The Reaction of *N*-Acylpyridinium Salts with Indole.

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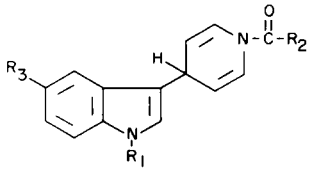
Depending on the solvent used and the ratio of the reactants, *N*-acylpyridinium salts condense with indole to give 3-(*N*-acyl-1,4-dihydro-4-pyridyl)indole (**1**) or 4-(*N*-acyl-3-indolyl)pyridinium chloride (**3**). Compound **1** is an intermediate in the formation of compound **3**. The reaction mechanism has been studied, and a hydrogen transfer reaction is suggested as a key step. Alkaline hydrolysis, *e.g.*, of 4-(*N*-acetyl-3-indolyl)pyridinium chloride (**3a**), gave 3-(4-pyridyl)indole (**2a**).

The reaction of α-chlorosubstituted acyl halides with indole, in the presence of pyridine constitutes a convenient synthesis of 3-chloroacylindoles.

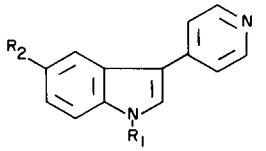
In an attempt to develop new acylation methods for indole, acylation with *N*-acylpyridinium salts was studied. This method was found to be successful only for the synthesis of some α-halosubstituted 3-acylindoles, notably 3-chloroacetylindole. Attempts to prepare, *e.g.* 3-acetylindole from indole and *N*-acetylpyridinium chloride, using pyridine as solvent, resulted in 3-(*N*-acetyl-1,4-dihydro-4-pyridyl)indole (**1a**), as reported by Goltzsche and von Dobeneck (1).

When *N*-acetylpyridinium chloride (1 mole) was reacted (2h/35°) with indole (1 mole) in dioxan or ethyl acetate, however, the condensation product **3a** was obtained as a solid in a reasonable yield (2). Addition of dilute alkali in the cold gave the free base **2c**. Hydrolysis with 2 *M* alkali gave 3-(4-pyridyl)indole (**2a**), whose sodium salt, prepared by reacting 3-(4-pyridyl)indole with sodium hydride, gave **2c** on treatment with acetyl chloride. These facts, together with UV-data, prove structure **3a** for the product, and exclude the isomeric structure **4**.



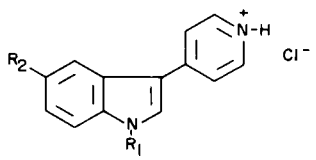
1

a $R_1 = R_3 = H$ $R_2 = CH_3$
b $R_1 = R_3 = H$ $R_2 = C_2H_5$
c $R_1 = R_3 = H$ $R_2 = n\text{-}C_3H_7$
d $R_1 = R_3 = H$ $R_2 = n\text{-}C_5H_{11}$
e $R_1 = R_3 = H$ $R_2 = C_6H_5$
f $R_1 = R_2 = CH_3$ $R_3 = H$
g $R_1 = H$ $R_2 = CH_3$ $R_3 = OCH_3$



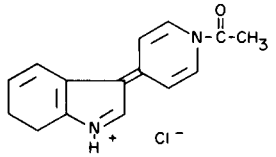
2

a $R_1 = R_2 = H$
b $R_1 = H$ $R_2 = OCH_3$
c $R_1 = COCH_3$ $R_2 = H$

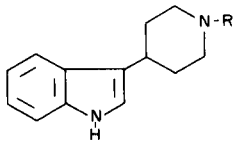


3

a $R_1 = COCH_3$ $R_2 = H$
b $R_1 = COC_3H_7$ $R_2 = H$
c $R_1 = COCH_3$ $R_2 = OCH_3$



4



5

a R = H
b R = $COCH_3$

Further experiments showed that *N*-acetylpyridinium chloride, but not pyridinium chloride, transforms **1a** and even **1e** into **3a**. The *N*-methylanalogue of **1a**, **1f**, did not undergo such transformation.

The earlier synthesis of 3-(4-pyridyl)indole (3-7) are both time-consuming and costly and, consequently, the above method is a more convenient synthesis of this compound. The over-all yield (35%) is similar or better than the yields obtained by previous methods.

To improve the total yield of 3-(4-pyridyl)indole and to gain some knowledge of the reaction mechanism of the condensation between indole and *N*-acetylpyridinium chloride, this reaction was studied in some detail.

A TLC-investigation showed, as expected (8), that *N*-acetylindole is not an intermediate in the formation of **3a**.

The influence of the molar ratio of the reactants (indole, pyridine and acetyl chloride) was studied next. The results are given in Table I (9).

TABLE I

Reactants (a)	Products (b)	
1:1:1	5	23
2:2:1	0	35
3:3:1	0	39
2:1:1	32	4
3:1:1	34	1
3:2:1	25	12

(a) Molar ratio of pyridine, acetyl chloride and indole, respectively. (b) Yield (in per cent) of **1a** and **3a**, respectively, based on indole.

From Table I it is evident that more than one molecule of *N*-acetylpyridinium chloride is more favorable for the formation of **3a**, and that *N*-acetylpyridinium chloride and pyridine probably form an addition complex capable of giving **1a** (and possibly the 2-pyridyl isomer, see below), but not **3a** with indole. In accordance with this, the transformation of **1a** and **1e** into **3a** with *N*-acetylpyridinium chloride does not take place in pyridine solution. In view of these findings, it is suggested that the reactions from *N*-acetylpyridinium chloride and indole to **3a** proceed as follows:

SCHEME I

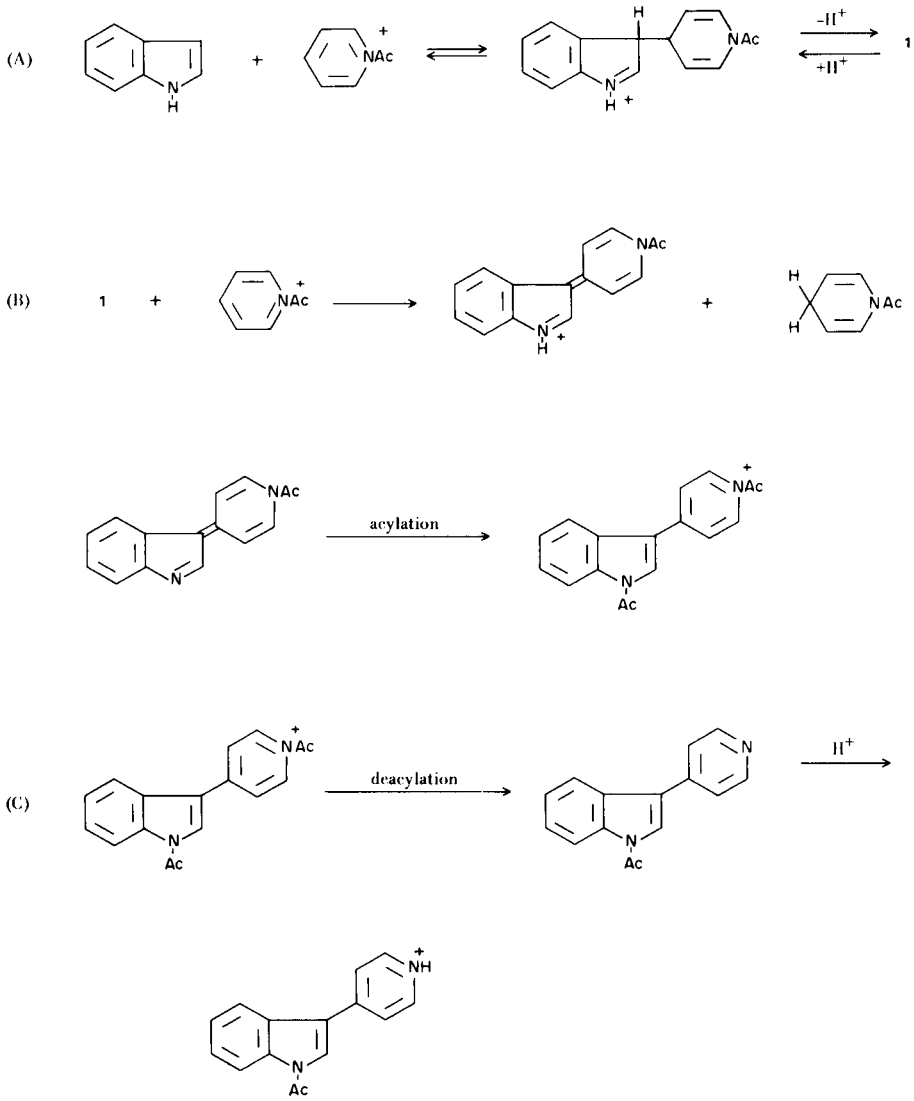


TABLE II

	Compound	Formula		Anal. Data Calcd.	Found	M.p. Yield
1b	3-(*N*-Propionyl-1,4-dihydro-4-pyridyl)indole	$C_{16}H_{16}N_2O$	C	76.2	76.4	140-142°
			H	6.4	6.5	18%
			N	11.1	11.0	
1c	3-(*N*-Butyryl-1,4-dihydro-4-pyridyl)indole	$C_{17}H_{18}N_2O$	C	76.7	76.6	157-158°
			H	6.8	6.8	35%
			N	10.5	10.6	
1d	3-(*N*-Hexanoyl-1,4-dihydro-4-pyridyl)indole	$C_{19}H_{22}N_2O$	C	77.5	77.8	118-119°
			H	7.5	7.6	43%
			N	9.5	9.6	
1f	3-(*N*-Acetyl-1,4-dihydro-4-pyridyl)-*N*-methylindole	$C_{16}H_{16}N_2O$	C	76.2	76.3	159-161°
			H	6.4	6.2	35%
			N	11.1	11.3	
1g	3-(*N*-Acetyl-1,4-dihydro-4-pyridyl)-5-methoxyindole	$C_{16}H_{16}N_2O_2$	C	71.6	71.7	163-165°
			H	6.0	6.0	47%
			N	10.4	10.4	

Undoubtedly the key step in Scheme 1 is the hydrogen transfer reaction (B). Similar reactions (*i.e.* hydrogen transfer between 3-*H*-indolylidenephenylmethane and *N*-benzyl-1,4-dihydropyridine-3-carboxamide) have recently been studied as possible models for yeast alcohol dehydrogenase (10). Attempts to isolate *N*-acetyl-1,4-dihydropyridine have not been successful, but indirect evidence for its formation was obtained by immediate catalytic hydrogenation in ethanol of the carefully evaporated mother liquor from **3a**. By this procedure *N*-acetylpiperidine could be isolated in about 20% yield. The low yield may be explained by partial polymerization of *N*-acetyl-1,4-dihydropyridine (*cf.* ref. 11 and 12).

Hydrogenation of 3-(*N*-acetyl-1,4-dihydro-4-pyridyl)-indole (**1a**) gave 3-(*N*-acetyl-4-piperidyl)indole (**5b**), easily hydrolyzed to the known 3-(4-piperidyl)indole (**5a**). Any hydrogenolysis of **1a** to *N*-acetylpiperidine could not be detected.

From the products of a high-temperature (210°) treatment of **1e**, Beck and Schenker (7) isolated some benzaldehyde. The analogous formation of acetaldehyde from **1a** does not seem to occur under the conditions given, as neither acetaldehyde nor secondary products such as 3,3'-di(indolyl) methylmethane could be detected when pure dioxan or ethyl acetate was used as solvent (13).

In Scheme 1 the possible formation of the 2-pyridyl isomer of **1** along with **1**, is not indicated, but its presence in the reaction mixture was probable in view of the following TLC-results: The spots from **1a** (R_f = 0.26), **1c** (R_f = 0.45) as well as **1d** (R_f = 0.57) were accompanied by very similar spots at R_f = 0.21, 0.39 and 0.48, respectively.

The synthesis of salts analogous to **3a** proceeded satisfactorily if R_1 = CH_3, n-C_3H_7 or p-$NO_2C_6H_5$, but was unsatisfactory when R_1 = C_2H_5, and failed when R_1 = i-C_3H_7 or C_6H_5. These differences may reflect various reactivities of the *N*-acylpyridinium chlorides or, in some cases, different ease of ketene generation.

The reaction between indole and trichloroacetyl chloride in the presence of pyridine gave 3-trichloroacetylindole in excellent yield (14). Pyrrole similarly gave 2-trichloroacetylpyrrole.

Attempts to prepare 3-chloroacetylindole and 3-(2-chloropropionyl)indole, attractive intermediates in the synthesis of 3-aminoacylindoles (15), tryptamines and β-hydroxytryptamines, by the same procedure as used for 3-trichloroacetylindole only gave tars. The required compounds could be prepared in fair yield, by a modified procedure (slow addition of the α-chloroacyl chloride to indole and pyridine in dioxan at 60°). Attempted acylations with chloroacetyl chloride in the temperature range 0-45° or > 75° did not give the required compound.

EXPERIMENTAL

Thin layer chromatograms were run with 99:1 chloroform/-ethanol, on silica gel GF (Merck) and sprayed with phosphomolybdic acid. All R_f-values given were determined by TLC.

Chemicals.

The dioxan used in the determination of the data in Table I was purified according to Stumpf (16). In routine experiments dried commercial dioxan (Union Carbide) was sufficient.

N-Acetylpyridinium Chloride.

The whole preparation was made under nitrogen in a glove box. Dry pyridine (8.1 ml., 0.1 mole) was added at 20-25° to acetyl chloride (7.1 ml., 0.1 mole) in dioxan (80 ml.). The white precipitate was collected without recrystallization (17), and stored under reduced pressure (1 mm, 2 hours) to remove dioxan.

The IR-spectrum (potassium bromide) agreed satisfactorily with that recorded by Cook (18) using Nujol or Fluorolube.

3-(*N*-Acetyl-1,4-dihydro-4-pyridyl)indole (**1a**).

Pyridine (16.2 ml., 0.2 mole) was added at 20-25° to acetyl chloride (7.1 ml., 0.1 mole) in dioxan (80 ml.). Indole (11.7 g., 0.1 mole) in dioxan (20 ml.) was added. After 2 hours at 35° the mixture was poured into water (400 ml.). The light-brown oil was separated, washed with water and triturated with methanol. The crystals formed were recrystallized from methanol, yield 7.7 g. (32%), m.p. 155-156° (Lit. (3) 154-155°); IR (potassium bromide), 1652 cm^{-1} (C=O), 3398 cm^{-1} (NH).

The compounds shown in Table II were prepared using the above method.

4-(*N*-Acetyl-3-indolyl)pyridinium Chloride (**3a**).

Pyridine (161.6 ml., 2 mole) was added at 20-25° to acetyl-chloride (142.2 ml., 2 mole) in dioxan (1000 ml.). *N*-Acetyl-pyridinium chloride was immediately formed as a white solid. Indole (117 g., 1 mole) in dioxan (150 ml.) was added. The temperature was kept at 35° for 2 hours. During this time the solid dissolved and was gradually replaced by another precipitate. The mixture was cooled (10-15°), filtered, and the crude product (150 g.), which contained some pyridinium chloride, was recrystallized from ethanol/methanol (3:1), yield 93 g. (35%), m.p. 212-217°; IR (potassium bromide), 1722 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{13}ClN_2O$: C, 66.1; H, 4.8; N, 10.3; Cl, 13.0. Found: C, 66.0; H, 4.6; N, 10.2; Cl, 13.3.

Ethyl acetate, instead of dioxan, gives slightly better yields (0-5%).

Catalytic Hydrogenation of the Products in the Dioxan Mother Liquor from 4-(*N*-Acetyl-3-indolyl)pyridinium Chloride.

The above mother liquor was evaporated under reduced pressure. The residue was dissolved in ethanol (100 ml.) and hydrogenated using Adams catalyst. The catalyst was filtered off and the solvent evaporated. Fractionation of the residue gave *N*-acetylpiperidine 2.5 g. (20%), b.p. 122-124°/28 mm.

3-(*N*-Acetyl-4-piperidyl)indole (**5b**).

3-(*N*-Acetyl-1,4-dihydro-4-pyridyl)indole (**1a**) (2.0 g.) in hot ethanol (100 ml.) was hydrogenated, using Adams catalyst (200 mg.). The mixture was filtered and the solvent removed. The residue recrystallized from methanol gave 1.4 g. (70%), m.p. 178-180°; IR (potassium bromide), 1609 cm^{-1} (C=O), 3191 cm^{-1} (NH).

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.4; H, 7.5; N, 11.6. Found: C, 74.1; H, 7.5; N, 11.8.

3-(4-Piperidyl)indole (**5a**).

Method A.

3-(*N*-Acetyl-4-piperidyl)indole (1,2 g.) was refluxed with 10 ml. of 2 *M* sodium hydroxide and 10 ml. of ethanol for 3 hours. The ethanol was distilled off, the mixture cooled, the base filtered off and recrystallized from ethyl acetate, giving 0.75 g. (75%), m.p. 218-220° (Lit. (7) m.p. 214-215°).

Method B.

Sodium (9.0 g.) was added during 10 minutes to a mechanically stirred refluxing solution of 3-(4-pyridyl)indole (1.95 g.) in 1-butanol (150 ml.). The refluxing was continued until all the sodium was dissolved. Water (100 ml.) was added to the cooled reaction solution. The butanol layer was separated and evaporated to dryness under reduced pressure. The water phase was extracted with ether and the ether phase combined with the distillation residue. The water-washed, ethereal solution was extracted with dilute hydrochloric acid. The free base was liberated and taken up in ether. The residue of the evaporated extract recrystallized from benzene gave 1.4 g. (70%), m.p. 218-220°.

4-(*N*-Butyryl-3-indolyl)pyridinium Chloride (**3b**).

The same procedure as for **3a** was used on the 0.1 mole scale. The crude product was recrystallized from water, yield 30%, m.p. 208-213°; IR (potassium bromide), 1720 cm^{-1} (C=O).

Anal. Calcd. for $C_{17}H_{17}ClN_2O$: C, 67.8; H, 5.6; N, 9.3; Cl, 11.8. Found: C, 68.1; H, 5.4; N, 9.0; Cl, 11.5.

4-[*N*-Acetyl-3-(5-methoxy)indolyl]pyridinium Chloride (**3c**).

The same procedure as above was applied. The crude product was recrystallized from ethanol, yield 25%, m.p. 219-224°; IR (potassium bromide), 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{16}H_{15}ClN_2O_2$: C, 63.5; H, 4.9; N, 9.3; Cl, 11.7. Found: C, 63.1; H, 5.0; N, 9.3; Cl, 11.9.

3-(4-Pyridyl)indole (**2a**).

4-(*N*-Acetyl-3-indolyl)pyridinium chloride (**3a**) (10 g.) was refluxed (2 hours) with 2 *M* sodium hydroxide (75 ml.) and ethanol (75 ml.). Water (350 ml.) was slowly added giving crystals of **3a**, yield 6.4 g. (90%), m.p. and mixed m.p. 218-219° (Lit. (5,3) 219-220°, 210-212°); UV (ethanol) λ max 221, 275, 313 nm (log ε 4.55, 4.02, 4.24); Lit. (7) λ max 221, 275, 315 nm (ε 31,600, 10,200, 16,600).

3-(4-Pyridyl)-5-methoxyindole (**2b**).

Yield 90%, m.p. 176-177°; UV (ethanol), λ max 222, 279, 316 nm (log ε 4.52, 4.90, 4.22).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 75.0; H, 5.4; N, 12.5. Found: C, 74.8; H, 5.5; N, 12.6.

N-Acetyl-3-(4-pyridyl)indole (**2c**).

Method A.

3-(4-Pyridyl)indole (3.9 g., 0.020 mole) in dimethylformamide (10 ml.) was added dropwise at 35° to a mixture of dimethylformamide (20 ml.) and sodium hydride (0.022 mole, added as 1.05 g. of a 50% suspension in mineral oil). When the generation of hydrogen had ceased, acetyl chloride (1.71 g., 0.022 mole) in dioxan (5 ml.) was added to the stirred mixture. After 1 hour at 35° the mixture was poured into water (200 ml.) and extracted with ether. Evaporation and recrystallization from 80% ethanol of the dried (magnesium sulfate) extract gave needles, yield 3.7 g. (78%), m.p. 160-162°; UV (ethanol), λ max 223, 252, 305 nm (log ε 4.30, 4.15, 4.11); IR (potassium bromide), 1710 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.3; H, 5.1; N, 11.9. Found: C, 76.4; H, 5.0; N, 11.6.

Method B.

4-(*N*-Acetyl-3-indolyl)pyridinium chloride (2.2 g.) was dissolved in water (30 ml.) at 25° and added with stirring to 300 ml. of 0.1 *M* sodium hydroxide at 8-10°. The mixture was stirred for one hour, filtered, and washed with water. Recrystallization from 80% ethanol gave needles identical with those obtained with method A.

Reaction of 3-(*N*-Acetyl-1,4-dihydro-4-pyridyl)indole with *N*-Acetylpyridinium Chloride.

3-(*N*-Acetyl-1,4-dihydro-4-pyridyl)indole (2.4 g., 0.01 mole) was added to *N*-acetylpyridinium chloride (from acetyl chloride 0.71 ml., 0.01 mole and pyridine 0.81 ml., 0.01 mole) in dioxan (15 ml.). After 2 hours at 35° the mixture was worked up as described above giving 4-(*N*-acetyl-3-indolyl)pyridinium chloride (**3a**), yield 0.7 g. (28%).

Reaction of 3-(*N*-Benzoyl-1,4-dihydro-4-pyridyl)indole (**1e**) with *N*-Acetylpyridinium Chloride.

The above procedure was used, giving 4-(*N*-acetyl-3-indolyl)-pyridinium chloride (**3a**), yield 15%.

3,3'-Di(indolyl)methylmethane.

Indole (11.7 g.), commercial dioxan (100 ml.) and 85% phosphoric acid (5 ml.) were refluxed for 3 hours. Water (300 ml.) was added to the cooled mixture. The solid (14 g.) formed, crystallized from ethanol (with final cooling to −30°) gave big crystals of 3,3'-di(indolyl)methylmethane as a dioxan complex, yield 9 g., m.p. 122-126° (with loss of dioxan). The elemental analysis agreed reasonably with a 2:1-complex of 3,3'-di(indolyl)-methylmethane.

Anal. Calcd. for $C_{18}H_{16}N_2 \cdot \frac{1}{2}C_4H_8O_2$: C, 78.9; H, 6.6; N, 9.2. Found: C, 77.9; H, 6.3; N, 9.6.

The dioxan could not be removed by repeated recrystallizations from ethanol, however, heating to 100° at 10 mm for 3 hours removed the dioxan. Recrystallization of the residue from ethanol gave pure 3,3'-di(indolyl)methylmethane 6.5 g. (50%), m.p. 161-162° (Lit. (19,20) 162-163°, 162°); NMR ($DMSO_{d6}$), τ = 8.24 (d, 3, CH_3), τ = 5.38 (q, 1, CH).

Recrystallization of pure 3,3-di(indolyl)methylmethane from ethanol containing 1.5% dioxan reformed the complex.

3-Trichloroacetylindole.

Method A.

Trichloroacetyl chloride (20.0 g., 0.11 mole) followed by indole (11.7 g., 0.10 mole) was added to a solution of pyridine (9.0 ml., 0.11 mole) in dioxan (120 ml.). After 1 hour at 25° the mixture was poured into water (400 ml.), dried and recrystallized from ethanol giving 18.5 g. (71%), m.p. 235-237° (Lit. (21,22) 235-237°, 228°).

Method B.

Indole (5.85 g.) and trichloroacetic anhydride (15.4 g.) in ether (40 ml.) were stored for 2 days at 20° and then cooled to −5°. The crystals formed were recrystallized from ethanol 7.2 g. (53%), m.p. 235-237°.

5-Methoxy-3-trichloroacetylindole.

Method A above was used, yield 85%, m.p. 210-212°.

Anal. Calcd. for $C_{11}H_8Cl_3NO_2$: C, 45.2; H, 2.8; N, 4.8. Found: C, 45.2; H, 2.8; N, 4.8.

2-Trichloroacetylpyrrole.

Trichloroacetyl chloride (20.0 g., 0.11 mole) followed by pyrrole (6.7 g., 0.10 mole) were added to a solution of pyridine (9.0 ml., 0.11 mole) in methyl acetate (120 ml.). After 2 hours at 30° the solvent (after water washing and drying) was evaporated and the residue distilled. The fraction 140-145°/10 mm was taken. The distillate was recrystallized from cyclohexane giving 14.0 g. (68%), m.p. 72-73° (Lit. (23) 70°).

3-Chloroacetylindole.

Chloroacetyl chloride (16.9 g., 0.15 mole) in dioxan (25 ml.) was added dropwise during 1 hour to a well-stirred solution of indole (11.7 g., 0.10 mole) and pyridine (12.2 ml., 0.15 mole) in dioxan (75 ml.) at 60°. The mixture was stirred for another hour, cooled and poured into a mixture of water (400 ml.) and ether (100 ml.). The resulting mixture was filtered and the crude product recrystallized from ethanol 7.5 g. (41%), m.p. 230-232° (Lit. (24) 230-232°).

3-(2-Chloropropionyl)indole.

The same procedure as above was used, yield 56%, m.p. 193-194° (Lit. (25) 192-193°).

5-Methoxy-3-chloroacetylindole.

The same method as above was used. The crude product was recrystallized from propanol giving 17.1 g. (75%), m.p. 210-212°.

Anal. Calcd. for $C_{11}H_{10}ClNO_2$: C, 59.2; H, 4.5; N, 6.3. Found: C, 59.6; H, 4.3; N, 6.2.

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(10) T. Hino and M. Nakagawa, *J. Am. Chem. Soc.*, 91, 4598 (1969) and references therein.

(11) Fr. Pat- 1,481,448 (1967) (to General Electric Co.).

(12) N. C. Cook and J. E. Lyons, *J. Am. Chem. Soc.*, 88, 3396 (1966).

(13) If impure dioxan, which always contains acetaldehyde diethyl acetal, was used, 3,3'-di(indolyl)methylmethane was formed. As a matter of fact refluxing of indole with impure dioxan under slightly acid conditions is a convenient preparative method of 3,3'-di(indolyl)methylmethane.

(14) Products of type **1** or **3** could not be detected.

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