The Reaction of Some Indoles with Acetic-Formic Anhydride.

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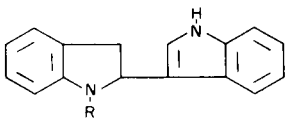
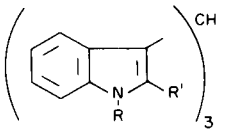
In connection with a study (1) of acylation reactions of indole, the reaction of indole with acetic-formic anhydride has been explored.

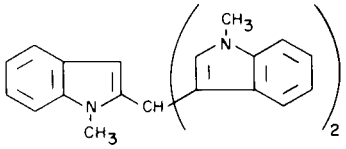
Reaction of indole at 20° with acetic-formic anhydride gave the dimeric product **1c**. Noland and Hammer (2,3) have obtained a similar product, **1d**, from indole and maleic anhydride (*cf.* also ref. 4). Lithium aluminium hydride reduction of **1c** gave a product identical with the mixed dimer (**1b**) of indole and 1-methylindole (5). Formylation of the indolylindoline (**1a**) gave **1c**.



1a R = H
b R = CH_3
c R = CHO
d R = maleyl
e R = $COCH_3$



2a R = CH_3, R' = H
b R = H, R' = CH_3
c R = R' = H



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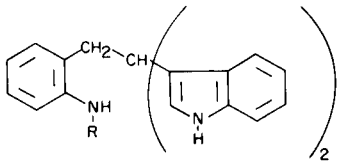
Reaction of 1-methylindole and 2-methylindole with acetic-formic anhydride gave **2a** and **2b**, respectively, in good yields. Compounds of type **2** (partly *N*-formylated) were obtained also with indole as reactant, especially at higher (50°) temperatures.

Compounds of type **2** could also be prepared by condensing indoles with the appropriate 3-formylindole (*cf.* ref. 6, 7 and 8). 1-Methylindole and 1-methyl-2-formylindole similarly gave **3**.

During the reaction of 3-methylindole with acetic-formic anhydride an intense violet-coloration, indicating formation of cyanin dyes (9-12) was observed. Distillation of the crude reaction product gave 1-formyl-3-methylindole. Neither 2-formyl-3-methylindole (11,13) nor tris-2-(3-methylindolyl)methane (14) could be detected. The reaction of indole with acetic-trifluoroacetic anhydride in ether at 20° gave crystals of compound **4c** in modest yield. The mother liquor contained several substances, among others **1e**, as shown by TLC.



4a R = H
b R = CHO
c R = $COCH_3$

Interestingly enough, **4b** does not seem to be formed in the reaction of indole with acetic-formic anhydride.

EXPERIMENTAL

Chemicals.

Acetic-formic anhydride was prepared from acetic anhydride and formic acid (15). A reagent prepared from ketene and formic acid (16,17) gave very similar results. TLC was accomplished on silica gel GF (Merck), chloroform-ethanol 99:1.

1-Formyl-2-(3-indolyl)indoline (**1c**).

Method A.

Indole (11.7 g.) was added to acetic-formic anhydride (35 ml.). After 24 hours at 20° in the dark the solid was collected (the mother liquor contained tris-(3-indolyl)methane as the main product) and recrystallized twice from ethanol, yield, 3.4 g. (26%) m.p. 192-193°.

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.8; H, 5.4; N, 10.7, Mw. 262. Found: C, 77.5; H, 5.7; N, 10.7; Mw. 262 (MS).

Method B.

Indole dimer (18) (**1a**) (2.0 g.) was dissolved in acetic-formic anhydride (15 ml.) at 30°, heated to 50° for 5 minutes, cooled, filtered and recrystallized from ethanol, yield, 1.8 g. (80%), m.p. and mixed m.p. 192-193°.

1-Methyl-2-(3-indolyl)indoline (**1b**).

1-Formyl-2-(3-indolyl)indoline (2.6 g.) was added to lithium aluminum hydride (0.8 g.) in ether (150 ml.) and the mixture refluxed with stirring under nitrogen for 4 hours. The remaining lithium aluminum hydride was destroyed by careful addition of water. The ether phase was dried with potassium carbonate, filtered and the solvent evaporated. The residue was crystallized from toluene/methylcyclohexane (1:1), yield, 1.7 g. (69%), m.p. and mixed m.p. 128-129° (Lit. (5) 128-129°).

Reaction of Indole with Acetic-Formic Anhydride at 50°.

Indole (11.7 g.) was added to acetic-formic anhydride (35 ml.). After 24 hours (nitrogen, light-protection) at 50° the cooled mixture was poured while stirring into methanol/water (1:2) (350 ml.). The light-sensitive solid formed was filtered, washed with water and dried. The mixture was chromatographed on silica gel, using benzene/methylene chloride (5:1). Three main fractions were taken. Fraction 1 contained a mixture (6.2 g.) of *N*-formyltris-(3-indolyl)methane and *N,N*-diformyltris-(3-indolyl)methane as shown by IR and MS. This mixture has not been further separated. Fraction 2 contained tris-(3-indolyl)methane (2.1 g.) as shown by MS and comparison with an authentic sample (see below). Fraction 3 contained 1-formyl-2-(3-indolyl)indoline (1.5 g.).

Tris-3-(1-methylindolyl)methane (**2a**).

Method A.

A light-protected solution of 1-methylindole (6.1 g.), 1-methyl-3-formylindole (**19**) (4.0 g.) and acetic acid (4 ml.) in ethanol (35 ml.) was heated to 80° for 10 minutes. The solid formed upon cooling was crystallized from pyridine, yield, 5.8 g. (63%), m.p. 268-270°.

Anal. Calcd. for $C_{28}H_{25}N_3$: C, 83.3; H, 6.3; N, 10.4. Found: C, 83.6; H, 6.1; N, 10.2.

The following compounds were similarly prepared:

Tris-3-(2-methylindolyl)methane (**2b**).

Yield, 65%, m.p. 319-320° (Lit. (20) 319-320°).

Tris-(3-indolyl)methane (**2c**).

Yield, 59%, m.p. 244-246° (Lit. (6) 244-246°).

Bis-3-(1-methylindolyl)-2-(1-methylindolyl)methane (**3**).

Yield, 78%, m.p. 246-248°.

Anal. Calcd. for $C_{28}H_{25}N_3$: C, 83.3; H, 6.3; N, 10.4. Found: C, 83.2; H, 6.2; N, 10.1.

Tris-3-(1-methylindolyl)methane (**2a**).

Method B.

1-Methylindole (13.1 g.) was added to acetic formic anhydride (35 ml.). After 24 hours at 20° in the dark the mixture was poured while stirring into methanol/water (1:2) (350 ml.). The light-sensitive solid formed was collected, washed with water and dried. Crystallization from pyridine gave 10.3 g. (73%), m.p. and mixed m.p. 168-270°.

Tris-3-(2-methylindolyl)methane (**2b**).

Method B.

Yield, 7.6 g. (55%) m.p. 319-320° (Lit. (20) 319-320°).

1-Formyl-3-methylindole.

3-Methylindole (13.1 g.) was reacted with acetic-formic anhydride (35 ml.) as described above. The reaction mixture was poured into water (300 ml.). The dark oil (**21**) was extracted with ether. The ether phase was washed with water, dried and the solvent evaporated. The residue was distilled 148-150°/8 mm (Lit. (13) 98-100°/0.03 mm) giving a colourless thick oil which was dissolved in methanol. On cooling (-25°) crystals separated, yield, 4.5 g. (28%), m.p. 30-31°, C=O 1695 cm^{-1}.

Acknowledgment.

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(21) TLC and IR showed the presence of 3-methylindole. Tris-2-(3-methylindolyl)methane could not be detected.