A Facile Synthesis of 7-Chloromethyl-1*H*-indole-2-carboxylates: Replacement of a Sulfonic Acid Functionality by Chlorine

Béla Pete*

Research Group of the Hungarian Academy of Sciences, Department of Organic Chemical Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary

Frigyes Varga and János Kovács

Department of Organic Chemical Technology, Budapest University of Technology and Economics, H-1521 Budapest, Hungary

Received November 1, 2004

Valuable new synthetic intermediates, 7-chloromethyl-1*H*-indole-2-carboxylates (**3a-d**), were prepared by the facile elimination of sulfur dioxide under the influence of thionyl chloride from 2-ethoxycarbonyl-1*H*-indole-7-methanesulfonic acids (**1a-d**), easily accessible by Fischer-type indolisation. The 7-chloromethylindoles easily underwent methanolysis and aminolysis.

J. Heterocyclic Chem., **42**, 615 (2005).

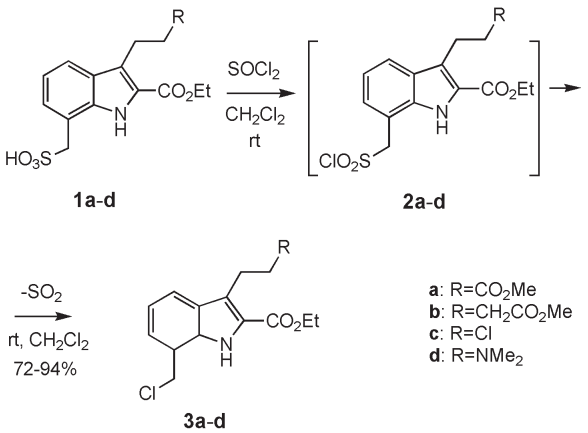
The synthesis of highly substituted indoles continues to attract the attention of synthetic organic chemists for many years. The regioselective introduction of substituents with at least one carbon on the benzenoid part of the heterocycle relies mainly on halogen-metal exchange [1] or directed lithiation reactions [2]. The strongly basic circumstances associated with this methodology, however, preclude other base-sensitive functionalities in the molecule. Although this difficulty can be avoided by transition-metal-based couplings, still there is a need for an indole substituent which, like halogens, can easily be introduced regioselectively on the benzenoid part but its transformation toward the desired functionalities requires acidic or neutral conditions.

Earlier we reported that the 2-ethoxycarbonyl-1*H*-indole-4-, 5- and 6-methanesulfonic acids were easily transformed into 4-, 5- and 6-chloromethyl-1*H*-indole-2-carboxylates, respectively, using typical conditions for the formation of sulfonyl chlorides [3]. The elimination and replacement of the sulfonic acid group by chlorine of these methanesulfonic acids is actually so facile that the sulfonic acid group may be regarded as a kind of latent chlorine atom. Such type of "functional group chemistry" is little known in the literature, and unprecedented in the chemistry of the indoles. To the best of our knowledge, only two examples exist where this type of transformation has been used for preparative purposes: Barber and co-workers developed a general method for the preparation of aryloxymethyl chlorides from aryloxymethanesulfonates and phosphorus pentachloride at rt [4]. Moreover, a number of 2-benzimidazolyl chlorides were prepared in good yields from the corresponding 2-benzimidazolylsulfonic acids by treatment with phosphorus pentachloride and phosphorus oxychloride [5].

The formation of alkyl chlorides and even alkylamines has been observed by the elimination of sulfur dioxide from alkylsulfonyl chlorides [6] or sulfonamides [7], respectively, but the reactions have not been shown to have any synthetic utility.

In this paper we report the synthesis of 2-ethoxycarbonyl-1*H*-indole-7-methanesulfonic acids **1a-d**, which, like the regioisomeric indolylmethanesulfonic acids [3], underwent the same type of facile elimination and replacement of sulfonic acid group by chlorine yielding 7-chloromethyl-1*H*-indole-2-carboxylates **3a-d** (Scheme 1). These chloromethylindoles **3a-d** are very reactive compounds decomposing quickly when exposed to atmospheric moisture. They reacted easily with methanol even in the absence of base at rt to give ethers **4** and **5** and suffered aminolysis within a few minutes at 0 °C to give **6** and **7** with the chloroethyl group of **3c** remaining intact.

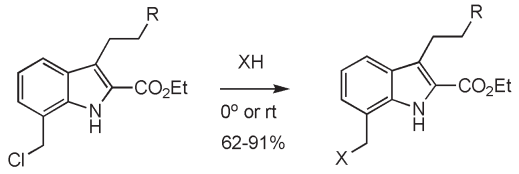
Scheme 1



The reaction conditions for the replacement of the sulfonic acid group to chlorine are similar to those applied to removal of an acid-sensitive protecting group: simply a few hours stirring in dichloromethane–thionyl chloride suspension at rt until the solid dissolves. The chloromethylindoles **3a-d** were formed in almost quantitative

yields and were isolated as crystalline solids simply by evaporating the solvent.

Scheme 2



3a-d **4, 5, 6, 7**

4 R=CO_2Me X=OMe
5 R=CH_2CO_2Me X=OMe
6 R=Cl X=NMe_2
7 R=NMe_2 X=NMe_2

The regioselective synthesis of 7-substituted indoles as reactive synthetic intermediates is an important aspect in the chemistry of this heterocycle. 7-Indolylacetonitriles are key intermediates in the synthesis of potent Cyclin D1/CDK4 inhibitors [8] while 7-alkenyl-3-indolylcarboxamide as indole analogue of Mycophenolic acid is a potential antineoplastic agent [9]. 7-Ethylindole forms the core of the important pharmaceutical compound Etodolac [10]. Indoles substituted at C7 are also important intermediates for the synthesis of a wide range of natural products of pharmacological importance such as pyrrolophenanthridone alkaloids [11], asterriquinones [12] or teleocidines [13].

The preparation of indole-7-methanesulfonic acids (Scheme 3) started by the Japp-Klingemann reaction of diazotized *ortho*-aminophenylmethanesulfonic acid **9** and β-oxoester derivatives **8a-d** to yield hydrazones **10a-d**. Potassium acetate or potassium hydrogen carbonate was used to adjust the pH to 4-5 during condensation, the hydrazones either separated from the reaction mixture (**10a**, **b**, **d**) or were isolated by evaporating the aqueous solution to dryness and extracting the solid residue with methanol (**10c**). The regiochemical structure of the hydrazones was not investigated. The Fischer indolisation was carried out either in formic acid (**10a**, **b**) or in acetic acid-gaseous hydrogen chloride (**10c**, **d**) at reflux temperature. The sulfonic acids were isolated by evaporating the solvent and were purified by crystallisation from water in good overall yield.

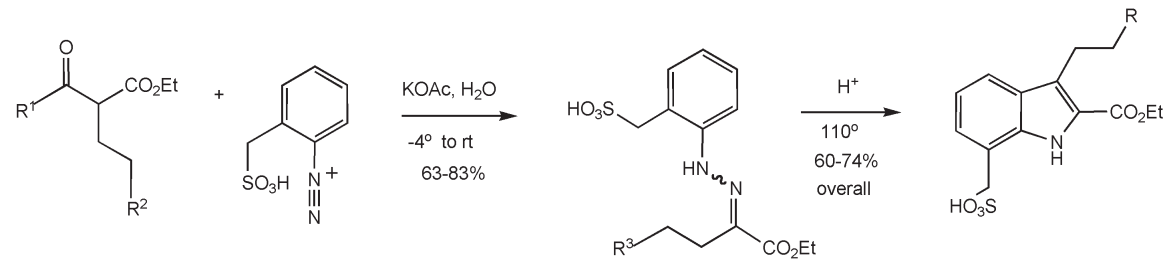
Although (alkylphenyl)hydrazones have the propensity for rearrangements to occur in Fischer indolisation, sulfonic acids **11**, **12**, **1c**, **1d** were the only indoles formed.

The method described here enables the facile and regioselective introduction of sulfomethyl group at C7 of indole-2-carboxylates. The sulfo group of these indole-7-methanesulfonic acids, while extremely stable in refluxing formic acid, acetic acid-gaseous hydrogen chloride or methanol-thionyl chloride, is easily replaced by chlorine in dichloromethane-thionyl chloride at room temperature. The 7-chloromethylindoles formed are useful "acidic" alternatives of 7-lithioindoles as synthetic intermediates for introduction of a carbon-chain at C7 of indoles.

EXPERIMENTAL

^1H nmr and ^{13}C nmr spectra were recorded at 300.13 MHz or 75.46 MHz, respectively, on a Bruker DRX 300 spectrometer. All values are given in ppm, TMS or sodium 3-(trimethylsilyl)-1-propanesulfonate was used as an internal standard. IR spectra were measured on Perkin-Elmer 1600 series FTIR spectrophotometer. All chemicals were reagent grade and used without

Scheme 3



8a - d **9** **10a - d** **11, 12, 1c, d**

8a $R^1+R^2=CH_2$
b $R^1+R^2=(CH_2)_2$
c R^1=OH, $R^2=CH_2Cl$
d R^1=Me, $R^2=CH_2NMe_2$

i: MeOH, $SOCl_2$, -25° to rt, 24 h

10a $R^3=CH_2CO_2H$
b $(CH_2)_2CO_2H$
c CH_2Cl
d CH_2NMe_2

11 R=CO_2H i
1a R=CO_2Me
12 R=CH_2CO_2H i
1b R=CH_2CO_2Me
1c R=Cl
1d R=NMe_2

further purification. (2-Aminophenyl)methanesulfonic acid [14] and 2-acetyl-5-dimethylaminopentanoic acid ethyl ester **8d** [15] were prepared as described. 3-Chloropropyl)malonic acid monoethylester **8c** was prepared according to the procedure given in [16]. Melting points are uncorrected. Most sulfonic acid derivatives did not have definite melting points but ranges instead.

General Procedure for the Japp-Klingeman Reaction of Diazotized (2-Aminophenyl)methanesulfonic acid (**9**) with Ketoesters **8a-d**.

(2-Aminophenyl)methanesulfonic acid (1 g, 5.3 mmol) suspended in water (20 mL) and concentrated hydrochloric acid (4 mL) was diazotized by adding sodium nitrite (0.37 g, 5.4 mmol) at –4°. The appropriate β-oxoester (6 mmol) was then added without solvent at the same temperature while stirring vigorously (ethyl 2-oxocyclopentanecarboxylate **8a** for **10a** ethyl 2-oxo-cyclohexanecarboxylate **8b** for **10b**; 2-acetyl-5-dimethylaminopentanoic acid ethyl ester **8d** for **10d**). (3-Chloropropyl)malonic acid monoethylester **8c** (for **10c**) was added in ethanol prepared as follows: diethyl (3-chloropropyl)malonate (1.43 g, 6 mmol) in dry ethanol (5 mL) was cooled to 5° then potassium hydroxide (0.38 g, 6.7 mmol) in dry ethanol (8 mL) was added at the same temperature over a period of 1 hour. The reaction mixture was kept at room temperature for 8 hours, cooled to 0° then added to the diazonium solution over a period of 0.5 hour. Having introduced the β-oxoester, the pH of the reaction mixture was rendered to 4-5 by adding potassium acetate (in case of **1d** potassium hydrogen carbonate) still at the same temperature. The yellow solution was stirred for 4-5 hours at room temperature to complete the separation of hydrazones **10a**, **b**, **d** isolated by filtration. In case of **10c** the aqueous solution was evaporated to dryness and the solid residue was triturated with methanol to separate **10c** from inorganic salts. The methanol was removed *in vacuo* and the solid residue was crystallised from acetone to give pure **10c**. The raw hydrazones **10a**, **b**, **d** still contained 10-20% potassium acetate but were used without further purification. Their yields refer to the recrystallised material from water.

2-[[2-(Sulfomethyl)phenyl]hydrazono]hexanedioic Acid 1-Ethyl Ester (**10a**).

This compound was obtained as yellow crystals, 1.7 g (72%), mp 236-240°; ir (KBr): 3480, 1692, 1254, 1168; ^{1}H nmr (D_2O): 1.52 (t, 3H, J = 7.0 Hz), 2.09 (m, 2H), 2.60 (m, 2H), 2.78 (m, 2H), 4.42 (s, 2H), 4.46 (q, 2H, J = 7.0 Hz), 7.29 (dd, 1H, J = 8.0, 7.5 Hz), 7.47 (d, 1H, J = 7.3 Hz), 7.57 (dd, 1H, J = 8.3, 7.6 Hz), 7.68 (d, 1H, J = 7.9 Hz). ^{13}C nmr (D_2O): 15.86, 21.91, 26.23, 35.68, 56.48, 64.72, 119.39, 121.40, 125.70, 131.94, 135.17, 139.68, 144.30, 168.83, 180.28.

Anal. Calcd. for $C_{15}H_{18}K_2N_2O_7S$: C, 40.16 H, 4.04 N, 6.24. Found: C, 40.00 H, 4.10 N, 6.14.

2-[[2-(Sulfomethyl)phenyl]hydrazono]heptanedioic Acid 1-Ethyl Ester (**10b**).

This compound was obtained as yellow crystals, 2.03 g (83%), mp 190-194°; ir (KBr): 3488, 1692, 1252, 1163; ^{1}H nmr (D_2O): 1.48 (t, 3H, J = 7.0 Hz), 1.78 (m, 4H), 2.55 (m, 2H), 2.66 (m, 2H), 4.29 (s, 2H), 4.45 (q, 2H, J = 7.0 Hz), 7.21 (dd, 1H, J = 8.1, 7.3 Hz), 7.45 (d, 1H, J = 7.4 Hz), 7.53 (dd, 1H, J = 8.4, 7.7 Hz), 7.67 (d, 1H, J = 8.6 Hz); ^{13}C nmr (D_2O): 12.21, 22.32, 25.13, 30.55, 31.87, 51.91, 58.64, 113.18, 118.90, 119.57, 125.83, 126.86, 130.51, 140.93, 160.58, 172.80.

Anal. Calcd for $C_{16}H_{20}K_2N_2O_7S$: C, 41.54 H, 4.36 N, 6.06. Found: C, 41.32 H, 4.41 N, 5.95.

5-Chloro-2-[[2-(sulfomethyl)phenyl]hydrazono]pentanoic Acid Ethyl Ester (**10c**).

This compound was obtained as white crystals, 1.36 g (64%), mp 72-76°; ir (KBr): 3448, 1701, 1248, 1197; ^{1}H nmr ($CDCl_3$+ DMSO-d_6): 1.19 (t, 3H, J = 7.0 Hz), 1.83 (m, 2H), 2.55 (m, 2H), 3.42 (m, 2H), 4.00 (s, 2H), 4.11 (q, 2H, J = 7.0 Hz), 6.72 (dd, 1H, J = 7.3, 7.4 Hz), 7.03 (dd, 1H, J = 7.7, 8.3 Hz), 7.07 (d, 1H, J = 7.5 Hz), 7.39 (d, 1H, J = 8.1 Hz), 10.02 (s, 1H). ^{13}C nmr ($CDCl_3$): 14.15, 22.75, 28.04, 44.49, 54.86, 60.71, 116.41, 119.69, 121.97, 128.54, 132.33, 136.00, 143.02, 165.04.

Anal. Calcd for $C_{14}H_{18}ClKN_2O_5S$: C, 41.94 H, 4.53 N, 6.99. Found: C, 41.77 H, 4.45 N, 6.90.

5-Dimethylamino-2-[[2-(sulfomethyl)phenyl]hydrazono]pentanoic Acid Ethyl Ester (**10d**).

This compound was obtained as white crystals, 1.24 g (63%), mp 172-176°; ir (KBr): 3452, 1696, 1239, 1175; ^{1}H nmr (D_2O): 1.42 (t, 3H, J = 7.0 Hz), 1.98 (m, 2H), 2.67 (m, 2H), 2.94 (s, 6H), 3.26 (m, 2H), 4.34 (s, 2H), 4.37 (q, 2H, J = 7.0 Hz), 7.20 (ddd, 1H, J = 1.3, 7.3, 7.5 Hz), 7.37 (dd, 1H, J = 1.3, 7.5 Hz), 7.47 (ddd, 1H, J = 1.5, 7.3, 8.3 Hz), 7.56 (dd, 1H, J = 1.3, 8.3 Hz).; ^{13}C nmr (D_2O): 13.45, 19.41, 21.55, 42.75, 54.35, 57.04, 62.52, 117.37, 119.44, 123.76, 129.68, 132.83, 136.05, 141.80, 166.27.

Anal. Calcd. for $C_{16}H_{25}N_3O_5S$: C, 51.74 H, 6.78 N, 11.31. Found: C, 51.53 H, 6.71 N, 11.25.

General Procedure for the Fischer Indolisation of Hydrazones **10a-d**.

The Fischer indolisation of raw hydrazones obtained from (2-aminophenyl)methanesulfonic acid (1 g, 5.3 mmol) was carried out either in formic acid (15 mL, **10a**, **b**) at reflux for 3 hours or in acetic acid-gaseous hydrogen chloride (12 mL, 1.5% HCl, **10c**, **d**) at 100° for 1 hour. After evaporation of solvents the solid residues were recrystallised from water to give **11**, **12**, **1c**, **1d**. Yields refer to the (2-aminophenyl)methanesulfonic acid.

3-(2-Carboxyethyl)-7-sulfomethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**11**).

This compound was obtained as white crystals, 1.40 g (67%), mp 248-252°; ir (KBr) : 3448, 1679, 1202; ^{1}H nmr (D_2O): 1.53 (t, 3H, J = 7.0 Hz), 2.69 (m, 2H), 3.31 (m, 2H), 4.47 (q, 2H, J = 7.0 Hz), 4.49 (s, 2H), 7.27 (dd, 1H, J = 7.2, 7.7 Hz), 7.41 (d, 1H, J = 7.0 Hz), 7.75 (d, 1H, J = 8.0 Hz); ^{13}C nmr (D_2O): 11.49, 19.38, 36.42, 51.08, 59.59, 113.34, 117.97, 118.43, 120.72, 122.29, 125.34, 125.89, 133.08, 161.37, 180.51.

Anal. Calcd. for $C_{15}H_{16}KNO_7S$: C, 45.79 H, 4.10 N, 3.56. Found: C, 45.57 H, 4.01 N, 3.50.

3-(3-Carboxypropyl)-7-sulfomethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**12**).

This compound was obtained as white crystals, 1.60 g (74%), mp 229-233°; ir (KBr): 3452, 1682, 1211; ^{1}H nmr (DMSO-d_6+$CDCl_3$): 1.36 (t, 3H, J = 7.0 Hz), 1.85 (m, 2H), 2.21 (m, 2H), 3.06 (m, 2H), 4.22 (s, 2H), 4.32 (q, 2H, J = 7.0 Hz), 6.99 (dd, 1H, J = 7.2, 7.8 Hz), 7.12 (d, 1H, J = 7.0 Hz), 7.53 (d, 1H, J = 8.0 Hz), 11.06 (s, 1H); ^{13}C nmr (DMSO-d_6+$CDCl_3$): 14.87, 24.23, 26.51, 34.03, 55.89, 60.61, 119.53, 120.12, 120.18, 123.57, 123.84, 127.75, 128.39, 136.56, 162.32, 175.01.

Anal. Calcd. for $C_{16}H_{18}KNO_7S$: C, 47.16 H, 4.45 N, 3.44. Found: C, 46.96 H, 4.51 N, 3.38.

3-(2-Chloroethyl)-7-sulfomethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**1c**).

This compound was obtained as beige crystals, 1.22 g (60%), mp 234-236°; ir (KBr) : 3448, 1684, 1220; ^{1}H nmr (DMSO-d_6): 1.32 (t, 3H, J = 7.0 Hz), 3.33 (m, 2H), 3.71 (m, 2H), 4.30 (s, 2H), 4.34 (q, 2H, J = 7.0 Hz), 7.03 (dd, 1H, J = 7.5, 8.2 Hz), 7.17 (d, 1H, J = 6.9 Hz), 7.56 (d, 1H, J = 8.2 Hz), 11.17 (s, 1H); ^{13}C nmr (DMSO-d_6): 12.73, 26.65, 42.89, 53.51, 58.80, 117.41, 117.54, 117.77, 118.50, 122.53, 125.86, 126.27, 134.31, 159.97.

Anal. Calcd. for $C_{14}H_{16}ClNO_5S$: C, 48.63 H, 4.66 N, 4.05. Found: C, 48.41 H, 4.58 N, 3.95.

3-[2-(Dimethylamino)ethyl]-7-sulfomethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**1d**).

This compound was obtained as white crystals, 1.33 g (71%), mp 282-285°; ir (KBr) : 3448, 1681, 1218; ^{1}H nmr (D_2O): 1.41 (t, 3H, J = 7.0 Hz), 2.92 (s, 6H), 3.42 (m, 2H), 3.48 (m, 2H), 4.43 (q, 2H, J = 7.0 Hz), 4.57 (s, 2H), 7.24 (dd, 1H, J = 7.6, 8.1 Hz), 7.39 (d, 1H, J = 7.9 Hz), 7.73 (d, 1H, J = 7.7 Hz); ^{13}C NMR (DMSO-d_6): 15.01, 20.38, 43.14, 55.27, 57.44, 61.62, 117.90, 119.62, 120.12, 121.15, 124.70, 127.94, 128.68, 136.45, 162.23.

Anal. Calcd. for $C_{16}H_{22}N_2O_5S$: C, 54.22 H, 6.26 N, 7.90. Found: C, 54.02 H, 6.19 N, 7.84.

General Procedure for the Esterification of Carboxylic Acids **1a**, **1b**.

To methanol (200 mL) cooled to -25 °C was added thionyl chloride (10 mL) at the same temperature over a period of 0.5 hour and kept for additional 0.5 hour at -25 °C. Indolylmethanesulfonic acid **11** or **12** (30 mmol) was added as a solid and the reaction mixture was allowed to reach room temperature and stirred for 24 hours. The clear solution was evaporated to dryness to give **1a** or **1b** quantitatively.

3-[2-(Methoxycarbonyl)ethyl]-7-sulfomethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**1a**).

This compound was obtained as white crystals, 10.20 g (92%), mp 188-192°; ir (KBr) : 1726, 1677, 1209; ^{1}H nmr (D_2O): 1.52 (t, 3H, J = 7.0 Hz), 2.75 (m, 2H), 3.37 (m, 2H), 3.68 (s, 3H), 4.50 (q, 2H, J = 7.0 Hz), 4.53 (s, 2H), 7.28 (dd, 1H, J = 7.4, 7.5 Hz), 7.44 (d, 1H, J = 7.2 Hz), 7.76 (d, 1H, J = 8.3 Hz); ^{13}C nmr (D_2O): 13.48, 19.96, 34.66, 52.02, 53.40, 61.65, 115.97, 120.03, 120.29, 122.49, 123.28, 127.41, 128.13, 135.36, 163.07, 175.82.

Anal Calcd. for $C_{16}H_{19}NO_7S$: C, 52.02; H, 5.18; N, 3.79. Found: C, 51.80; H, 5.21; N, 3.71.

3-[3-(Methoxycarbonyl)propyl]-7-sulfomethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**1b**).

This compound was obtained as white crystals, 10.80 g (94%), mp 152-154°; ir (KBr) : 1728, 1683, 1203; ^{1}H nmr (DMSO-d_6): 1.33 (t, 3H, J = 7.0 Hz), 1.86 (m, 2H), 2.32 (m, 2H), 3.06 (m, 2H), 3.57 (s, 3H), 4.20 (s, 2H), 4.33 (q, 2H, J = 7.0 Hz), 7.01 (dd, 1H, J = 7.3, 7.5 Hz), 7.14 (d, 1H, J = 7.1 Hz), 7.54 (d, 1H, J = 8.0 Hz), 11.20 (s, 1H); ^{13}C nmr (DMSO-d_6+$CDCl_3$): 14.91, 24.08, 26.47, 33.59, 51.86, 55.69, 60.79, 119.54, 120.33, 123.44, 123.77, 127.92, 128.29, 136.60, 162.32, 173.90.

Anal. Calcd. for $C_{17}H_{21}NO_7S$: C, 53.25; H, 5.52; N, 3.65. Found: C, 53.03; H, 5.41; 3.55.

General Procedure for the Reaction of Sulfonic Acids **1a-d** with Thionyl Chloride.

The sulfonate salt (**1a-c**, 1 mmol) was stirred in dichloromethane (25 mL) containing dimethylformamide (0.06 mL) and thionyl chloride (1 mL, 14 mmol) at room temperature until the suspension became almost a clear solution (ca. 4 hours). In case of **1d** chloroform was used at reflux temperature. The solutions were filtered and the filtrate was evaporated to dryness to give **3a-d** as crystalline solids in almost quantitative yields. The chloromethylindoles **3a-d** decomposed quickly when exposed to atmospheric moisture.

3-[2-(Methoxycarbonyl)ethyl]-7-chloromethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**3a**).

This compound was obtained as beige solid, 0.29 g (90%); ^{1}H nmr ($CDCl_3$): 1.44 (t, 3H, J = 7.0 Hz), 2.70 (m, 2H), 3.43 (m, 2H), 3.66 (s, 3H), 4.46 (q, 2H, J = 7.0 Hz), 4.90 (s, 2H), 7.11 (dd, 1H, J = 7.3, 7.7 Hz), 7.28 (d, 1H, J = 7.2 Hz), 7.73 (d, 1H, J = 8.0 Hz), 9.24 (s, 1H); ^{13}C nmr ($CDCl_3$): 14.46, 20.52, 35.17, 43.66, 51.68, 61.19, 120.29, 120.81, 121.90, 123.26, 124.20, 126.03, 128.55, 134.38, 162.12, 173.59.

3-[3-(Methoxycarbonyl)propyl]-7-chloromethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**3b**).

This compound was obtained as beige solid, 0.32 g (94%); ^{1}H nmr ($CDCl_3$): 1.48 (t, 3H, J = 7.0 Hz), 2.06 (m, 2H), 2.41 (m, 2H), 3.20 (m, 2H), 3.67 (s, 3H), 4.45 (q, 2H, J = 7.0 Hz), 4.91 (s, 2H), 7.13 (dd, 1H, J = 7.3, 7.9 Hz), 7.26 (d, 1H, J = 7.2 Hz), 7.72 (d, 1H, J = 8.1 Hz), 8.98 (s, 1H); ^{13}C nmr ($CDCl_3$): 14.50, 24.07, 25.97, 33.69, 43.70, 51.53, 61.05, 120.14, 120.70, 121.96, 124.08, 124.25, 125.92, 128.86, 134.42, 162.28, 174.05.

3-(2-Chloroethyl)-7-chloromethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**3c**).

This compound was obtained as white solid, 0.28 g (92%); ^{1}H nmr ($CDCl_3$): 1.48 (t, 3H, J = 7.0 Hz), 3.59 (m, 2H), 3.80 (m, 2H), 4.48 (q, 2H, J = 7.0 Hz), 4. 92 (s, 2H), 7.16 (dd, 1H, J = 7.2 Hz, 8.1 Hz), 7.29 (d, 1H, J = 7.2 Hz), 7.74 (d, 1H, J = 8.3 Hz), 9.18 (s, 1H); ^{13}C nmr ($CDCl_3$): 14.51, 28.56, 43.63, 44.34, 61.41, 120.64, 120.68, 120.88, 121.92, 124.69, 126.21, 128.86, 134.25, 161.90.

3-[2-(Dimethylamino)ethyl]-7-chloromethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**3d**).

This compound was obtained as white solid, 0.22 g (72%); ^{1}H nmr (DMSO-d_6): δ 1.41 (t, 3H, J = 7.0 Hz), 2.83 (s, 3H), 2.84 (s, 3H), 3.19 (m, 2H), 3.51 (m, 2H), 4.43 (q, 2H, J = 7.0 Hz), 5.22 (s, 2H), 7.15 (dd, 1H, J = 7.5, 7.4 Hz), 7.40 (d, 1H, J = 6.9 Hz), 7.88 (d, 1H, J = 8.2 Hz), 11.83 (s, 1H); ^{13}C nmr (DMSO-d_6): δ 14.30, 19.75, 41.81, 42.96, 56.26, 60.72, 117.73, 120.13, 121.11, 122.09, 124.59, 126.78, 127.59, 134.37, 161.35.

General Procedure for the Preparation of Methoxymethylindoles **4** and **5**.

The sulfonate salt **11** or **12** (1 mmol) was stirred in dichloromethane (20 mL) containing dimethylformamide (0.06 mL) and thionyl chloride (0.5 mL, 7 mmol) at room temperature until the suspension became almost a clear solution (ca. 4 hours). The solution was filtered and evaporated to dryness. The solid residue was dissolved in methanol (15 mL) and left standing at room temperature for 1 hour. Methanol was evaporated and the solid residue was recrystallised from hexane.

3-[2-(Methoxycarbonyl)ethyl]-7-methoxymethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**4)**.

This compound was obtained as white crystals, 0.29 g (91%), mp 90-92°; ir (KBr) : 3271, 1735, 1682, 1200; ^{1}H nmr ($CDCl_3$): 1.35 (t, 3H, J = 7.0 Hz), 2.61 (m, 2H), 3.32 (m, 2H), 3.45 (s, 3H), 3.57 (s, 3H), 4.35 (q, 2H, J = 7.0 Hz), 4.72 (s, 2H), 7.01 (dd, 1H, J = 7.5, 7.7 Hz), 7.05 (d, 1H, J = 6.8 Hz), 7.59 (d, 1H, J = 8.1 Hz), 9.15 (s, 1H); ^{13}C nmr ($CDCl_3$): 14.44, 20.47, 35.21, 51.54, 58.07, 60.92, 73.27, 119.93, 120.44, 121.77, 122.63, 123.65, 124.38, 128.02, 134.65, 162.09, 173.62.

Anal. Calcd. for $C_{17}H_{21}NO_5$: C, 63.94 H, 6.63 N, 4.39. Found: C, 63.70 H, 6.54 N, 4.35.

3-[3-(Methoxycarbonyl)propyl]-7-methoxymethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**5**).

This compound was obtained as beige crystals, 0.25 g, (76%), mp 80-82°; ir (KBr) : 3280, 1741, 1676, 1251; ^{1}H nmr ($CDCl_3$): 1.44 (t, 3H, J = 7.0 Hz), 2.04 (m, 2H), 2.38 (m, 2H), 3.18 (m, 2H), 3.42 (s, 3H), 3.66 (s, 3H), 4.43 (q, 2H, J = 7.0 Hz), 4.80 (s, 2H), 7.09 (dd, 1H, J = 8.2, 6.9 Hz), 7.15 (d, 1H, J = 6.9 Hz), 7.64 (d, 1H, J = 8.2 Hz), 9.17 (s, 1H); ^{13}C nmr ($CDCl_3$): 14.57, 24.13, 26.01, 33.89, 51.56, 58.17, 60.86, 73.36, 119.95, 120.68, 121.87, 123.73, 123.78, 124.41, 128.53, 134.85, 162.39, 174.19.

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85 H, 6.95 N, 4.20. Found: C, 64.60 H, 6.84 N, 4.18.

General Procedure for the Preparation of Dimethylaminomethylindoles **6** and **7**.

The solution of chloromethylindoles (**3c** or **3d**, 1 mmol) in dichloromethane (20 mL) was added dropwise to aqueous dimethylamine solution (2 mL, 35%) at 0° while stirring. After 10 minutes at 0° the organic phase was separated, washed with water (2x3 mL) and evaporated to dryness to give **6** or **7**.

3-(2-Chloroethyl)-7-dimethylaminomethyl-1*H*-indole-2-carboxylic Acid Ethyl Ester (**6**).

This compound was obtained as beige crystals (hexane), 0.26 g (85%), mp 63-64°; ir: (KBr),1732, 1700, 1228; ^{1}H nmr ($CDCl_3$): 1.46 (t, 3H, J = 7.0 Hz), 2.28 (s, 6H), 3.57 (m, 2H), 3.75 (s, 2H), 3.79 (m, 2H), 4.45 (q, 2H, J = 7.0 Hz), 7.12 (m, 2H), 7.62 (dd, 1H, J = 1.9, 7.4 Hz), 10.13 (s, 1H); ^{13}C nmr ($CDCl_3$): 14.24, 28.78, 44.27, 45.94, 60.96, 63.11, 119.43, 119.59, 120.27, 123.14, 123.83, 124.55, 128.00, 135.54, 162.19.

Anal. Calcd. for $C_{16}H_{21}ClN_2O_2$: C, 62.23 H, 6.85 N, 9.07. Found: C, 62.01 H, 6.94 N, 8.97.

3-[2-(Dimethylamino)ethyl]-7-dimethylaminomethyl-1*H*-indole-2-Carboxylic Acid Ethyl Ester (**7**).

This compound was obtained as a pale oil, 0.20 g (62%); ir (neat): 3396, 1698, 1225; ^{1}H nmr ($CDCl_3$): 1.36 (t, 3H, J = 7.0 Hz), 2.18 (s, 6H), 2.30 (s, 6H), 2.52 (m, 2H), 3.22 (m, 2H), 3.63 (s, 2H), 4.35 (q, 2H, J = 7.0 Hz), 6.98 (m, 2H), 7.52 (d, 1H, J = 7.5 Hz), 9.88 (s, 1H); ^{13}C nmr ($CDCl_3$): 14.54, 23.18, 45.31, 45.57, 60.35, 60.58, 62.92, 119.45, 119.82, 121.69, 122.96, 123.25, 124.31, 127.97, 135.62, 162.48.

Anal. Calcd. for $C_{18}H_{27}N_3O_2$: C, 68.11 H, 8.57 N, 13.24. Found: C, 67.86 H, 8.49 N,13.01.

Acknowledgment.

The authors would like to thank the National Fund for Science and Research (OTKA Project No. T038329) for financial support.

REFERENCES AND NOTES

[1] L. Li and A. Martins, *Tetrahedron Lett.*, **44**, 689 (2003).

[2a] C. G. Hartung, A. Fecher, B. Chapell and V. Snieckus, *Organic Lett.*, **5**, 1899 (2003); [b] T. Fukuda, R. Maeda and M. Iwao, *Tetrahedron*, **55**, 9151 (1999); [c] J. Kondo, S. Kojima and T. Sakamoto, *Heterocycles*, **43**, 2741 (1996); [d] T. M. Sielecki and A. I. Meyers, *J. Org. Chem*., **57**, 3673 (1992).

[3a] B. Pete and L. Tőke, *Tetrahedron Lett.*, **42**, 3373 (2001); [b] B. Pete and Gy. Parlagh, *Tetrahedron Lett.*, **44**, 2537 (2003); [c] B. Pete and Gy. Parlagh, *Tetrahedron*, **60**, 8829 (2004).

[4] H. J. Barber, R. F. Fuller, M. B. Green and H. T. Zwartouw, *J. Appl. Chem*., **3**, 266 (1953).

[5] J. M. Hinkley, A. R. Porcari, J. A. Walker II, E. E. Swayze and L. B. Townsend, *Synth. Commun*., **28**, 1703 (1998).

[6a] S. P. McManus, M. R. Smith, F. T. Herrmann and R. A. Abramovitch, *J. Org. Chem*. **43**, 647 (1978); [b] J. M. King and K. C. Khemani, *Can. J. Chem*., **63**, 619 (1985).

[7] M. Takahashi and S. Muta, *Synthesis*, 866 (1997).

[8] S. P. Kolis, M. T. Clayton, J. L. Grutsch and M. M. Faul, *Tetrahedron Lett.*, **44**, 5707 (2003).

[9] G. Lai and W. K. Anderson, *Tetrahedron*, **56**, 2583 (2000).

[10] R. A. Jones, *Inflammopharmacology*, **9**, 63 (2001).

[11] M. F. Grundon, *Nat. Prod. Rep*., **6**, 79 (1989).

[12a] M. C. Pirrung, K. Park and Z. Li, *Organic Lett.*, **3**, 365 (2001); [b] K. Liu, H. B. Wood and A. B. Jones, *Tetrahedron Lett.*, **40**, 5119 (1999).

[13] J. E. Tønder and D. Tanner, *Tetrahedron*, **59**, 6937 (2003).

[14] W. Marckwald and H. H. Frahne, *Chem. Ber*., **31**, 1854 (1898).

[15] G. P. Moloney, A. D. Robertson, G. R. Martin, S. MacLennan, N. Mathews, S. Dodsworth, P. Y. Sang, C. Knight and R. Glen, *J. Med. Chem*. **40**, 2347 (1997).

[16] L. Novák, M. Hanania, P. Kovács, J. Rohály, P. Kolonits and Cs. Szántay, *Heterocycles*, **45**, 2331 (1997).