6H_5 (**2d**)	1.5	80 °C	**3d**	86.8	10.7	

a) As we found[2g] that Friedel-Crafts acylation of **1a** gave ethyl 5-acylindole-2-carboxylate (**11**) in some cases, after the present work was completed, we reexamined some of the reaction mixtures (runs 1 and 4) by high-performance liquid chromatography and found that the reaction mixture contained **11** in 1/20 or less amount of the corresponding 3-acylindole derivative (**3**). The by-product (**11**) could easily be removed by recrystallization. *b*) r.t., room temperature. *c*) Other glycine derivatives (**2**, R = $TsNHCH_2$– and $EtOCONHCH_2$–) gave similar results. *d*) A positional isomer of the acyl group. The actual position was not identified. *e*) Polyphosphoric acid was used in place of phosphoric acid.

TABLE II. The Chemical Shifts of C_4-H and $-OCH_2CH_3$ of Ethyl 3-Acylindole-2-carboxylates (**3**), and the Difference Values (Δ, ppm) from the Corresponding 3-Unsubstituted Indoles (**1**)



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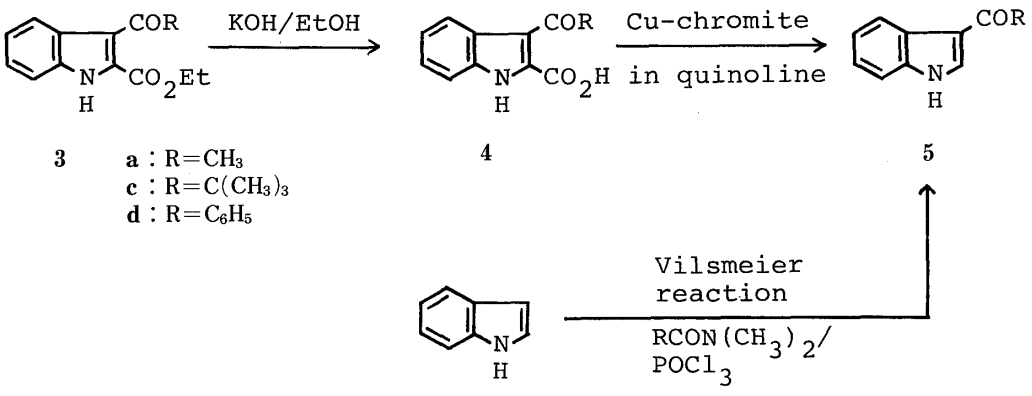
Compound	X	Y	R	C_4-H[a,c]	$-OCH_2-$[a]	$-CH_3$[a]
1a	H	H	—	7.68	4.42	1.44
1b	CH_3O	H	—	7.07	4.41	1.41
1c	Cl	H	—	7.72	4.41	1.41
1d	H	$PhCH_2$	—	7.65	4.29	1.32
3a	H	H	CH_3	8.10 (−0.42)	4.55 (−0.13)	1.57 (−0.13)
3b	H	H	$CH_3(CH_2)_2$	7.89 (−0.21)	4.47 (−0.05)	1.45 (−0.01)
3c	H	H	$(CH_3)_3C$	7.49[b] (0.19)	4.39 (0.03)	1.39 (0.05)
3d	H	H	C_6H_5	?	4.08 (0.34)	0.94 (0.50)
3e	H	H	*p*-$CH_3OC_6H_5$	?	4.19 (0.23)	1.05 (0.39)
3f	H	H	2,4,6-Trimethylphenyl	7.69 (−0.01)	4.11 (0.31)	1.17 (0.27)
3g	H	H	*p*-$NO_2C_6H_5$	?	4.08 (0.34)	0.97 (0.47)
3h	H	H	$ClCH_2$	8.10 (−0.42)	4.54 (−0.12)	1.54 (−0.10)
3i	CH_3O	H	$CH_3(CH_2)_2$	7.40 (−0.33)	4.42 (−0.01)	1.41 (0)
3j	CH_3O	H	C_6H_5	?	4.01 (0.40)	0.87 (0.54)
3k	Cl	H	$CH_3(CH_2)_2$	8.01 (−0.29)	4.57 (−0.16)	1.61 (−0.20)
3l	Cl	H	C_6H_5	?	4.03 (0.38)	0.88 (0.53)
3m	H	$PhCH_2$	CH_3	8.07 (−0.42)	4.35 (−0.06)	1.27 (0.05)
3n	H	$PhCH_2$	$(CH_3)_3C$	7.50 (0.15)	4.29 (0)	1.27 (0.05)
3o	H	$PhCH_2$	C_6H_5	?	3.79 (0.50)	0.80 (0.52)

a) The − sign denotes a low-field shift. *b*) This proton is tentatively identified as the C-4 proton, because the C-7 proton appears near (7.42 ppm) to the C-4 proton when measured by 400 MHz ^{1}H-NMR. The assignment may be reversed. *c*) The ? sign indicates that the C-4 proton could not be identified among the complex patterns of aromatic signals.

this tendency coincides with that of ethyl 3-formylindole-2-carboxylate,[12] and other aliphatic acylindoles except pivaloylindoles (**3c** and **3n**) show analogous shifts of the C-4 proton, their acyl groups should also be at the C-3 position. That the C-4 proton of **3c**, **3f**, and **3n** does not show the apparent low-field shift may be due to deviation from coplanarity between the C-4 proton and the carbonyl group of the bulky 3-acyl group, which interacts sterically with the 2-carboethoxy group, because the ^{1}H-NMR spectrum of a decarboxylated product, 3-pivaloylindole (**5c**), shows the same large low-field shift of the C-4 proton as that of 3-acetylindole (**5a**). The C-4 proton of aroyl indoles can not be observed, because it is buried in a complex pattern of aromatic protons.

The present method is suitable for acylation of ethyl indole-2-carboxylates (**1**). We also tried the Vilsmeier–Haack reaction of **1a** with $POCl_3$/*N*,*N*-dimethylacetamide, but failed to obtain the corresponding 3-acetylindole derivative (**3a**) (**1a** was recovered), although indole itself (**6**) was reported[13] to give the corresponding **5a**. This method is also useful for preparation of 3-acylindoles from simple indoles. The process from ethyl indole-2-carboxylate (**1a**) to acylindole (**5**) consists of three steps, but can be easily handled. On the other hand, the Vilsmeier–Haack method involves the troublesome preparation of the corresponding reagent, $RCON(CH_3)_2$, if it is not commercially available. The yields of both routes are comparable, as shown in Table III.

Finally we tried to apply this reaction to simple indoles (**6** and **7**); the results are shown in Chart 3. The reaction of indole itself (**6**) with acetic acid gave only a 7.8% yield of **5a** after



3 a : R=CH_3
c : R=$C(CH_3)_3$
d : R=C_6H_5

4

5

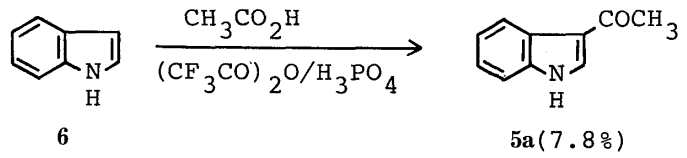
6

Chart 2

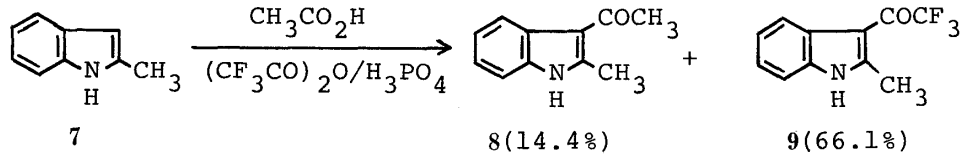
TABLE III. Preparation of 3-Acylindoles (**5**) by Two Routes

A	Starting material R	Yield (%) 3→4	4→5	Total (1a→5)	B	Starting material	Reagent R	Yield of 5 (%) (Reported yield)
	CH_3 (**3a**)	98.1	74.2	46.6		**6**	CH_3	**5a** 44.9 (22.4[13a])
	$(CH_3)_3C$ (**3c**)	94.3	87.8	77.2		—		
	C_6H_5 (**3d**)	89.8	79.5	44.4		**6**	C_6H_5	**5d** 28.5 (51[13a])

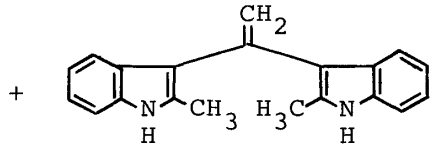
A, **5** from **1a** *via* decarboxylation; B, **5** from **6** by Vilsmeier–Haack Reaction.



6 5a(7.8%)



7 8(14.4%) 9(66.1%)



10(14.0%)

Chart 3

isolation from a complex mixture. The reaction of 2-methylindole (**7**) with acetic acid gave the 3-trifluoroacetyl derivative (**9**) as the major product and the desired 3-acetyl derivative (**8**) as a minor product. Dimeric by-product (**10**) would be formed[14] by the reaction of 3-acetyl-2-methylindole (**8**) with unreacted **7**.

After all of the above experiments had been completed, we found that the use of polyphosphoric acid (PPA) instead of phosphoric acid increased the acylation yield (runs 19

TABLE IV. Physical and Analytical Data for Ethyl 3-Acylindole-2-carboxylates (**3**)

Compound	Melting point (°C)	Recrystallization solvent	Crystal form	Formula	Analysis (%) Calcd (Found)		
					C	H	N
3a	96—97.5	Ether–pentane	Colorless needles	$C_{13}H_{13}NO_3$	67.52 (67.27	5.67 5.45	6.06 5.95)
3b	57—58	Benzene–hexane	Colorless plates	$C_{15}H_{17}NO_3$	69.48 (69.55	6.61 6.73	5.40 5.47)
3c	103.5—105	Benzene–hexane	Colorless prisms	$C_{16}H_{19}NO_3$	70.31 (70.57	7.01 7.15	5.12 5.20)
3d	135—136.5	Benzene–hexane	Colorless needles	$C_{18}H_{15}NO_3$	73.71 (73.41	5.15 5.06	4.78 4.72)
3e	134—136.5	Ethyl acetate–hexane	Colorless needles	$C_{19}H_{17}NO_4$	70.58 (70.95	5.30 5.31	4.33 4.41)
3f	170—172.5	Ethyl acetate–hexane	Colorless needles	$C_{21}H_{21}NO_3$	75.20 (75.40	6.31 6.42	4.18 4.23)
3g	189—190.5	Benzene–hexane	Yellow needles	$C_{18}H_{14}N_2O_5$	63.90 (64.09	4.17 4.14	8.28 8.41)
3h	114—115.5	Chloroform–hexane	Colorless needles	$C_{13}H_{12}ClNO_3$	58.77 (58.86	4.55 4.53	5.27 5.49)
3i	84.5—85.5	Hexane	Colorless prisms	$C_{16}H_{19}NO_4$	66.42 (66.09	6.62 6.57	4.84 4.83)
3j	132.5—134	Benzene	Colorless prisms	$C_{19}H_{17}NO_4$	70.58 (70.90	5.30 5.38	4.33 4.43)
3k	126—128.5	Ethyl acetate–hexane	Colorless needles	$C_{15}H_{16}ClNO_3$	61.33 (61.27	5.49 5.45	4.77 4.66)
3l	166—167.5	Benzene–hexane	Colorless needles	$C_{18}H_{14}ClNO_3$	65.96 (65.94	4.31 4.09	4.27 4.52)
3m	55—57	Hexane–ether	Colorless needles	$C_{20}H_{19}NO_3$	74.75 (74.57	5.96 6.01	4.36 4.17)
3n	103—105	Benzene–hexane	Colorless needles	$C_{23}H_{25}NO_3$	76.01 (76.04	6.93 7.03	3.85 3.88)
3o	82—83.5	Benzene–hexane	Colorless needles	$C_{25}H_{21}NO_3$	78.31 (78.51	5.52 5.52	3.65 3.61)

and 20 in Table I). Polyphosphoric acid may shift the equilibrium between acid anhydride (TFAA) and mixed anhydride to the latter more effectively than phosphoric acid. This alteration may also be useful in the acylation of other compounds.

In conclusion, the present method offers a simple and efficient acylation of **1a** and its derivatives using usual carboxylic acids to provide ethyl 3-acylindole-2-carboxylates (**3**), which can be converted to 3-acylindoles (**5**). However, this method is not effective for the acylation of simple indoles (**6** and **7**).

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). ^{1}H-NMR spectra were recorded on Hitachi R-24B (60 MHz) and JEOL GX-400 (400 MHz) spectrometers in deuteriochloroform unless otherwise stated, with tetramethylsilane as an internal reference. Mass spectra (MS) were measured on a JEOL JMS-01-SG-2 spectrometer with a direct inlet system. For column chromatography, Silica gel 60 (70—230 mesh ASTM, Merck), and for thin layer chromatography (TLC), Silica gel 60 F_{254} (Merck) were used. All identification of products was done by melting point, IR, ^{1}H-NMR, and TLC comparisons, or by mixed melting point determination with an authentic sample. The abbreviations used are as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet; br, broad; dif, diffused; arom, aromatic. The assignment of NH signals was confirmed by disappearance of the signal after addition of deuterium oxide.

General Procedure for Acylation of Ethyl Indole-2-carboxylate Derivatives (1)——TFAA (0.345 ml, 2.4 mmol) was added to a solution of a carboxylic acid (**2**) (2.4 mmol) and 85% H_3PO_4 (31 mg, 0.27 mmol) or PPA (73 mg) in acetonitrile (1.8 ml) at room temperature under an argon atmosphere, and the whole was stirred for 5 to 10 min. Then a solution of an indole derivative (**1**) (0.8 mmol) in acetonitrile (1.8 ml) was added at room temperature. The reaction mixture was stirred as described in Table I with monitoring by TLC, then poured into ice-water and extracted with ether or ethyl acetate. The organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl successively, and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give the corresponding ethyl 3-acylindole-2-carboxylate (**3**) as a crude product, which was purified by column chromatography on silica gel using a mixture of hexane–ethyl acetate as the eluting solvent. Yields and physical data are listed in Tables I and IV, respectively.

Spectral Data for Ethyl 3-Acylindole-2-carboxylates (3)——Ethyl 3-Acetylindole-2-carboxylate (**3a**): IR ν_{max} cm^{-1}: 3200 (NH), 1720, 1630 (C=O). ^{1}H-NMR δ: 1.57 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 2.86 (3H, s, $COCH_3$), 4.55 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.05—7.62 (3H, m, arom H), 8.10 (1H, m, C_4–H), 9.47 (1H, br s, NH). MS m/z: 231 (M^+).

Ethyl 3-Butyrylindole-2-carboxylate (**3b**): IR ν_{max} cm^{-1}: 3325 (NH), 1680, 1655 (C=O). ^{1}H-NMR δ: 1.03 (3H, t, J=8.0 Hz, $CH_2CH_2C\underline{H}_3$), 1.45 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 1.35—2.16 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.10 (2H, t, J=8.0 Hz, $C\underline{H}_2CH_2CH_3$), 4.47 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 6.98—7.56 (3H, m, arom H), 7.89 (1H, m, C_4–H), 9.17 (1H, br s, NH). MS m/z: 259 (M^+).

Ethyl 3-Pivaloylindole-2-carboxylate (**3c**): IR ν_{max} cm^{-1}: 3340 (NH), 1695, 1690 (C=O). ^{1}H-NMR δ: 1.38 [9H, s, $C(CH_3)_3$], 1.42 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 4.42 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 7.05—7.65 (4H, m, arom H), 9.07 (1H, br s, NH). MS m/z: 273 (M^+).

Ethyl 3-Benzoylindole-2-carboxylate (**3d**): IR ν_{max} cm^{-1}: 3320 (NH), 1700, 1660 (C=O). ^{1}H-NMR δ: 0.94 (1H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 4.08 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 7.00—9.10 (9H, m, arom H), 9.40 (1H, br s, NH). MS m/z: 293 (M^+).

Ethyl 3-(*p*-Anisoyl)indole-2-carboxylate (**3e**): IR ν_{max} cm^{-1}: 3310 (NH), 1680, 1630 (C=O). ^{1}H-NMR δ: 1.05 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 3.90 (3H, s, OCH_3), 4.19 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 6.76—8.16 (8H, m, arom H), 9.55 (1H, br s, NH). MS m/z: 323 (M^+).

Ethyl 3-(2,4,6-Trimethylbenzoyl)indole-2-carboxylate (**3f**): IR ν_{max} cm^{-1}: 3150 (NH), 1735, 1600 (C=O). ^{1}H-NMR δ: 1.16 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 2.14 (6H, s, arom $CH_3\times2$), 2.30 (3H, s, arom CH_3), 4.11 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 6.84 (2H, s, arom H), 6.97—7.48 (3H, m, arom H), 7.69 (1H, m, C_4–H), 9.75 (1H, br s, NH). MS m/z: 335 (M^+).

Ethyl 3-(*p*-Nitrobenzoyl)indole-2-carboxylate (**3g**): IR ν_{max} cm^{-1}: 3300 (NH), 1700, 1640 (C=O). ^{1}H-NMR δ: 0.97 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.08 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.10—8.45 (8H, m, arom H), 9.38 (1H, br s, NH). MS m/z: 338 (M^+).

Ethyl 3-(Chloroacetyl)indole-2-carboxylate (**3h**): IR ν_{max} cm^{-1}: 3325 (NH), 1698, 1675 (C=O). ^{1}H-NMR δ: 1.54 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 4.54 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 4.95 (2H, s, CH_2Cl), 7.10—7.55 (3H, m, arom H), 8.10 (1H, m, C_4–H), 9.50 (1H, br s, NH). MS m/z: 267 (M^++2, 36.1% of M^+), 265 (M^+).

Ethyl 3-Butyryl-5-methoxyindole-2-carboxylate (**3i**): IR ν_{max} cm^{-1}: 3340 (NH), 1735, 1660 (C=O). ^{1}H-NMR δ: 0.99 (3H, t, J=8.0 Hz, $CH_2CH_2C\underline{H}_3$), 1.41 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 1.40—2.15 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.08 (2H, t, J=8.0 Hz, $C\underline{H}_2CH_2CH_3$), 3.82 (3H, s, OCH_3), 4.42 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 6.95 (1H, dd, J=9.0, 2.5 Hz, C_6–H), 7.28 (1H, d, J=9.0 Hz, C_7–H), 7.40 (1H, dif s, C_4–H), 9.20 (1H, br s, NH). MS m/z: 289 (M^+).

Ethyl 3-Benzoyl-5-methoxyindole-2-carboxylate (**3j**): IR ν_{max} cm^{-1}: 3310 (NH), 1690, 1640 (C=O). ^{1}H-NMR δ: 0.87 (3H, t, J=7.5 Hz, $CH_2C\underline{H}_3$), 3.76 (3H, s, OCH_3), 4.01 (2H, q, J=7.5 Hz, $OC\underline{H}_2CH_3$), 6.85—8.00 (8H, m, arom H), 9.60 (1H, br s, NH). MS m/z: 323 (M^+).

Ethyl *x*-Benzoyl-5-methoxyindole-2-carboxylate: See run 12 in Table I. Colorless needles, mp 83—97 °C (not recrystallized). IR ν_{max} cm^{-1}: 3325 (NH), 1695, 1650 (C=O). ^{1}H-NMR δ: 1.36 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 3.70 (3H, s, OCH_3), 4.37 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 6.98—8.26 (8H, m, arom H), 9.39 (1H, br s, NH). MS m/z: 323 (M^+).

Ethyl 3-Butyryl-5-chloroindole-2-carboxylate (**3k**): IR ν_{max} cm^{-1}: 3290 (NH), 1690, 1670 (C=O). ^{1}H-NMR δ: 1.20 (3H, t, J=7.5 Hz, $CH_2CH_2C\underline{H}_3$), 1.61 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 1.38—2.45 (2H, m, $CH_2C\underline{H}_2CH_3$), 3.24 (2H, t, J=7.5 Hz, $C\underline{H}_2CH_2CH_3$), 4.57 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.35 (2H, dif s, arom H), 8.01 (1H, dif s, C_4–H), 9.38 (1H, br s, NH). MS m/z: 295 (M^++2, 33.7% of M^+), 293 (M^+).

Ethyl 3-Benzoyl-5-chloroindole-2-carboxylate (**3l**): IR ν_{max} cm^{-1}: 3270 (NH), 1690, 1640 (C=O). ^{1}H-NMR δ: 0.88 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 4.03 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 7.13—8.05 (8H, m, arom H), 9.53 (1H, br s, NH). MS m/z: 329 (M^++2, 37.2% of M^+), 327 (M^+).

Ethyl 3-Acetyl-1-benzylindole-2-carboxylate (**3m**): IR ν_{max} cm^{-1}: no NH, 1720, 1650 (C=O). ^{1}H-NMR δ: 1.27 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 2.60 (3H, s, $COCH_3$), 4.35 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 5.49 (2H, s, $C\underline{H}_2Ph$), 6.90—7.55 (8H, m, arom H), 8.07 (1H, m, C_4–H). MS m/z: 321 (M^+).

Ethyl 1-Benzyl-3-pivaloylindole-2-carboxylate (**3n**): IR ν_{max} cm^{-1}: no NH, 1695, 1690 (C=O). ^{1}H-NMR δ: 1.27 (3H, t, J=8.0 Hz, $CH_2C\underline{H}_3$), 1.30 [9H, s, $C(CH_3)_3$], 4.29 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 5.79 (2H, s, $C\underline{H}_2Ph$), 6.89—7.40 (8H, m, arom H), 7.50 (1H, m, C_4–H). MS m/z: 363 (M^+).

Ethyl 3-Benzoyl-1-benzylindole-2-carboxylate (**3o**): IR ν_{max} cm^{-1}: no NH, 1740, 1680 (C=O). ^{1}H-NMR δ: 0.80 (3H, t, J=8.0 Hz, $CH_2\underline{CH}_3$), 3.79 (2H, q, J=8.0 Hz, $OC\underline{H}_2CH_3$), 5.76 (2H, s, $C\underline{H}_2Ph$), 6.89—8.25 (14H, m, arom H). MS m/z: 383 (M^+).

General Procedure for the Hydrolysis of Ethyl 3-Acylindole-2-carboxylates (3)——A 3-acyl ester (**3**) (1.3 mmol) was added to a solution of KOH (4.6—5.2 mmol) in ethanol (15—25 ml) and the whole was refluxed for 1.5—4.5 h. The reaction mixture was concentrated to 1/3 volume *in vacuo*, poured into ice-water (150 ml), and extracted with ethyl acetate. The aqueous layer was acidified with 10% aqueous HCl, and extracted with ethyl acetate. The extracts were washed with water and dried over anhydrous $MgSO_4$. Removal of the solvent *in vacuo* gave the almost pure carboxylic acid (**4**).

3-Acetylindole-2-carboxylic Acid (**4a**): Colorless needles, mp 253—255 °C, from ethyl acetate–hexane. *Anal.* Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.97; H, 4.27; N, 6.90. IR ν_{max} cm^{-1}: 3240 (NH), 1680 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.78 (3H, s, $COCH_3$), 7.19—7.78 (3H, m, arom H), 7.99 (1H, m, C_4–H), 12.73 (1H, br s, NH). MS m/z: 203 (M^+).

3-Pivaloylindole-2-carboxylic Acid (**4c**): Colorless needles, mp 254—255.5 °C, from ethyl acetate–hexane. *Anal.* Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.47; H, 6.13; N, 5.74. IR ν_{max} cm^{-1}: 3260 (NH), 1680, 1665 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 1.21 [9H, dif s, $C(CH_3)_3$], 6.90—7.62 (4H, m, arom H), 11.86 (1H, br s, NH). MS m/z: 245 (M^+).

3-Benzoylindole-2-carboxylic Acid (**4d**): Pale yellow needles, mp 213—217 °C,[15] from EtOH. *Anal.* Calcd for $C_{16}H_{11}NO_3$: C, 72.45; H, 4.18; N, 5.28. Found: C, 72.29; H, 4.14; N, 5.16. IR ν_{max} cm^{-1}: 3250 (NH), 1695 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 6.90—7.89 (9H, m, arom H), 12.27 (1H, br s, NH). MS m/z: 265 (M^+).

General Procedure for Decarboxylation of 3-Acylindole-2-carboxylic Acids (4). Preparation of 3-Acylindoles (5)——A carboxylic acid (**4**) (0.6 mmol) and copper chromite[16] (24 mg) were suspended in quinoline (1.8 ml) under argon and the whole was stirred for 25 min—1 h at 200 °C (bath temperature). After cooling, the reaction mixture was poured into water (60 ml) and extracted with ethyl acetate. The organic layer was washed successively with 3% aqueous HCl, water, saturated aqueous $NaHCO_3$, and water, and dried over anhydrous $MgSO_4$. The crude product obtained by removal of the solvent *in vacuo* was purified by column chromatography on silica gel using benzene–ethyl acetate as the eluting solvent.

3-Acetylindole (**5a**): Colorless needles, mp 189—190.5 °C, from 95% EtOH. This sample was identical with an authentic sample prepared from indole (**6**) according to the reported method, as described later.

3-Pivaloylindole (**5c**): Colorless needles, mp 163—164.5 °C (lit.,[13b] mp 159—161 °C), from benzene–hexane. *Anal.* Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.86; H, 7.65; N, 6.88. IR ν_{max} cm^{-1}: 3220 (NH), 1615 (C=O). ^{1}H-NMR δ: 1.48 [9H, s, $C(CH_3)_3$], 7.13—7.41 (3H, m, arom H), 7.87 (1H, d, J=3.0 Hz, C_2–H), 8.45 (2H, m, C_4–H and NH). MS m/z: 201 (M^+).

3-Benzoylindole (**5d**): Colorless needles, mp 243—245 °C, from 95% EtOH. This sample was identical with an authentic sample prepared from indole (**6**) according to the reported method, as described later.

Attempted Vilsmeier–Haack Reaction of Ethyl Indole-2-carboxylate (1a) with *N,N*-Dimethylacetamide——Compound **1a** (300 mg, 1.6 mmol) was added to an ice-cooled solution of $POCl_3$ (0.75 ml, 8.0 mmol) in *N,N*-dimethylacetamide (4.5 ml, 48.4 mmol), and the whole was heated at 120 °C (bath temperature) for 4.5 h. Usual work-up gave only the starting material (**1a**) (260 mg, 86.7%).

Attempted Reaction of 1a with Benzoic Anhydride——A solution of **1a** (151 mg, 0.8 mmol) in acetonitrile (2.5 ml) was added to a solution of benzoic anhydride (0.462 ml, 2.4 mmol), TFA (0.187 ml, 2.4 mmol), and H_3PO_4 (32 mg, 0.27 mmol) in acetonitrile (1.8 ml), and the whole was stirred at room temperature for 3 h and at 60 °C for 2 h. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The usual work-up gave recovered **1a** (150 mg, 99.3%).

The Reaction of Indole (6) with Acetic Acid/TFAA/PPA——TFAA (0.69 ml, 4.9 mmol) was added to a solution of acetic acid (0.28 ml, 4.9 mmol) and H_3PO_4 (61 mg, 0.53 mmol) in acetonitrile (3.6 ml) at room temperature under an argon atmosphere, and the whole was stirred for 10 min. To this solution was added a solution of indole (**6**) (187 mg, 1.6 mmol) in acetonitrile (3.4 ml), and the whole was stirred for 5.25 h at room temperature. The reaction mixture was treated as described for the acylation of **1a**. The crude extracts gave an intractable mixture of many products, from which **5a** was obtained by column chromatography on silica gel with benzene–ethyl acetate as the eluting solvent. Recrystallization from benzene–ethyl acetate gave colorless needles (20 mg, 7.8%), mp 187.5—189.5 °C, which were identical with an authentic sample[7] prepared as described later.

The Reaction of 2-Methylindole (7) with Acetic Acid/TFAA/PPA——2-Methylindole (**7**) (262 mg, 2.0 mmol) was dissolved in acetonitrile (4.3 ml) and allowed to react with a mixture of TFAA (0.86 ml, 6.0 mmol), acetic acid (0.33 ml, 6.0 mmol), and H_3PO_4 (77 mg, 0.67 mmol) in acetonitrile (4.5 ml) in the same manner as in the above acetylation of indole (**6**). The crude extract was chromatographed on a silica gel column using benzene–ethyl acetate to give 3-acetyl-2-methylindole (**8**) (50 mg, 14.4%), 2-methyl-3-(trifluoroacetyl)indole (**9**) (300 mg, 66.1%), and 3,3′-vinylidenebis(2-methylindole) (**10**) (80 mg, 14.0%) in that order.

3-Acetyl-2-methylindole (**8**): Colorless needles from benzene–hexane, mp 199—201 °C (lit.,[13a] mp 195—196 °C). *Anal.* Calcd for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.10; H, 6.31; N, 7.75. IR ν_{max} cm^{-1}: 3180 (NH),

1610 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.58 (3H, s) and 2.73 (3H, s) for $COCH_3$ and arom CH_3, 6.94—7.48 (3H, m, arom H), 8.00 (1H, m, C_4–H), 11.70 (1H, br s, NH). MS *m/z*: 173 (M^+).

2-Methyl-3-(trifluoroacetyl)indole (**9**): Colorless needles from benzene–hexane, mp 153.5—154.5 °C (lit.,[17] mp 152 °C). *Anal.* Calcd for $C_{11}H_8F_3NO$: C,58.16; H, 3.54; N, 6.17. Found: C, 58.24; H, 3.39; N, 6.34. IR ν_{max} cm^{-1}: 3240 (NH), 1620 (C=O). ^{1}H-NMR (DMSO-d_6) δ: 2.75 (3H, s, CH_3), 7.09—7.68 (3H, m, arom H), 7.92 (1H, m, C_4-H), 12.52 (1H, br s, NH). MS *m/z*: 227 (M^+).

3,3′-Vinylidenebis(2-methylindole) (**10**): Colorless needles from benzene–hexane, mp 202—204 °C (lit.,[18] mp 200—202 °C). *Anal.* Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78. Found: C, 83.97; H, 6.10; N, 9.47. IR ν_{max} cm^{-1}: 3380 (NH). ^{1}H-NMR (DMSO-d_6) δ: 2.25 (6H, s, $CH_3 \times 2$), 5.41 (2H, s, $C=CH_2$), 6.68—7.47 (8H, m, arom H), 10.88 (2H, br s, NH × 2). MS *m/z*: 286 (M^+).

Authentic 3-Acetylindole (5a) by Vilsmeier–Haack Reaction[13a]——The following procedure was performed according to the reported method,[13a] except that we used *N*,*N*-dimethylacetamide in place of *N*-methylacetamide. A solution of indole (**6**) (1.00 g, 8.5 mmol) in *N*,*N*-dimethylacetamide (3.6 ml) was added to an ice-cooled solution of $POCl_3$ (0.86 ml, 9.2 mmol) in *N*,*N*-dimethylacetamide (10.3 ml, 0.11 mol), and the whole was stirred at 40 °C for 2 h and at 70 °C for 1 h. The reaction mixture was poured into ice-water, basified with 25% aqueous NaOH, refluxed for 10 min, and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and evaporated to dryness *in vacuo*. The residue was chromatographed on silica gel using benzene–ethyl acetate, and recrystallized from 95% ethanol to give **5a** (610 mg, 44.9%). Further recrystallization gave colorless needles, mp 190—194 °C (lit.,[13a] mp 191—193 °C).

Authentic 3-Benzoylindole (5d) by Vilsmeier–Haack Reaction[13a]——Indole (**6**) (1.00 g, 8.5 mmol) was treated with $POCl_3$ (1.08 ml, 11.6 mmol) and *N*,*N*-dimethylbenzamide (2.77 g, 18.6 mmol) at 90 °C for 2 h in the same manner as described above. The crude extracts were purified by column chromatography on silica gel using benzene–ethyl acetate, and recrystallization of the product from 95% EtOH gave **5d** (539 mg, 28.6%), mp 242.5—246.5 °C (lit.,[13a] mp 241—243.5 °C).

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References and Notes

1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.
2) Our previous papers form a series of "Synthetic Studies on Indoles and Related Compounds" as follows: *a*) Part I: Y. Murakami and Y. Yokoyama, *Heterocycles*, **12**, 1571 (1979); *b*) Part II: Y. Murakami, M. Tani, K. Tanaka, and Y. Yokoyama, *ibid.*, **14**, 1939 (1980); *c*) Part III: Y. Murakami, Y. Yokoyama, C. Sasakura, and M. Tamagawa, *Chem. Pharm. Bull.*, **31**, 423 (1983); *d*) Part IV: Y. Murakami, Y. Yokoyama, and N. Okuyama, *Tetrahedron Lett.*, **24**, 2189 (1983); *e*) Part V: H. Ishii, Y. Murakami, T. Watanabe, H. Suzuki, Z. Yasuda, N. Ikeda, H. Mitsui, and S. Tani, *Chem. Pharm. Bull.*, **31**, 4391 (1983); *f*) Part VI: H. Ishii, Y. Murakami, T. Watanabe, H. Suzuki, and H. Maejima, *ibid.*, **31**, 4401 (1983); *g*) Part VII: Y. Murakami, M. Tani, K. Tanaka, and Y. Yokoyama, *Heterocycles*, **22**, 241 (1984); *h*) Part VIII: Y. Murakami, Y. Yokoyama, T. Miura, H. Hirasawa, Y. Kamimura, and M. Izaki, *ibid.*, **22**, 1211 (1984); *i*) Part IX: Y. Murakami, Y. Yokoyama, and T. Aoki, *ibid.*, **22**, 1493 (1984); *j*) Part X: H. Ishii, Y. Murakami, T. Watanabe, A. Iwazaki, H. Suzuki, T. Masaka, and Y. Mizuma, *J. Chem. Res.*, **1984**, (S) 326, (M) 2974; *k*) Part XI: Y. Murakami, T. Watanabe, A. Kobayashi, and Y. Yokoyama, *Synthesis*, **1984**, 738.
3) A part of this work was reported in a preliminary form.[2b]
4) *a*) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York and London, 1970, p. 33; *b*) W. A. Remers, "Heterocyclic Compounds, Indole Part 1," ed. by W. J. Houlihan, John Wiley & Sons, Inc., New York, 1972, p. 111; *c*) *Idem, ibid.*, Part 3, 1979, p. 357; *d*) A. P. Kozikowski and A. Ames, *J. Am. Chem. Soc.*, **102**, 860 (1980).
5) For example; *a*) G. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Org. Chem.*, **30**, 2897 (1965); *b*) H. Ishii and Y. Murakami, *Tetrahedron*, **31**, 933 (1975); *c*) M. Harris, D. S. Grierson, C. Riche, and H.-P. Husson, *Tetrahedron Lett.*, **21**, 1957 (1980); *d*) C. J. Moody, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1333; *e*) M. D. Meyer and L. I. Kruse, *J. Org. Chem.*, **49**, 3195 (1984); *f*) Our previous papers cited in the reference 2.
6) For example; *a*) N. N. Suvorov, Zh. D. Ovchinnikova, and Yu. N. Sheinker, *Zh. Obshch. Khim.*, **31**, 2333 (1961) [*Chem. Abstr.*, **56**, 3478*e* (1962)]; *b*) R. J. S. Beer, B. E. Jennings, and A. Robertson, *J. Chem. Soc.*, **1954**, 2679.
7) R. C. Parish and L. M. Stock, *J. Org. Chem.*, **30**, 927 (1965).
8) D. Taub, N. N. Girotra, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, S. Weber, and N. L. Wendler, *Tetrahedron*, **24**, 2443 (1968).
9) C. Galli, *Synthesis*, **1979**, 303.
10) E. J. Bourne, M. Stacey, J. C. Tatlow, and J. M. Tedder, *J. Chem. Soc.*, **1951**, 718.
11) F. Effenberger and G. Epple, *Angew. Chem. Int. Ed. Engl.*, **11**, 299 (1972).

12) H. Ishii, Y. Murakami, T. Furuse, K. Hosoya, H. Takeda, and N. Ikeda, *Tetrahedron*, **29**, 1991 (1973).
13) *a*) W. C. Anthony, *J. Org. Chem.*, **25**, 2049 (1960); *b*) Upjohn Co., Brit. Patent 869775 (1961) [*Chem. Abstr.*, **56**, 3457*c* (1962)]. The yield of **5c** was not described.
14) R. M. Roberts, A. M. El-Khawaga, and S. Roengsumran, *J. Org. Chem.*, **49**, 3180 (1984).
15) R. A. Khmel'nitskii, N. A. Klyuev, T. A. Kozik, V. N. Rusinova, and N. N. Suvorov, *Khim. Geterotsikl. Soedin.*, **1974**, 1240 [*Chem. Abstr.*, **82**, 57510*p* (1975)]. The melting point of **4d** was not described.
16) W. A. Lazier and H. R. Arnold, "Organic Syntheses," Coll. Vol. II, ed. by A. H. Blatt, John Wiley and Sons, Inc., New York, 1943, p. 142.
17) W. B. Whalley, *J. Chem. Soc.*, **1954**, 1651.
18) A. K. Kiang and F. G. Mann, *J. Chem. Soc.*, **1953**, 594.