The Synthesis of Some 3-Acylindoles Revisited

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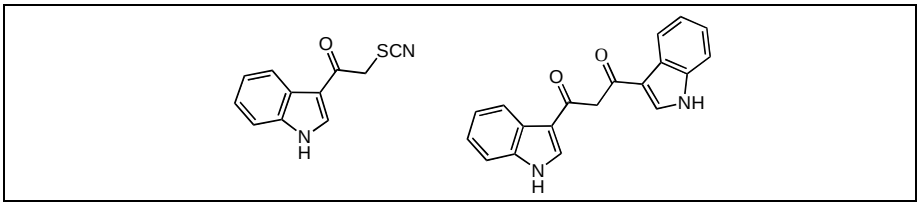

A study probing the scope of acylation of indoles with dicarboxylic acids in acetic anhydride has been performed, resulting in products incorporating 3-acylindole- or 1-acylindole motifs depending on the choice of the acid reactant. Synthetically useful results were only obtained from reactions involving malonic acid or Meldrum's acid. Correlations to previous studies have also been made and discussed.

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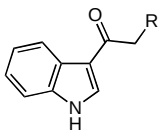
INTRODUCTION

Acylation reactions are highly useful tools for functionalization of indoles, and have consequently been studied in considerable detail over the years. The common practical routes to 3-acylindoles and related compounds involve for instance treatment of indoles with acyl chlorides in the presence of pyridine [1], exposure of zincated indoles to acyl chlorides [2], Friedel–Crafts type acylation of indoles with acyl chlorides in the presence of Lewis acids [3,4], or Friedel–Crafts reactions of indoles possessing electron withdrawing N-substituents [5]. In addition, dimeric 3-acylindoles connected by long alkyl chains have been prepared by exposure of indole to bisimidazoline derivatives in acetic anhydride [6]. A recent contribution to this field features a new useful technique for facile preparation of 3-(cyanoacetyl)indole derivatives by acylation employing cyanoacetic acid in acetic anhydride [7]. The resulting 3-(cyanoacetyl)-indoles, for instance the parent molecule **1**, are very useful starting materials for construction of other related indole containing systems [8], whereas the similarly prepared phosphonate **2** has been employed in a stereoselective synthesis of the alkaloid murrayacarine [9]. Further synthetic applications of 3-(cyanoacetyl)indole **1** have emerged recently, leading to preparation of cytotoxic analogues of the marine natural product meridianin D [10] *via* the previously reported enamine product originating from treatment of **1** with DMFDMA [8].



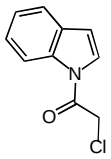
1 R = CN
2 R = P(O)(OEt)$_2$

RESULTS AND DISCUSSION

It is well established that heating of indole with chloroacetyl chloride in toluene gives 1-(chloroacetyl)-indole **3** [11], which has previously also been obtained from the reaction of indole with chloroacetic anhydride in refluxing dioxane [12]. Therefore, we were rather surprised to learn that a very recent paper claims preparation of 3-(chloroacetyl)indole **4** by heating indole with chloroacetyl chloride in refluxing dioxane [13]. However, the reported melting point of the resulting product (mp. 105 °C [13]) does not match that of the well-known compound **4** (mp. 233–234 °C [14], 230–232 °C [1]), but is quite close to that previously recorded for 1-(chloroacetyl)indole **3** (mp 116–117 °C [12], 115 °C [11], 120–121 °C [15]). The structure of **3** as a 1-substituted derivative of indole has also been rigorously proven a long time ago by dehydrogenation of 1-(chloroacetyl)-indole with DDQ [12]. Not unexpectedly, a repetition of the experiment described by Elnagdi [13] gave a product which was easily identified as the known 1-(chloroacetyl)indole **3**. This assignment was supported by ^{1}H NMR data in DMSO-d_6, which displayed a characteristic doublet of a doublet at δ 6.81 corresponding to the indole H-3, coupling to a doublet at δ 7.87 (indole H-2), as well as the absence of an acidic hydrogen resonance at low field. The ^{13}C NMR spectrum in combination with a DEPT experiment revealed the presence of six doublets, giving further indication that substitution had occurred at the indole nitrogen atom. In addition, the IR absorption observed for the carbonyl functionality (ν = 1698 cm^{-1}) is typical for an *N*-acylated indole. It was therefore clear that Elnagdi and co-workers have in fact obtained 1-(chloroacetyl)indole **3** instead of the claimed compound **4**. Moreover, the ^{1}H NMR data for **3** recorded in $CDCl_3$ were in good agreement with those attributed to **4** in Elnagdi's

paper [13]. Ottoni and co-workers have published an interesting procedure (unduly criticized by Elnagdi) involving pre-mixing of indole in dichloromethane with a Lewis acid (*e.g.* $SnCl_4$), followed by addition of the appropriate acid halide [3]. We have prepared 3-(chloroacetyl)indole **4** in good yield using this method, which is in fact competitive with the most commonly used literature procedure [1]. The advantage with the Brazilian method is the higher yield, and the drawback is a somewhat more laborious procedure.

The incorrect assignment by Elnagdi discussed above has serious consequences for some other reactions embodied in their paper. For example, a substitution experiment involving their material and ammonium thiocyanate does of course not lead to the purported product 2-(1*H*-indol-3-yl)-2-oxoethyl thiocyanate **5**. This was easy to verify by treatment of an authentic sample of 3-(chloroacetyl)indole **4** prepared according to the well-established literature procedure [1] with ammonium thiocyanate in refluxing acetonitrile, which gave the new compound **5** in good yield. This material displayed data fully consistent with the expected structure, including an indole NH resonace at δ 12.21 in the ^{1}H NMR recorded in DMSO-d_6, a ketone carbonyl signal at δ 186.1 in the ^{13}C NMR spectrum, as well as a typical ketone absorption at ν = 1616 cm^{-1} in the IR spectrum. In addition, the conversion of the claimed **4** with cyanide into 3-(cyanoacetyl)indole **1** described by Elnagdi [13] is hard to understand unless some mysterious rearrangement leading to transfer of the acyl group from the indole nitrogen to C-3 was in operation, which is an unlikely scenario under the reported reaction conditions.



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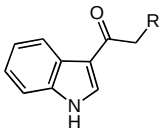
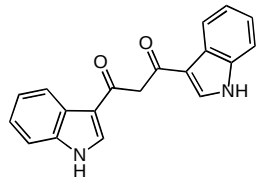


4 R = Cl
5 R = SCN

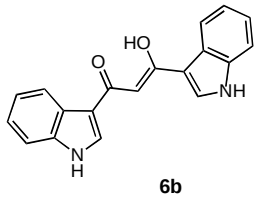
A deeper scrutiny of some other of the experiments detailed by Elnagdi [13] revealed additional inconsistencies. It was stated that treatment of indole with a reagent generated from malonic acid in acetic anhydride gives the symmetrical product 1,3-di(1*H*-indol-3-yl)propane-1,3-dione **6** as a mixture of the tautomers **6a**/**6b** in a good yield. However, there are no ketone resonances in the listed ^{13}C NMR data, while an IR absorption at ν = 1701 cm^{-1} raised instead our suspicion that the actual product may instead incorporate at least one indole unit connected via its nitrogen atom. It should also be noted that compound **6** had already been reported in 1922 by Sanna from the reaction of the indole Grignard reagent with malonyl chloride, and displayed the melting point 287 °C [16], which is considerably higher than that reported by Elnagdi (152 °C) [13]. In order to shed some light on these discrepancies, the reaction involving two equivalents of indole with malonic acid in acetic anhydride was performed essentially as described by Elnagdi, giving a rather complex mixture of products. Repeated crystallization of the crude product mixture or purification using column chromatography gave a low yield of a material which was unsymmetrical, as it exhibited two sets of indolic resonances in the NMR spectrum. Moreover, the ^{1}H NMR data featured only one acidic hydrogen signal, whereas the ^{13}C NMR and IR spectra suggested the presence of two different carbonyl functionalities, namely one ketonic and one amidic. Based on these data, the product was assigned the previously described unsymmetrical bisindole structure **7** [17]. There were no indications of keto–enol tautomerism in any of the NMR spectra. It is also important to note that Elnagdi used malonic acid and indole in the molar ratio 1:1. When repeated, this experiment also failed to give the product **6**, leading instead to isolation of 3-acetylindole as the major component after careful column chromatography of the complex crude product mixture. In addition, small amounts of the diindole derivative **8** could be obtained. Interestingly enough, all ^{13}C NMR resonances recorded for the indole derivative **8** find rather good matches in the data given by Elnagdi for the purported compound **6**, suggesting that he might perhaps have isolated an impure sample of **8**. Furthermore, we found that heating of indole with Meldrum's acid (2,2-dimethyl-1,3-dioxane-2,5-dione) in acetic anhydride gave the product **8** in 22% yield, proving a more convenient route despite the low yield. It should also be mentioned that there were no indications of tautomerism during NMR studies of **8** in DMSO-d_6 solution. In this context some interesting experiments reported by Majima and Shigematsu should be mentioned. After reaction of indole with diethyl malonate, they isolated in minimal amounts a product that was not further studied. We have not repeated this experiment, but we consider it likely that the Japanese workers had compound **8** in their hands. In a similar experiment with diethyl succinate they were able to isolate the 1,1'-connected isomer of **9** [18].

Finally, the target **6** could be obtained in a low yield by exposure of indole to freshly distilled malonyl chloride in dioxane. The NMR spectra in DMSO-d_6 clearly revealed the co-existence of the tautomers **6a**/**6b** in the ratio 1:0.33. However, neither of the forms **6a**/**6b** matched the data given by Elnagdi. For example, we found that the ketone carbon atom of the tautomer **6a** resonates at δ 189.4, just as might be expected for this type of structure, whereas the two most downfield signals reported by Elnagdi appear at δ 165.75 and 162.34, suggesting amide carbonyl signals. These facts, combined with the other

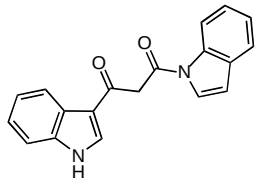
discrepancies discussed above raise serious doubts concerning the identity of Elnagdi's product.



6a



6b



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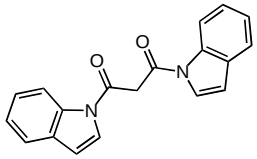

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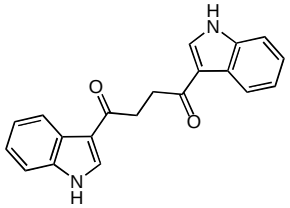
The situation becomes slightly different when longer chain dicarboxylic acids are involved in similar reactions, as the longer distance between the carbonyl units decrease the reactivity of the mixed anhydride. This may be illustrated by performing an acylation of indole with succinic acid in acetic anhydride (1:1 molar ratio) as described by Elnagdi, which does not give the known dione **9** [19,20], again giving rise to a complex mixture from which the well-known product 3-acetylindole could be isolated. The other products were present only in minute quantities and were not isolated or characterized. Interestingly enough, the data provided by Elnagdi for the purported dione **9** disagree with those published previously, in particular concerning the melting point (233 °C) [13], which does not match with the reported value (189 °C) [19,20]. Also in this case, the correctness of the assignment of Elnagdi's material must be questioned. In addition, there were no NMR data provided, thus precluding further comparison.



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In conclusion, it appears clear from the discussion above that many of the results presented in the Elnagdi paper are seriously flawed, as particularly illustrated by one of the key experiments claiming preparation of 3-(chloroacetyl)indole by heating indole with chloroacetyl chloride in dioxane, a reaction which in our hands gave the expected well-known isomeric product 1-(chloroacetyl)indole. The fact that Elnagdi *et al.* also have questioned previous results which have been verified and used [21-24] by numerous successors over the years is particularly misleading and ignorant, as they have clearly misinterpreted the spectral evidence which contradicts their conclusions and supports the previous findings. Readers interested in the preparation, reactivity, and applications of 3-acylindole derivatives are instead advised to consult the leading references cited in this work.

EXPERIMENTAL

General remarks. NMR spectra were recorded at 300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C, respectively, using the residual solvent signal as reference, unless otherwise stated. Coupling constants are given in Hz. The IR spectra were acquired using a FT-IR instrument. Melting points were determined on a capillary melting point or a hot stage apparatus. All reagents were commercially available and used as received. All solvents were purified by distillation or were of analytical grade. Chromatographic separations were performed on silica gel (35–70 μm particle size).

1-(Chloroacetyl)indole [2-Chloro-1-(1*H*-indol-1-yl)-ethanone] (3). This material was prepared by heating choroacetyl chloride with indole in 1,4-dioxane as described by Elnagdi [13]. The resulting pinkish crystalline solid was identified as **3**, mp 115–117 °C (lit.[12] 116–117 °C, lit.[11] 115 °C, lit.[15] 120–121 °C); ir (neat): 1698 (CO) cm^{-1}; ^{1}H nmr (DMSO-d_6): 8.33 (dd, J = 8.1, 0.6 Hz, 1H), 7.87 (d, J = 3.8 Hz, 1H), 7.66–7.63 (m, 1H), 7.39–7.27 (m, 2H), 6.81 (dd, J = 3.8, 0.6 Hz, 1H), 5.12 (s, 2H); ^{1}H nmr ($CDCl_3$, 500.2 MHz): 8.44 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.43 (d, J = 4.1 Hz, 1H), 7.41–7.38 (m, 1H), 7.33–7.30 (m, 1H), 6.72 (d, J = 4.1 Hz, 1H), 4.58 (s, 2H); ^{13}C nmr (DMSO-d_6): 165.4 (s), 135.0 (s), 130.1 (s), 126.2 (d), 124.9 (d), 123.9 (d), 121.0 (d), 115.7 (d), 109.1 (d), 43.5 (t); MS (ESI+) *m/z* 194 [M + H]$^{+}$.

3-(Chloroacetyl)indole [2-Chloro-1-(1*H*-indol-3-yl)-ethanone] (4). The procedure described here is based on a communication by Ottoni *et al.* [3]. Indole (5.85 g, 50 mmol) was dissolved in CH_2Cl_2 (80 mL) whereupon $SnCl_4$ (13.0 g, 50 mmol) was added with stirring at 0–5 °C. After completed addition, chloroacetyl chloride (5.65 g, 50 mmol) was added dropwise to the blue mixture. Addition of nitromethane (30 mL) as a co-solvent was necessary. This mixture was left at room temperature for 12 h, whereupon water (80 mL) and conc. HCl (25 mL) were added. The solid formed was collected after 2 h at room temperature and washed carefully with 2-propanol which gave 4.65 g (48%) of 3-(chloroacetyl)indole. Evaporation of the organic phase followed by trituration with ethanol gave an additional quantity (3.05 g, 31%) of **4** after rather laborious purification. The total yield of **4** was 79%. All data are in excellent agreement with those published previously [1,14].

2-(1*H*-Indol-3-yl)-2-oxoethyl thiocyanate (5). A mixture of 3-(chloroacetyl)indole [1] (**4**) (1.94 g, 10 mmol), ammonium thiocyanate (1.52 g, 20 mmol) and a catalytic amount of tetrabutylammonium iodide (18 mg) in anhydrous acetonitrile (50 mL) was heated at reflux for 3 h, and was thereafter allowed to cool to room temperature. Removal of the solvent *in vacuo* gave a solid residue, which was triturated with water (50 mL) giving a beige precipitate. This material was collected by filtration, dried, and crystallized from ethanol/acetonitrile to provide the title compound **5** (1.11 g) as tan crystals. A second crop (0.30 g) could be collected from the mother liquor. The total yield of **5** was 1.31 g (61%). Tan crystals, mp 218–219 °C (decomp.); ir (neat): 3250 (NH), 2158 (SCN), 1616 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): 12.21 (s, 1H), 8.49 (s, 1H), 8.16–8.13 (m, 1H), 7.53–7.50 (m, 1H), 7.27–7.23 (m, 2H), 4.85 (s, 2H); ^{13}C nmr (DMSO-d_6): 186.1 (s), 136.6 (s), 135.7 (d), 125.1 (s), 123.3 (d), 122.3 (d), 121.0 (d), 113.9 (s), 113.2 (s), 112.4 (d), 40.9 (t); MS (ESI–) *m/z* 215 $[M - H]^-$. *Anal.* Calcd. for $C_{11}H_8N_2OS$: C, 61.09; H, 3.73; N, 12.95. Found: C, 61.18; H, 3.80; N, 12.86.

1,3-Di(1*H*-indol-3-yl)propane-1,3-dione (6a/6b). Freshly distilled malonyl chloride (1.41 g, 10 mmol) was added to indole (2.34 g, 20 mmol) in dioxane (20 mL). The resulting solution was kept at 60 °C for 10 min., allowed to cool, and poured into water. The resulting semi-solid was treated with 2-propanol which gave the title compound in a low yield (350 mg). However, slow concentration of the mother liquor gave a more substantial quantity (650 mg), totalling the yield to 1.0 g (30%). White solid with a pinkish tinge, mp 290–292 °C (lit.[16] 287 °C); ir (neat): 3294 (NH), 1597 (CO) cm^{-1}; ^1H nmr (DMSO-d_6, 500.2 MHz) (only resonances for **6a** are listed): 12.01 (s, 2H), 8.42 (d, J = 3.2 Hz, 2H), 8.16 (d, J = 7.8 Hz, 2H), 7.49–7.47 (m, 2H), 7.16–7.23 (m, 4H), 4.46 (s, 2H); ^{13}C nmr (DMSO-d_6) (only resonances for **6a** are listed): 189.4 (s), 136.7 (s), 135.4 (d), 125.5 (s), 123.0 (d), 121.9 (d), 121.3 (d), 116.8 (s), 112.2 (d), 52.3 (t); MS (ESI+) *m/z* 303 $[M + H]^+$.

The nmr resonances (in particular for ^1H) of the enol tautomer **6b** overlap much with those of **6a**, but the diagnostic signals for the alkene unit at 6.88 (s) in the ^1H nmr and 92.1 (d) in the ^{13}C nmr could be discerned clearly.

1-(1*H*-Indol-1-yl)-3-(1*H*-indol-3-yl)propane-1,3-dione (7). This reaction was performed according to Elnagdi, but using the starting materials indole and malonic acid in a molar ratio 2:1. A suspension of malonic acid (1.04 g, 10 mmol) in acetic anhydride (10 mL) was heated to 85 °C for 10 min. The resulting solution was then treated with indole (2.34 g, 20 mmol), heated at reflux for 30 min, allowed to cool to room temperature, and poured over ice/water (200 g). The obtained solid was collected by filtration, washed with several portions of water, dried, and purified by column chromatography (EtOAc/*n*-heptane 1:2) to yield 1-(1*H*-indol-1-yl)-3-(1*H*-indol-3-yl)propane-1,3-dione (**7**) (154 mg, 5%) which displayed data as below.

Alternatively, the reaction was performed using indole (23.4 g, 0.2 mol) and malonic acid (10.4 g, 0.1 mol) in acetic anhydride (100 mL). Workup as above, followed by suspension of the crude complex product mixture in 2-propanol give a solid material, which was finally subjected to repeated crystallizations from acetonitrile/DMF providing small amounts of **7** (1.5 g, 5%) as a white crystalline solid, mp 246–248 °C (lit.[17] 237–238 °C); ir (neat): 3213 (NH), 1697 (CO), 1617 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): 12.15 (s, 1H), 8.53 (d, J = 3.2 Hz, 1H), 8.38 (d, J = 8.0 Hz, 1H), 8.14 (d, J = 7.1 Hz, 1H), 7.88 (d, J = 3.8 Hz, 1H), 7.65–7.62 (m, 1H), 7.52 (d, J = 7.3 Hz, 1H), 7.35–7.20 (m, 4H), 6.75 (d, J = 3.7 Hz, 1H), 4.77 (s, 2H); ^{13}C nmr (DMSO-d_6): 187.6 (s), 167.4 (s), 136.7 (s), 135.6 (d), 135.0 (s), 130.4 (s), 127.3 (d), 125.3 (s), 124.7 (d), 123.7 (d), 123.2 (d), 122.1 (d), 121.1 (s), 120.9 (d), 115.9 (d), 115.9 (d), 112.3 (d), 108.5 (d), 47.9 (t); MS (ESI+) *m/z* 303 $[M + H]^+$.

Treatment of indole with malonic acid in acetic anhydride. A suspension of malonic acid (3.12 g, 30 mmol) in acetic anhydride (30 mL) was heated to 85 °C for 10 min. The resulting solution was then treated with indole (3.52 g, 30 mmol), heated at reflux for 30 min, allowed to cool to room temperature, and poured over ice/water (250 g). The obtained solid was collected by filtration, washed with several portions of water, dried, and separated by column chromatography (EtOAc/*n*-heptane 1:2) to yield 1,3-di(1*H*-indol-1-yl)propane-1,3-dione (**8**) (93 mg, 1%), which gave data identical with those reported for the material prepared by exposure of indole to Meldrum's acid in acetic anhydride (see below), followed by 3-acetylindole (1.06 g, 22%). This procedure gave a plethora of products, most of which were present in trace quantities, thus only the two components indicated above were isolated and characterized. Data for 3-acetylindole: 191.5–192 °C (lit.[2] 187–189 °C; lit.[14] 191–193 °C), ir (neat): 3118 (NH), 1610 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): 11.9 (br s, 1H), 8.30 (s, 1H), 8.20–8.17 (m, 1H), 7.48–7.45 (m, 1H), 7.21–7.16 (m, 2H), 2.45 (s, 3H); ^{13}C nmr (DMSO-d_6): 192.6 (s), 136.7 (s), 134.3 (d), 125.3 (s), 122.7 (d), 121.6 (d), 121.3 (d), 116.8 (s), 112.1 (d), 27.3 (q).

1,3-Di(1*H*-indol-1-yl)propane-1,3-dione (8). Indole (1.10 g, 9.4 mmol) was added to a mixture of Meldrum's acid (2,2-dimethyl-1,3-dioxane-2,5-dione) (0.65 g, 4.5 mmol) in acetic anhydride (20 mL) at 70 °C. The resulting mixture was heated at 70 °C for 2 h, and was thereafter allowed to cool and concentrated to a semisolid. Trituration of this material with Et_2O afforded **8** (0.30 g, 22%) as a yellowish solid, mp 192.5–193.5 °C; ir (neat): 1695, 1677 (CO) cm^{-1}; ^1H nmr (DMSO-d_6): 8.35 (d, J = 7.8 Hz, 2H), 7.97 (d, J = 3.8 Hz, 2H), 7.67–7.64 (m, 2H), 7.39–7.28 (m, 4H), 6.81 (d, J = 3.8 Hz, 2H), 5.03 (s, 2H); ^{13}C nmr (DMSO-d_6): 166.0 (s), 135.1 (s), 130.5 (s), 127.2 (d), 124.9 (d), 124.0 (d), 121.0 (d), 115.9 (d), 109.0 (d), 44.8 (t); MS (ESI+) *m/z* 303 $[M + H]^+$.*Anal.* Calcd. for

$C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.61; H, 4.60; N, 9.20.

Treatment of indole with succinic acid in acetic anhydride. A solution of succinic acid (1.18 g, 0.01 mol) in acetic anhydride (10 mL) was heated to 85 °C for 10 min. The resulting solution was then treated with indole (1.17 g, 0.01 mol), heated at reflux for 30 min, allowed to cool to the room temperature, and poured over ice/water (150 g). The obtained solid was collected by filtration, washed with several portions of water, dried, and purified by column chromatography (EtOAc/*n*-heptane 1:2) to yield 3-acetylindole (0.67 g, 42%) which displayed data as above.

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