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THE CHEMISTRY OF THE INDOLE GRIGNARD REAGENT

I. THE REACTION OF INDOLE MAGNESIUM IODIDE WITH ETHYL CHLOROFORMATE[1]

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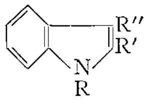
ABSTRACT

In contrast to previous reports in the literature, it has been shown that both 1- and 3-carbethoxyindole are obtained from the reaction of indole magnesium iodide with 1 or 2 moles of ethyl chloroformate. The formation of 1-carbethoxyindole was favored at low temperatures (i.e. −10°), whereas maximum yields of 3-carbethoxyindole were obtained at 10°. Significant quantities of 1,3-dicarbethoxyindole are only formed in the presence of 2 equivalents of ethyl chloroformate and when the reaction is carried out at higher temperatures (i.e. 35°).

Paper and gas–liquid chromatographic systems have been developed for the qualitative and quantitative analysis of mixtures containing indole, 1-, 2-, and 3-carbethoxyindole, and 1,3-dicarbethoxyindole.

The main product of the reaction between indole magnesium iodide and ethyl chloroformate was originally reported to be 2-carbethoxyindole (I) by Oddo and Sessa more than 50 years ago (1). However, Majima and Kotake subsequently claimed that the major product was not I but 3-carbethoxyindole (II) (2, 3), and that under ideal conditions yields of up to 78% of this ester could be obtained (3). The Japanese authors further reported that 1,3-dicarbethoxyindole (III) was invariably formed together with the monoester II, and that when the reaction was carried out in the presence of 2 moles of ethyl chloroformate the diester III was formed in sufficient quantity to allow its isolation from the final reaction mixture by fractional crystallization (3).

In the 36 years that have elapsed since Majima and Kotake's second paper appeared, several authors have employed essentially the same method for the preparation of II, without reporting precise reaction conditions or yields obtained (cf. refs. 4–6). However, Brown and Garrison claimed that the procedure described by Majima and Kotake was unsatisfactory and that better results were obtained by carrying out the reaction between −15 and −5° (5) instead of at the higher temperature (up to 35°) employed previously by the Japanese workers. Noland and Rieke prepared II by Majima and Kotake's method in an unspecified yield, but reported that the melting point of II could be raised from 118–119° to 126–127° by chromatographic purification on alumina (6).



I $R = R'' = H; R' = COOC_2H_5$
II $R = R' = H; R'' = COOC_2H_5$
III $R' = H; R = R'' = COOC_2H_5$
IV $R = R' = R'' = H$
V $R = COOC_2H_5; R' = R'' = H$
VI $R = CONH_2; R' = R'' = H$
VII $R = C_6H_5CONHCO; R' = R'' = H$

In our hands, the yields of II obtained by the interaction of ethyl chloroformate and indole magnesium iodide, under the conditions previously described, were lower than anticipated. This fact, together with the general confusion in the literature on this subject, indicated that a comprehensive investigation of the effect of the systematic variation of several of the more important reaction parameters on the nature and composition of the

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products would be of value. A series of experiments was therefore performed in which the reaction between equivalent quantities of indole magnesium iodide and ethyl chloroformate was carried out at a number of different temperatures (between −10 and 20°) for a series of reaction times (between 5 and 140 min). The reaction mixtures were worked up in the usual way, and in each case the products were analyzed by means of paper and gas–liquid chromatographic procedures.

Satisfactory separations of authentic samples of all possible expected components of the reaction mixtures (i.e. indole (IV), 3-carbethoxyindole (II), 1,3-dicarbethoxyindole (III), and 2-carbethoxyindole (I)) could readily be obtained by radial paper chromatography with a formamide/(benzene – light petroleum (1:1)) system (cf. ref. 7). The chromogenic reagents commonly employed for the detection of indoles on developed chromatograms, such as Ehrlich's reagent, cinnamaldehyde, and *p*-dimethylaminocinnamaldehyde, were unsatisfactory in this case, since I, II, and III gave either no color or weak ill-defined colors with these reagents. However, these esters and unchanged indole gave characteristic colors with Gibb's reagent (*N*,2,6-trichloro-*p*-quinoneimine) and could easily be located on developed chromatograms by spraying with this reagent.

Gas–liquid chromatography has not so far been employed extensively for the analysis of indole derivatives, but simple indoles have been separated satisfactorily with silicone oil (8, 9) or "Versamid 900" (10, 11) as stationary phases. In the current investigation it was observed that IV and the esters I, II, and III could be separated on a 6 ft × $\frac{1}{8}$ in. column with the silicone gum rubber (SE-30) (5% on Chromosorb W) as the stationary phase. This stationary phase has previously been employed for the gas chromatography of tryptamine derivatives (12).

Paper chromatographic analysis of the products obtained from the interaction of indole magnesium iodide and 1 or 2 moles of ethyl chloroformate invariably indicated the presence of at least three main components (II, IV, and a substance or substances which travelled with the solvent front, gave a yellow color with Gibb's reagent, and was assumed to be the diester III). It appeared, at first, that gas chromatographic analysis of the reaction mixtures confirmed these results, but a careful study of the temperature dependence of the retention times of indole (IV), authentic samples of the expected reaction products I, II, and III (see Fig. 3), and the components of the reaction mixtures (see Fig. 1) indicated that, although II and IV were always present among the reaction products, the third main product was not the diester III. The gas chromatographic investigation further showed that, unless the reaction was carried out with 2 moles of ethyl chloroformate, only traces of III were formed (see Table II), and that only when the reaction was carried out at 35° were significant quantities of III formed (see Fig. 1B).

A careful reexamination of the paper chromatographic behavior of all the substances under investigation indicated that the component of the reaction mixture previously assumed to be III gave a somewhat different shade of yellow color with Gibb's reagent, and that the colored derivative was more stable than that obtained from an authentic sample of III. It was not possible to differentiate between these two compounds on formamide- or dimethylformamide-treated paper with a variety of nonpolar running solvents (see Table I).

The preparation of suitable calibration curves enabled a quantitative analysis of the reaction mixtures to be made by gas–liquid chromatography. In this manner it was ascertained that, in the reaction between indole magnesium iodide and 1 mole of ethyl chloroformate, between 20 and 30% of the original indole (IV) was invariably recovered unchanged, and that the yields of 3-carbethoxyindole (II) varied between 27 and 45%, the

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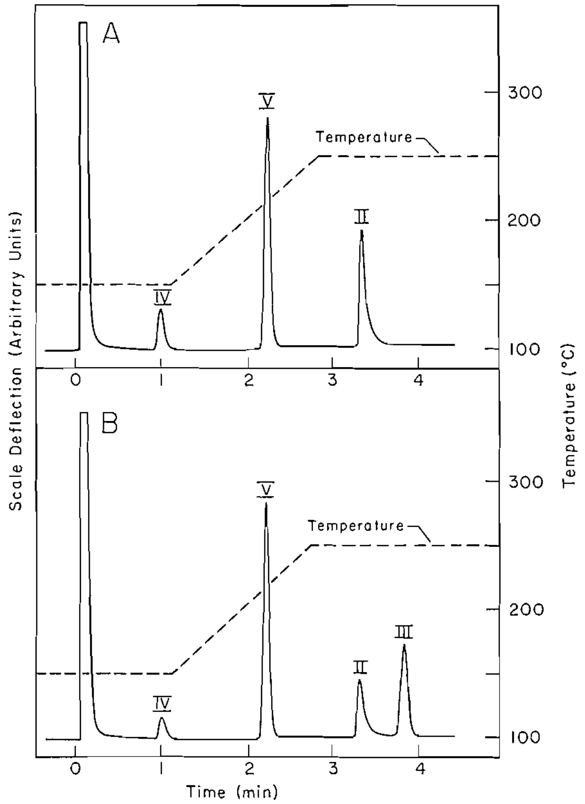

FIG. 1. Gas-liquid chromatograms of the ether-soluble products from the reaction of indole magnesium iodide with (A) 1 or 2 moles of ethyl chloroformate at temperatures below 0°, and (B) 2 moles of ethyl chloroformate at 35°. II = 3-carbethoxyindole; III = 1,3-dicarbethoxyindole; IV = indole; V = 1-carbethoxyindole.

maximum yield of II being obtained when the reaction was carried out at 10° for 100 min. This finding is in contrast to one of the more recent previous reports, which suggests that low temperatures favor the formation of II (5). However, under all the reaction conditions studied, significant quantities of the third component were always formed, and it appeared to be the main product when the reaction was carried out below −5°. It was possible to separate this substance from the other components by column chromatography on alumina or "Polyclar AT". The infrared spectrum of this product, which was obtained as a colorless oil, exhibited a strong ester carbonyl peak at 1 735 cm^{-1}, but showed no peaks in the NH stretching region. The proton magnetic resonance (p.m.r.) spectrum of the oil indicated the presence of four aromatic protons and the indole α and β protons (see Fig. 2) (cf. refs. 13–17). The spectroscopic results, together with the microanalytical data, suggest that the new product is the hitherto undescribed 1-carbethoxyindole (V),[3] which was obtained in a 30–40% yield and which gave indole (IV) on hydrolysis with aqueous alkali and a white crystalline solid, probably indole-1-carboxamide (VI), on treatment with aqueous ammonia. A substance reported to be the amide VI had previously been obtained by Dutcher and Kjaer by the hydrolysis of *N*-benzoylindole-1-carboxamide (VII) (18). However,

[3] *At the conclusion of our investigation we became aware of the fact that, although 1-carbethoxyindole had not previously been described in the literature, it was available commercially from the Regis Chemical Co., Chicago, Illinois, U.S.A.*

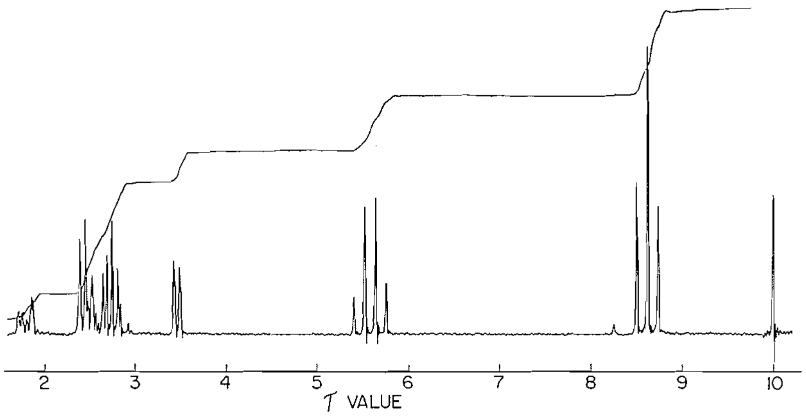

FIG. 2. The p.m.r. spectrum of 1-carbethoxyindole (V) in $CDCl_3$ (recorded on a Varian A-60-A instrument with tetramethylsilane as an internal standard).

these authors reported a slightly different melting point and different ultraviolet spectroscopic data for their product (18).

In conclusion, it may be stated, with regard to the reaction between indole magnesium iodide and either 1 or 2 moles of ethyl chloroformate, that (*i*) at low temperatures (i.e. $< -5°$) and for reaction times between 5 and 60 min the main product is 1-carbethoxyindole (V); (*ii*) 3-carbethoxyindole (II) is always formed, but in yields not exceeding 46%, the formation of II being favored by higher reaction temperatures (ca. 10°); (*iii*) some unreacted indole was always recovered unchanged; and (*iv*) significant quantities of 1,3-dicarbethoxyindole (III) are only formed when the reaction is carried out at temperatures of not less than 35° with 2 moles of ethyl chloroformate.

EXPERIMENTAL

The infrared spectra were recorded on a Perkin–Elmer model 237 recording spectrophotometer; the ultraviolet spectra were recorded on either a Bausch and Lomb "Spectronic 505" or a Beckman DU spectrophotometer, and the p.m.r. spectrum on a Varian A-60-A instrument.

Carbethoxyindoles

3-Carbethoxyindole (II)

A solution of indole-3-carboxylic acid (3 g) in dry ethanol (125 ml), saturated with hydrogen chloride, was boiled under reflux, in the dark, under anhydrous conditions for 2 h. The deep-red solution was then evaporated to dryness *in vacuo*, the residues were dissolved, as far as possible, in ether (200 ml), and the ether solution was washed with aqueous sodium bicarbonate solution and water. Recrystallization of the solid obtained on concentration of the dried (Na_2SO_4) ether solution from 50% ethanol gave 3-carbethoxyindole (1.57 g, 45%), m.p. 123–124°, ν_{max}^{Nujol} 3 250 cm^{-1} (NH) and 1 670 cm^{-1} (C=O), $\lambda_{max}^{C_2H_5OH}$ 282 and 288 mμ. As far as the authors are aware, there are no previous reports in the literature of the preparation of 3-carbethoxyindole by the direct esterification of indole-3-carboxylic acid, the compound having previously been obtained by the Grignard reaction described in this paper. The literature melting points for 3-carbethoxyindole are 118–119° (2), 124° (19), and 126–127° (6).

2-Carbethoxyindole (I)

2-Carbethoxyindole (m.p. 121–123°, ν_{max}^{Nujol} 3 300 cm^{-1} (NH) and 1 690 cm^{-1} (C=O), $\lambda_{max}^{C_2H_5OH}$ 293 mμ) was prepared by the method of Fischer and Pistor (20).

1,3-Dicarbethoxyindole (III)

1,3-Dicarbethoxyindole (m.p. 103–104°, ν_{max}^{Nujol} 1 750 and 1 715 cm^{-1} (C=O); $\lambda_{max}^{C_2H_5OH}$ 274, 285, and 292 (sh) mμ) was prepared by the method of Majima and Kotake (3).

1-Carbethoxyindole (V)

Freshly distilled ethyl chloroformate (1.1 ml) in dry ether (5 ml) was added, with stirring, at −10° during 15 min to indole magnesium iodide (prepared from indole (1.18 g) by the method of Doyle *et al.* (21)) in dry ether (10 ml). After 90 min at a temperature between −9 and −5°, crushed ice was added; the reaction mixture was acidified with dilute acetic acid and extracted with ether (3 × 30 ml). The combined ether extracts were washed with aqueous sodium bicarbonate and water, dried (Na_2SO_4), and concentrated *in*

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vacuo. The residue was dissolved in benzene (5 ml) and adsorbed on "Polyclar AT"[4] (24 × 3 cm). Elution of the column with benzene – light petroleum[5] (1:3) (100 ml) gave 1-carbethoxyindole (0.75 g, 40%), which was obtained as a colorless oil (b.p. 150–151° at 13–14 mm)[6] on vacuum distillation of the crude product, $\nu_{\text{max}}^{\text{Nujol}}$ 1 735 cm^{-1} (C=O); $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 254, 260, 284, and 291 mμ ($\epsilon_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 10 898, 10 599, 3 693, and 5 365). The p.m.r. spectrum in $CDCl_3$ indicated the presence of six protons in the region between τ 1.78 and 3.45; the doublet of doublets observed at τ 3.45 with splittings of 3.7 ($J_{2,3}$) and 0.7 ($J_{3,7}$) c.p.s. can be assigned to the β indole proton, and the complex multiplet with an average τ value of 1.78 is probably caused by the 7-proton (cf. ref. 22). The signals caused by the α indole proton and the remaining aromatic protons are observed as a complex series of peaks between τ 2.83 and 2.34 (see Fig. 2).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.85; N, 7.40. Found: C, 69.62; H, 5.65; N, 7.64.

Indole (0.3 g) and 3-carbethoxyindole (0.6 g) could also be obtained by further elution of the column with benzene – light petroleum (1:1) mixtures and benzene, respectively.

Ammonolysis of 1-Carbethoxyindole

A suspension of 1-carbethoxyindole (0.7 g) in concentrated aqueous ammonia solution (20 ml) was stirred at room temperature for 8 h. A white solid was obtained which gave indole-1-carboxamide (VI) (0.2 g) as colorless plates, m.p. 174–175° (hot stage microscope), after repeated recrystallizations from ether – light petroleum (b.p. 60–80°); $\nu_{\text{max}}^{\text{Nujol}}$ 3 340, 3 175 (amide NH_2), 1 728, 1 625, 1 605, 1 588, and 1 530 cm^{-1}; $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$ 256, 262, 284, and 292 mμ.

Anal. Calcd. for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.85; H, 4.72; N, 17.65.

Dutcher and Kjaer obtained a product described as indole-1-carboxamide by the alkaline hydrolysis of *N*-benzoyl-(1-carbamylindole) (VII), but reported a melting point (198–199°) and ultraviolet spectroscopic absorption maxima (18) which differed from those obtained in the current investigation.

Alkaline Hydrolysis of 1-Carbethoxyindole

A suspension of 1-carbethoxyindole (0.1 g) in 10% aqueous sodium hydroxide (10 ml) was heated on a boiling water bath for 1 h. The reaction mixture was cooled, neutralized with dilute sulfuric acid, and extracted with ether. Paper and gas–liquid chromatographic examination of the dried (Na_2SO_4) ether extracts indicated the presence of indole and unchanged 1-carbethoxyindole.

Paper Chromatography

The R_f values of 1-, 2-, and 3-carbethoxyindole and of 1,3-dicarbethoxyindole are given in Table I. The following notes apply.

Radial development with a suitable nonpolar solvent on paper pretreated with either formamide or dimethylformamide was used, the general procedure being the same as that described for the indole derivatives by Heacock and Mahon (7) (development time ~30 min). The esters (and indole) could be located on the developed chromatograms by spraying with Gibb's reagent (a 2% solution of *N*,2,6-trichloro-*p*-quinoneimine in ethanol).

TABLE I

R_f values* of indole and some carbethoxyindoles

	I	II	III	IV	V
System A†	0.96	0.50	1.00	0.75	1.00
System B‡	0.48	0.13	1.00	0.27	1.00

*Radial development.
†System A = formamide/(benzene – light petroleum (b.p. 60–80°) (1:1)).
‡System B = dimethylformamide–*n*-hexane.
NOTE: Colors given with Gibb's reagent: (I) brown, turning grey after 24 h; (II) brown; (III) yellow-green; (IV) violet; (V) yellow.

Gas–Liquid Chromatography

Determination of Retention Times

A Varian Aerograph model 204 dual-column instrument fitted with two hydrogen-flame ionization detectors was used. The 6 ft × ⅛ in. stainless-steel columns (5% SE-30 on 60–80 Chromosorb W) were used independently. The injector and detector temperatures were maintained at 270 and 250°, respectively. The nitrogen carrier gas flow rate was 14 ml/min and the hydrogen flow rate was 25 ml/min. The column was maintained at the appropriate temperatures during the determination of the relative retention times of I, II, III, IV, and V as a function of the column temperature. The dependence of the retention times of these compounds on column temperature is shown in Fig. 3.

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[4] *"Polyclar AT" is a cross-linked polyvinylpyrrolidone, obtained from Chemical Developments of Canada Ltd. (Montreal). Similar separations could be obtained on activated alumina (Peter Spence, type "H", 100–200 mesh).*

[5] *British Drug Houses Analar grade (b.p. 60–80°).*

[6] *The commercial product (Regis Chemical Co.) has a boiling point of 155° at 14 mm. The melting point of 153–155° quoted in the 1965 Regis Chemical Co. catalogue was due to a misprint (personal communication from Dr. W. F. Gannon).*

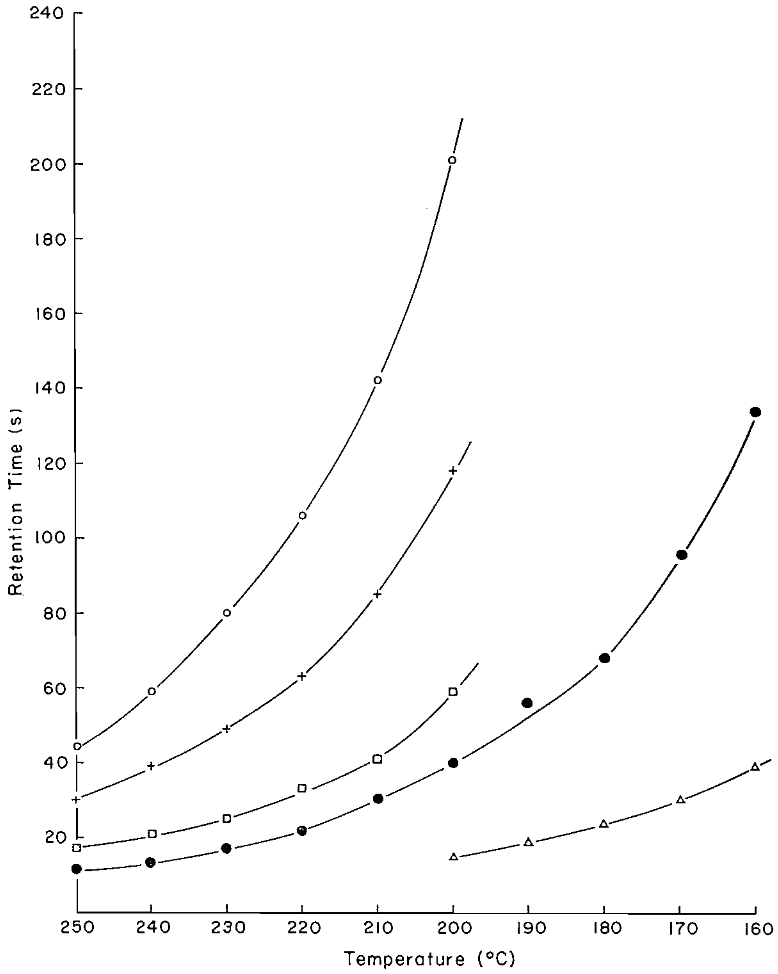

FIG. 3. Temperature dependence of the retention times (measured from the leading edge of the solvent peak) of: △, indole; ●, 1-carbethoxyindole; □, 2-carbethoxyindole; +, 3-carbethoxyindole; ○, 1,3-dicarbethoxyindole.

Analysis of Reaction Products

The reaction between indole magnesium iodide (prepared from 1.18 g indole) and ethyl chloroformate (1.1 ml) was carried out for the times and at the temperatures specified in Table II, in the manner described above for the preparation of 1-carbethoxyindole. The resulting mixture of products was dissolved in absolute ethanol (200 ml), and 1 μl samples of this solution were used for both qualitative and quantitative analysis. The gas flow rates and the temperatures of the injection compartment and the detector were as previously specified.

For *qualitative* analysis, the temperature of the column was maintained at 150° after injection of the sample until the peak caused by indole was observed; the column temperature was then raised during 105 s to 250° and finally maintained at this temperature for several minutes. The second peak observed (when the column temperature reached ca. 220°) was caused by 1-carbethoxyindole, and finally peaks caused by 3-carbethoxyindole and 1,3-dicarbethoxyindole, respectively, were observed with the column temperature at 250°.

For *quantitative* analysis of all four possible components of the reaction mixture, suitable calibration curves were prepared by the peak height method. A slight modification of the procedure used for the qualitative analysis was employed for the quantitative work. One sample was used for the determination of indole and 1-carbethoxyindole, and a second sample for the determination of the other two components. In the first case, the sample was injected with the column temperature at 150°; after the indole peak was observed the temperature was rapidly raised to 220° to obtain the peak caused by 1-carbethoxyindole. In the second case, the peaks caused by 3-carbethoxyindole and 1,3-dicarbethoxyindole were obtained with isothermal runs at

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250°, the early peaks caused by the other two components being disregarded. The two-stage procedure was used to ensure maximum peak sharpness; some tailing of the peaks caused by 3-carbethoxyindole and 1,3-dicarbethoxyindole was observed when the initial column temperature was 150°. Each value was based on an average of not less than six determinations. In each case the yields of all the products could be estimated by reference to the calibration curves, and the results are shown in Table II.

TABLE II

Reaction temperature (°C)	Time required for the addition of ethyl chloroformate (min)	Reaction time (min)	% yield*	
			II	V
−10	5	0	27.0	32.8
−10	5	60	30.0	39.6
−10	5	90	30.0	36.0
0	10	30	29.6	32.8
0	10	60	28.6	32.8
0	10	90	29.6	34.4
0	10	120	33.9	31.8
10	10	30	30.7	31.8
10	10	60	35.0	31.8
10	10	90	46.6	32.8
10	10	120	43.4	35.4
20	20	30	37.0	31.8†
20	20	60	39.0	31.8†
20	20	90	37.0	31.8†
20	20	120	37.0	34.4†

*In all cases 20–30% of the original indole was recovered unchanged. II = 3-carbethoxyindole; V = 1-carbethoxyindole. These yields are considerably higher if one allows for the recovered starting material.

†Traces of 1,3-dicarbethoxyindole formed.

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