A Facile Synthesis of 4-, 6- and 7-Formyl-1*H*-Indole-2-Carboxylates: the CH_2SO_3H Functionality as a Masked Formyl Group.

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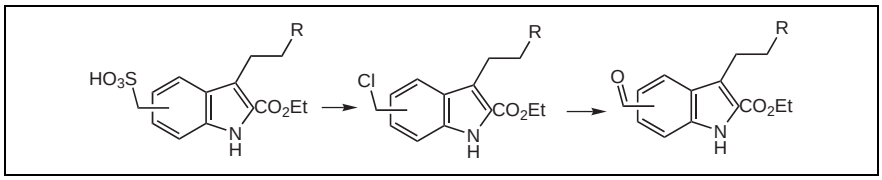

The valuable new synthetic intermediates, ethyl 4-, 6- and 7-formyl-1*H*-indole-2-carboxylates (**10**, **11**, **12**) were prepared from 2-ethoxycarbonyl-1*H*-indole-4-, 6- and 7-methanesulfonic acids (**1**, **2**, **3**), respectively. The transformation of sulfomethyl group to formyl function was accomplished through elimination of SO_2 to yield ethyl 4-, 6- and 7-chloromethyl-1*H*-indole-2-carboxylates (**4**, **5**, **6**), hydrolysed to ethyl 4-, 6- and 7-hydroxymethyl-1*H*-indole-2-carboxylates (**7**, **8**, **9**), then oxidized to aldehydes (**10**, **11**, **12**). Protection at N1 of indole was not necessary. A marked increase in the rate of hydrolysis of 7-chloromethyl-indoles compared to that of 4- and 6-(chloromethyl)indoles was observed.

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Introduction.

A wide variety of biologically active, or naturally occurring indoles contain substituents in the benzenoid portion of the indole nucleus. The 4-, 5-, 6- and 7-formyl-indoles are important intermediates in approaching the synthesis of such compounds. Teleocidine derivatives were prepared from 7-formylindole derivative [1], while 6-formylindole was utilized in the synthesis of natural product (*E*)-6-(3-methylbuta-1,3-dienyl)indole [2]. Chanoclavine-I was prepared starting from 4-formyl-indole [3]. There are only a few procedures to allow the introduction of a substituent at C4-C7 of indole regioselectively and none of them can be regarded as general in scope. Friedel-Crafts reaction of 2, 3-unsubstituted-1-acylindoles with chloroacetyl chlorides gives the corresponding 1,6-diacylindoles [4] in excellent yields. The acylation of indoles bearing electron-withdrawing substituents (ethoxycarbonyl at C2 [5, 6], or iminium at C3 [7]), under certain conditions, leads to substitution of the benzene part of the heterocycle especially at C5. However, when carrying out acylation of 2-ethoxycarbonylindole or 3-methylindole with dichloro-methyl methyl ether the products were 3-formyl- or *N*-formyl-derivatives, respectively, in good yields [6]. The Vilsmeier-Haack formylation of indole on the benzenoid ring has seldom preparative value because of the lack of regioselectivity. However, if the 1-, 2- and 3-positions are substituted, as in 1-alkyltetrahydrocarbazoles, formylation occurs at C6 of the indole-ring [8]. Formylation at C5 of the indole can be accomplished indirectly *via* indolines [9]. Vilsmeier-Haack formylation of 1-methylindoline followed by dehydrogenation with chloranil affords a good yield of 1-methylindole-5-carbaldehyde.

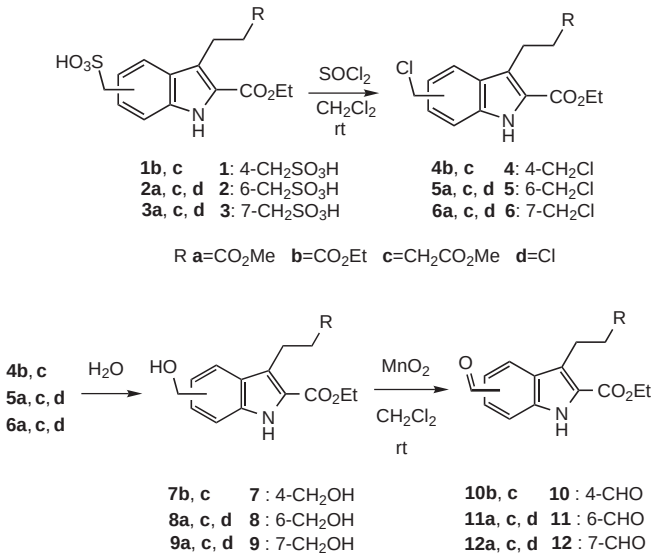
In far more cases are the substituents introduced prior to the elaboration of the indole ring. Due to the rather harsh conditions required by the indolization step it is necessary to utilize fairly robust benzenoid precursors compatible with the required conditions. As a result, halogen or carboxy group is applied for further elaboration. The known syntheses of formylindoles, *i.e.* the ones starting from 4-, 5-, 6- and 7-bromoindoles are effected by the sequence of lithiation with *tert*-butyllithium and condensation with dimethylformamide [10]. An alternative procedure utilises 4-alkoxycarbony-lindoles [11a] or 5- and 7-alkoxycarbonylindoles [11b] reduced by lithium aluminum hydride to benzylalcohols followed by manganese dioxide mediated oxidation. These strongly basic conditions exclude other base-sensitive functionalities in the targeted formylindoles. Although 4-, 5-, 6- and 7-bromoindoles are starting materials for cyanoindoles transformed to formylindoles in excellent yields [12], the reaction conditions (CuCN, quinoline, 230° for substitution and Raney-nickel, sodium hypophosphyte for the reduction) also do not tolerate sensitive substituents.

Results and Discussion.

Earlier we reported the synthesis of ethyl 5-formyl-1*H*-indole-2-carboxylates from ethyl 5-chloromethyl-

1*H*-indole-2-carboxylates [13]. In this paper we reveal our results on the facile preparation of ethyl 4-, 6- and 7-formyl-1*H*-indole-2-carboxylates (**10**, **11**, **12**) from ethyl 4-, 6-chloromethyl-1*H*-indole-2-carboxylates (**4**, **5**) [14a] and ethyl 7-chloromethyl-1*H*-indole-2-carboxylates (**6**) [14b], obtained from 2-ethoxycarbonyl-1*H*-indole-4-, 6-methanesulfonic acids (**1**, **2**) [14a] and 2-ethoxycarbonyl-1*H*-indole-7-methanesulfonic acids (**3**) [14b], respectively. The reaction conditions to obtain indolemethanesulfonic acids and (chloromethyl)indoles are slightly acidic while the latter are converted to formylindoles under neutral conditions (Scheme). Thus the overall procedure completes nicely the existing ones to obtain formylindoles as it offers a new synthetic entry for these compounds carrying base-sensitive functionalities.

Scheme



The hydrolysis of (chloromethyl)indoles (**4**, **5**, **6**) took place under different conditions depending on the position of the chloromethyl group. While the 4- and 6-(chloromethyl)indoles (**4**, **5**) required one hour in water-dioxane at 50° to complete hydrolysis, 7-(chloromethyl)indoles (**6**) reacted with water at 0° instantaneously, just as 5-(chloromethyl)indoles did [13]. The (hydroxymethyl)-indoles (**7**, **8**, **9**) can be isolated in 61-84% yields simply by evaporation of the solvents. With respect to yields and purity, the best method to effect oxidation to aldehydes (**10**, **11**, **12**) is the activated manganese dioxide mediated one, other oxidizing agents – potassium permanganate, potassium dichromate, potassium bromate - being less effective. Attempted direct conversion of (chloromethyl)-indoles (**4**, **5**, **6**) to aldehydes (**10**, **11**, **12**) either failed (with hexamethylenetetramine) or resulted in low yields (with dimethyl sulfoxide and sodium hydrogen carbonate at 110°).

There is not much known about the chemistry of regioisomers at C4-C7 of indoles as far as their reactivity is concerned. The 5- and 7-formylindole-2-carboxylates [6], 6-formylindole-2-carboxylates [15a], 4-formylindole-2-carboxylates [15b], or 5- and 7-bromoindole-2-carboxylates [16a], 4- and 6-bromoindole-2-carboxylates [16b] are known, but the reactivity of 4-, 5-, 6- and 7-substituents has not been compared yet. The increase in the rate of hydrolysis of 5- and 7-(chloromethyl)indoles compared to that of 4- and 6-isomers is the first example of such observation. The considerable difference can be explained in simple resonance terms: according to the resonance structures contributing to the overall π-electron structure of indole, the electron-releasing N1 atom causes a higher proportion of negative charge on C5 and C7 compared to C4 and C6 [14a]. As the Hammet reaction constant of hydrolysis of benzyl chloride, $\rho = -1.3$ (in water) [17], that is, electron releasing substituents favour the reaction, the hydrolysis is accelerated at C5 and C7 compared to C4 and C6.

In case of methanolysis, **6** reacted also much faster than **4** and **5** [14].

In summary, transformation of indolemethanesulfonates (**1**, **2**, **3**) to (chloromethyl)indoles (**4**, **5**, **6**) followed by hydrolysis and oxidation provides a general and regioselective methodology for the direct synthesis of formylindoles (**10**, **11**, **12**) carrying base-sensitive substituents. This procedure has the advantages of ready accessibility of the reagents, absence of side reactions, good yields and experimental simplicity as there is no need for protective groups.

EXPERIMENTAL

^{1}H nmr and ^{13}C nmr spectra were recorded at 300.13 MHz or 75.46 MHz, respectively, on a Bruker DRX 300 spectrometer. All δ values are given in ppm, tetramethylsilane (in deuteriochloroform or dimethylsulfoxide-d_6) or sodium 3-(trimethylsilyl)-1-propanesulfonate (in deuterium oxide) was used as an internal standard. IR spectra were measured on Perkin-Elmer 1600 series FTIR spectrophotometer in potassium bromide discs. The chloromethylindoles (**4c**, **5a**, **c**) [14a] and (**6a**, **c**, **d**) [14b] were prepared as described. All chemicals were reagent grade and used without further purification. Melting points are uncorrected.

3-(2-Ethoxycarbonyl-ethyl)-4-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (**1b**).

A suspension of 3-(2-carboxy-ethyl)-4-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester [14a] (3.55 g, 10 mmol) was stirred in dry ethanol (30 mL) for 24 hours at room temperature.

The solution was filtered and the filtrate was evaporated to dryness to give 3.52 g (92%) of pure **1b** as a beige solid, mp: 196-200° (water, dec); ^{1}H nmr (deuterium oxide): δ 1.35 (t, 3H, J=7 Hz), 1.53 (t, 3H, J=7 Hz), 2.51 (m, 2H), 3.60 (m, 2H), 4.23 (q, 2H, J=7 Hz), 4.48 (q, 2H, J=7 Hz), 4.57 (s, 2H), 7.23 (d, 1H, J=6.8 Hz), 7.45 (dd, 1H), 7.53 (d, 1H, J=8.0 Hz); ^{13}C nmr (deuterium oxide): δ 12.18, 12.22, 19.86, 34.33, 53.07, 60.52, 60.54, 111.26, 120.92, 122.53, 123.31, 123.68, 123.94, 124.06, 135.71, 161.93, 174.45; ir: 3325, 1730, 1689, 1252 cm^{-1}.

Anal. Calcd. for $C_{17}H_{21}NO_7S$: C, 53.25; H, 5.52; N, 3.65. Found: C, 52.87; H, 5.54; N, 3.60.

3-(2-Chloroethyl)-6-sulfomethyl-1*H*-indole-2-carboxylic acid ethyl ester (**2d**).

This compound was prepared from (3-aminophenyl)methanesulfonic acid and diethyl (3-chloropropyl)malonate according to the procedure described for the 7-sulfomethyl regioisomer [14b] and was separated from the 4-sulfomethyl regioisomer formed simultaneously by crystallisation from water to give **2d** as beige powder in 30% yield, mp: >270° (water); ^{1}H nmr (deuterium oxide): δ 1.32 (t, 3H, J=7 Hz), 3.39 (m, 2H), 3.74 (m, 2H), 4.19 (s, 2H), 4.30 (q, 2H, J=7 Hz), 7.10 (d, 1H, J=8.4 Hz), 7.36 (s, 1H), 7.64 (d, 1H, J=8.2 Hz); ^{13}C nmr (dimethylsulfoxide-d_6): δ 14.25, 28.05, 44.78, 58.05, 60.33, 113.83, 118.65, 119.13, 123.22, 123.59, 125.94, 132.41, 136.27, 161.64; ir: 3328, 1689, 1256 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}ClNO_5S$: C, 48.63; H, 4.66; N, 4.05. Found: C, 48.74; H, 4.61; N, 4.00.

General Procedure for Preparation of **4b** and **5d**.

The potassium salt of **1b** (4.21 g, 10 mmol) or **2d** (3.84 g, 10 mmol) was stirred in dry dichloromethane (50 mL) containing dimethylformamide (0.06 mL) and thionyl chloride (5 mL, 70 mmol) at room temperature until the suspension became almost a clear solution (*ca*. 4 hours). The solution was filtered and the filtrate was evaporated to dryness to give 3.03 g of **4b** (90%) or 2.76 g of **5d** (92%) as beige crystalline solids. Both compounds decomposed slowly when exposed to atmospheric moisture.

4-Chloromethyl-3-(2-ethoxycarbonyl-ethyl)-1*H*-indole-2-carboxylic acid ethyl ester (**4b**).

^{1}H nmr (deuteriochloroform): δ 1.22 (t, 3H, J=7 Hz), 1.42 (t, 3H, J=7 Hz), 2.73 (m, 2H), 3.64 (m, 2H), 4.14 (q, 2H, J=7 Hz), 4.43 (q, 2H, J=7 Hz), 5.04 (s, 2H), 7.12 (d, 1H, J=6.9 Hz), 7.26 (dd, 1H), 7.38 (d, 1H, J=8.2 Hz), 9.01 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.34, 14.44, 21.87, 36.43, 45.22, 60.44, 61.47, 113.57, 122.73, 123.53, 124.59, 124.66, 125.42, 131.77, 136.88, 162.26, 173.24;

3-(2-Chloroethyl)-6-chloromethyl-1*H*-indole-2-carboxylic acid ethyl ester (**5d**).

^{1}H nmr (deuteriochloroform): δ 1.48 (t, 3H, J=7 Hz), 3.54 (m, 2H), 3.76 (m, 2H), 4.44 (q, 2H, J=7 Hz), 4.72 (s, 2H), 7.21 (d, 1H, J=8.4 Hz), 7.42 (s, 1H), 7.70 (d, 1H, J=8.2 Hz), 8.94 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.49, 28.54, 44.30, 47.16, 61.37, 112.18, 120.00, 121.13, 121.46, 124.97, 127.97, 135.23, 135.67, 162.03;

General Procedure for Preparation of **7b**, **7c**, **8a**, **8c**, **8d**.

The (chloromethyl)indole **4b**, **4c**, **5a**, **5c**, **5d** (10 mmol) was dissolved in water-dioxane 1:5 mixture (200 mL) and kept at 50° for 1 hour (in case of **5d**, at room temperature for 48 hours). The solution was evaporated to dryness *in vacuo* and the solid residue was recrystallised from hexane to give pure **7b**, **7c**, **8a**, **8d**. In case of **8c** the residue remained an oil which was dissolved in hexane - ethyl acetate 3:1 (40 mL) and passed through neutral alumina (3 g) to give pure **8c** after evaporation of the solvent.

3-(2-Ethoxycarbonyl-ethyl)-4-hydroxymethyl-1*H*-indole-2-carboxylic acid ethyl ester (**7b**).

This compound was obtained as colourless fine needles, 2.61 g (82%), mp: 110-112° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.23 (t, 3H, J=7 Hz), 1.42 (t, 3H, J=7 Hz), 2.72 (m, 2H), 3.62 (m, 2H), 4.13 (q, 2H, J=7 Hz), 4.44 (q, 2H, J=7 Hz), 5.02 (s, 2H), 7.10 (d, 1H, J=7.0 Hz), 7.24 (dd, 1H), 7.38 (d, 1H, J=8.2 Hz), 9.05 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.15, 14.25, 21.70, 36.10, 60.49, 61.02, 63.59, 112.18, 121.08, 123.00, 123.80, 124.80, 125.20, 135.00, 136.62, 162.24, 173.65; ir: 3418, 1708, 1688, 1262 cm^{-1}.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.84; H, 6.60; N, 4.35.

4-Hydroxymethyl-3-(3-methoxycarbonyl-propyl)-1*H*-indole-2-carboxylic acid ethyl ester (**7c**).

This compound was obtained as colourless fine needles, 2.68 g (84%), mp: 128-130° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.44 (t, 3H, J=7 Hz), 2.03 (m, 2H), 2.51 (m, 2H), 3.31 (m, 2H), 3.69 (s, 3H), 4.42 (q, 2H, J=7 Hz), 5.08 (s, 2H), 7.14 (d, 1H, J= 6.8 Hz), 7.28 (dd, 1H), 7.35 (d, 1H, J=8.3 Hz), 8.86 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.59, 25.54, 27.24, 34.01, 51.78, 61.01, 63.87, 112.25, 121.23, 123.90, 124.66, 125.21, 125.45, 135.43, 136.78, 162.35, 174.65; ir: 3420, 1712, 1686, 1191 cm^{-1}.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.58; H, 6.68; N, 4.31.

6-Hydroxymethyl-3-(2-methoxycarbonyl-ethyl)-1*H*-indole-2-carboxylic acid ethyl ester (**8a**).

This compound was obtained as colourless fine needles, 2.47 g (81%), mp: 63-67° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.40 (t, 3H, J=7 Hz), 2.66 (m, 2H), 3.39 (m, 2H), 3.65 (s, 3H), 4.38 (q, 2H, J=7 Hz), 4.76 (s, 2H), 7.10 (d, 1H, J=8 Hz), 7.33 (s, 1H), 7.65 (d, 1H, J=8 Hz), 9.40 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.14, 20.27, 34.95, 51.45, 60.80, 65.19, 109.97, 119.47, 120.43, 122.29, 123.47, 126.72, 136.00, 138.65, 162.24, 173.63; ir: 3342, 1733, 1685, 1255 cm^{-1}.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.66; H, 6.32; N, 4.53.

6-Hydroxymethyl-3-(3-methoxycarbonyl-propyl)-1*H*-indole-2-carboxylic acid ethyl ester (**8c**).

This compound was obtained as pale yellow oil, 2.20 g (69%), ^{1}H nmr (deuteriochloroform): δ 1.45 (t, 3H, J=7 Hz), 2.06 (m, 2H), 2.39 (m, 2H), 3.18 (m, 2H), 3.67 (s, 3H), 4.44 (q, 2H, J=7 Hz), 4.82 (s, 2H), 7.16 (d, 1H, J=8.1 Hz), 7.40 (s, 1H), 7.68 (d, 1H, J=8.1 Hz), 8.81 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.49, 24.11, 26.04, 33.73, 51.60, 60.95, 65.60, 110.20, 119.69, 120.91, 123.61, 123.68, 127.46, 136.29, 138.94, 162.64, 174.33; ir: 3333, 1720, 1666, 1256 cm^{-1}.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.54; H, 6.68; N, 4.32.

3-(2-Chloroethyl)-6-hydroxymethyl-1*H*-indole-2-carboxylic acid ethyl ester (**8d**).

This compound was obtained as colourless fine needles, 2.03 g (72%), mp: 142-144° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.46 (t, 3H, J=7 Hz), 3.56 (m, 2H), 3.78 (m, 2H), 4.45 (q, 2H, J=7 Hz), 4.82 (s, 2H), 7.18 (d, 1H, J=8.4 Hz), 7.42 (s, 1H), 7.71 (d, 1H, J=8.4 Hz), 8.83 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.57, 28.72, 44.44, 61.30, 65.82, 110.26, 120.20, 120.23, 120.98, 124.49, 127.67, 136.09, 139.19, 162.20; ir: 3333, 1678, 1253 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.33; H, 5.68; N, 4.90.

General Procedure for Preparation of **9a**, **c**, **d**.

The (chloromethyl)indole **6a**, **c**, **d** (10 mmol) was dissolved in dry dichloromethane (50 mL) and added dropwise to ice (10 g) stirred vigorously. Potassium hydrogen carbonate (0.5 g) was then added and stirring was continued for 5 minutes. The organic phase was separated and dried (magnesium sulfate) to give, after rotary evaporation, crude **9a**, **c**, **d** which was dissolved in hexane - ethyl acetate 1:4 (60 mL) and passed through neutral alumina (4 g) to give pure **9a**, **c**, **d** after evaporation of the solvent.

7-Hydroxymethyl-3-(2-methoxycarbonyl-ethyl)-1*H*-indole-2-carboxylic acid ethyl ester (**9a**).

This compound was obtained as colourless fine needles, 1.98 g (65%), mp: 136-138° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.47 (t, 3H, J=7 Hz), 2.72 (m, 2H), 3.43 (m, 2H), 3.68 (s, 3H), 4.47 (q, 2H, J=7 Hz), 4.91 (s, 2H), 7.14 (dd, 1H), 7.29 (d, 1H, J=6.9 Hz), 7.75 (d, 1H, J=8.2 Hz), 9.02 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.53, 20.56, 35.22, 43.73, 51.76, 61.27, 120.33, 120.76, 122.01, 123.35, 124.21, 126.06, 128.60, 134.40, 162.16, 173.67; ir: 3342, 1733, 1685, 1255 cm^{-1}.

Anal. Calcd. for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 63.34; H, 6.32; N, 4.50.

7-Hydroxymethyl-3-(3-methoxycarbonyl-propyl)-1*H*-indole-2-carboxylic acid ethyl ester (**9c**).

This compound was obtained as colourless fine needles, 1.95 g (61%), mp: 118-120° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.47 (t, 3H, J=7 Hz), 2.06 (m, 2H), 2.40 (m, 2H), 3.19 (m, 2H), 3.68 (s, 3H), 4.47 (q, 2H, J=7 Hz), 4.91 (s, 2H), 7.13 (dd, 1H), 7.29 (d, 1H, J=7.2 Hz), 7.72 (d, 1H, J=7.8 Hz), 8.95 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.64, 24.17, 26.07, 33.79, 43.87, 51.67, 61.17, 120.26, 120.71, 122.17, 124.16, 124.42, 126.00, 129.00, 134.49, 162.32, 174.19; ir: 3331, 1729, 1679, 1252 cm^{-1}.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.54; H, 6.57; N, 4.32.

3-(2-Chloroethyl)-7-hydroxymethyl-1*H*-indole-2-carboxylic acid ethyl ester (**9d**).

This compound was obtained as colourless fine needles, 1.75 g (62%), mp: 163-165° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.46 (t, 3H, J=7 Hz), 3.52 (m, 2H), 3.77 (m, 2H), 4.47 (q, 2H, J=7 Hz), 4.90 (s, 2H), 7.15 (dd, 1H), 7.29 (d, 1H, J=7.2 Hz), 7.73 (d, 1H, J=8.2 Hz), 9.07 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.61, 28.72, 43.78, 44.37, 61.45, 120.66, 120.78, 120.87, 121.99, 124.77, 126.18, 128.99, 134.37, 161.99; ir: 3338, 1684, 1253 cm^{-1}.

Anal. Calcd. for $C_{14}H_{16}ClNO_3$: C, 59.68; H, 5.72; N, 4.97. Found: C, 59.28; H, 5.76; N, 4.90.

General Procedure for preparation of **10**, **11**, **12**:

The alcohol (**7**-**9**, 1 mmol) was stirred in dry dichloromethane (25 mL) with activated manganese dioxide (1.5 g) at room temperature for 72 hours, then the reaction mixture was filtered on celite, the manganese dioxide was washed with dichloromethane (10 mL) and the combined solution was evaporated to give pure **10**, **11**, **12**.

3-(2-Ethoxycarbonyl-ethyl)-4-formyl-1*H*-indole-2-carboxylic acid ethyl ester (**10b**).

This compound was obtained as colourless fine needles, 0.225 g (72%), mp: 89-91° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.17 (t, 3H, J=7 Hz), 1.37 (t, 3H, J=7 Hz), 2.62 (m, 2H), 3.67 (m, 2H), 4.07 (q, 2H, J=7 Hz), 4.38 (q, 2H, J=7 Hz), 7.37 (dd, 1H), 7.58 (d, 1H, J=8.2 Hz), 7.67 (d, 1H, J=6.9 Hz), 9.16 (bs, 1H), 10.35 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 14.19, 14.22, 22.61, 35.95, 60.30, 61.39, 118.62, 123.14, 124.33, 124.73, 126.08, 128.13, 131.99, 136.92, 162.10, 173.17, 192.04; ir: 3316, 1725, 1677, 1263 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.55; H, 6.07; N, 4.36

4-Formyl-3-(3-methoxycarbonyl-propyl)-1*H*-indole-2-carboxylic acid ethyl ester (**10c**).

This compound was obtained as colourless fine needles, 0.257 g (81%), mp: 138-140° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.47 (t, 3H, J=7 Hz), 2.02 (m, 2H), 2.47 (m, 2H), 3.52 (m, 2H), 3.67 (s, 3H), 4.47 (q, 2H, J=7 Hz), 7.47 (dd, 1H), 7.67 (d, 1H, J=8.2 Hz), 7.79 (d, 1H, J=6.9 Hz), 9.09 (bs, 1H), 10.51 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 14.54, 26.33, 26.87, 33.96, 51.65, 61.44, 118.50, 124.48, 124.66, 125.42, 126.02, 127.22, 132.28, 137.04, 162.17, 174.21, 192.09; ir: 3202, 1737, 1694, 1239 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.07; H, 5.96; N, 4.35.

6-Formyl-3-(2-methoxycarbonyl-ethyl)-1*H*-indole-2-carboxylic acid ethyl ester (**11a**).

This compound was obtained as colourless fine needles, 0.250 g (83%), mp: 126-130° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.43 (t, 3H, J=7 Hz), 2.69 (m, 2H), 3.46 (m, 2H), 3.62 (s, 3H), 4.43 (q, 2H, J=7 Hz), 7.67 (d, 1H, J=7.1 Hz), 7.83 (d, 1H, J=8.3Hz), 7.90 (s, 1H), 9.22 (bs, 1H), 10.05 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 14.51, 20.48, 35.21, 51.87, 61.67, 115.50, 120.54, 121.50, 122.66, 127.44, 132.31, 134.08, 135.29, 161.80, 173.60, 192.48; ir: 3330, 1735, 1689, 1267 cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.00; H, 5.67; N, 4.61.

6-Formyl-3-(3-methoxycarbonyl-propyl)-1*H*-indole-2-carboxylic acid ethyl ester (**11c**).

This compound was obtained as colourless fine needles, 0.247 g (78%) mp : 90-92° (hexane) ^{1}H nmr (deuteriochloroform): δ 1.48 (t, 3H, J=7 Hz), 2.04 (m, 2H), 2.39 (m, 2H), 3.16 (m, 2H), 3.66 (s, 3H), 4.42 (q, 2H, J=7 Hz), 7.68 (d, 1H, J=8.5 Hz), 7.82 (d, 1H, J=8.3 Hz), 7.93 (s, 1H), 9.18 (bs, 1H), 10.08 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 14.41, 23.96, 25.91, 33.64, 51.61,

61.41, 115.69, 120.17, 121.32, 123.45, 127.33, 132.47, 133.85, 135.44, 162.06, 174.04, 192.52; ir: 3333, 1742, 1678, 1326 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.14; H, 6.00; N, 4.44.

3-(2-Chloro-ethyl)-6-formyl-1*H*-indole-2-carboxylic acid ethyl ester (**11d**).

This compound was obtained as colourless fine needles, 0.207 g (74%), mp: 127-128° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.47 (t, 3H, J=7 Hz), 3.57 (m, 2H), 3.78 (m, 2H), 4.51 (q, 2H, J=7 Hz), 7.70 (d, 1H, J=8.4 Hz), 7.83 (d, 1H, J=8.4 Hz), 7.95 (s, 1H), 9.60 (bs, 1H), 10.08 (s, 1H); ^{13}C nmr (deuteriochloroform): δ 14.45, 28.43, 44.39, 61.79, 115.20, 120.02, 120.66, 121.37, 127.92, 132.60, 134.05, 135.33, 161.83, 192.51; ir: 3338, 1678, 1331 cm^{-1}.

Anal. Calcd. for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; N, 5.01. Found: C, 60.15; H, 4.98; N, 4.98.

7-Formyl-3-(2-methoxycarbonyl-ethyl)-1*H*-indole-2-carboxylic acid ethyl ester (**12a**).

This compound was obtained as colourless fine needles, 0.218 g (72%), mp: 100-102° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.45 (t, 3H, J=7 Hz), 2.72 (m, 2H), 3.46 (m, 2H), 3.64 (s, 3H), 4.46 (q, 2H, J=7 Hz), 7.32 (dd, 1H), 7.80 (d, 1H, J=7.2 Hz), 8.06 (d, 1H, J=7.9 Hz), 10.13 (s, 1H), 10.39 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.55, 20.32, 35.16, 51.74, 61.26, 120.06, 121.21, 123.11, 125.44, 128.23, 129.05, 132.44, 133.23, 161.41, 173.57, 192.97; ir: 3256, 1733, 1685, 1200 cm^{-1}.

Anal. Calcd. for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.64; H, 5.59; N, 4.55.

7-Formyl-3-(3-methoxycarbonyl-propyl)-1*H*-indole-2-carboxylic acid ethyl ester (**12c**).

This compound was obtained as colourless fine needles, 0.228 g (72%), mp: 66-68° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.47 (t, 3H, J=7 Hz), 2.06 (m, 2H), 2.41 (m, 2H), 3.23 (m, 2H), 3.68 (s, 3H), 4.47 (q, 2H, J=7 Hz), 7.33 (dd, 1H), 7.82 (d, 1H, J=6.9 Hz), 8.04 (d, 1H, J=7.8 Hz), 10.15 (s, 1H), 10.37 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.63, 23.88, 26.16, 33.70, 51.71, 61.20, 120.01, 121.25, 124.14, 125.39, 128.27, 129.41, 132.46, 133.39, 161.67, 174.18, 193.08; ir: 3329, 1731, 1680, 1251 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.04; H, 6.08; N, 4.38.

3-(2-Chloro-ethyl)-7-formyl-1*H*-indole-2-carboxylic acid ethyl ester (**12d**).

This compound was obtained as colourless fine needles, 0.206 g (74%), mp: 82-84° (hexane); ^{1}H nmr (deuteriochloroform): δ 1.47 (t, 3H, J=7 Hz), 3.60 (m, 2H), 3.80 (m, 2H), 4.47 (q, 2H, J=7 Hz), 7.35 (dd, 1H), 7.82 (d, 1H, J=7.2 Hz), 8.05 (d, 1H, J=7.9 Hz), 10.14 (s, 1H), 10.45 (bs, 1H); ^{13}C nmr (deuteriochloroform): δ 14.58, 28.33, 44.55, 61.41, 120.35, 120.59, 121.29, 125.91, 128.13, 129.46, 132.53, 133.18, 161.32, 192.98; ir: 3345, 1700, 1669, 1241 cm^{-1}.

Anal. Calcd. for $C_{14}H_{14}ClNO_3$: C, 60.11; H, 5.04; N, 5.01. Found: C, 59.85; H, 5.10; N, 4.92.

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