Attempted Synthesis of a Tenidap Isomer and Formation of an Unexpected Stable Water Adduct

Klára Esses-Reiter and József Reiter*
EGIS Pharmaceuticals Ltd., H-1475 Budapest, P.O. Box 100, Hungary
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Dedicated to the memory of Professor Raymond N. Castle

An attempt to synthesize the Tenidap isomer **13** was performed starting from 2-ethoxy-5-chloroindole (**9**). The acylation and carbamoylation reactions of **9** led to the expected intermediate **12,** however the hydrolysis of **12** in acidic or alkaline media did not yielded the expected **13**. Instead an unusually stable water adduct **18** or the cleavage product **16** was formed. The formation of the unexpectedly stable water adduct **18** was caused by the steric and electronic effect of the thienoyl group in position 1 as proved by the hydrolysis of **10** and **16**.

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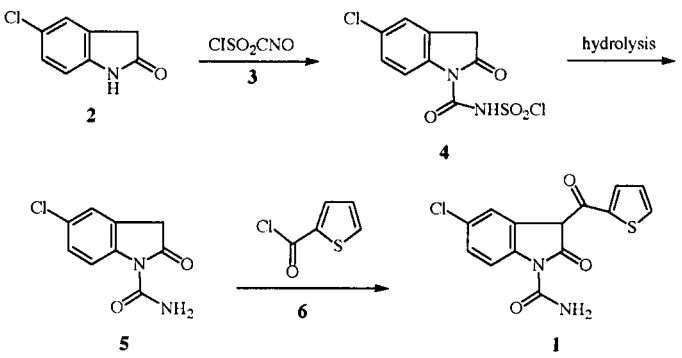
Tenidap (**1**) is a 5-lipoxygenase and cyclooxygenase inhibitor, developed by Pfizer Ltd. as an anti-inflammatory and anti-osteoarthritis agent [1,2]. Its synthesis was based on the selective reactivities of the NH-1 and CH_2-3 groups of 5-chlorooxindole (**2**) with chlorosulphonyl isocyanate (**3**) and thiophene-2-carbonyl chloride (**6**), respectively. Thus when **2** was reacted with chlorosulphonyl isocyanate (**3**), 5-chloro-1-chlorosulphonylcarbamoyloxindole (**4**) was formed that could be hydrolysed to 1-carbamoyl-5-chlorooxindole (**5**) which after acylation with thenoyl chloride (**6**) afforded **1** [3] (Scheme 1).

As a consequence of the selectivity of the above acylation agents both acylation steps could be interchanged. Thus the acylation of **2** with thenoyl chloride (**6**) led to 5-chloro-3-thienoyloxindole (**7**) that reacted with chlorosulphonyl isocyanate (**3**) to yield 5-chioro-1-chlorosulphonylcarbamoyl-3-thienoyloxindole (**8**) that after hydrolysis also afforded **1** [3] (Scheme 2).

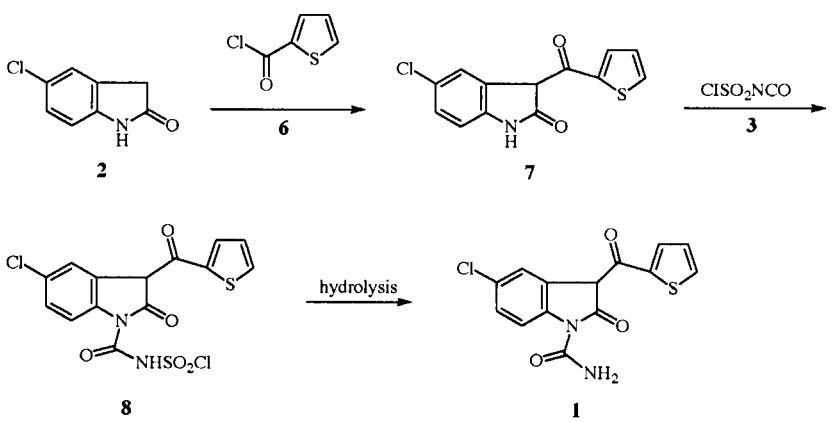
However, tenidap was rejected by the FDA [4] because it caused reduced bone mineral density and proteinuria in long term administration. In an effort to get rid of the above toxicological problems we tried to synthesise its isomer **13** (Scheme 3).

Scheme 1

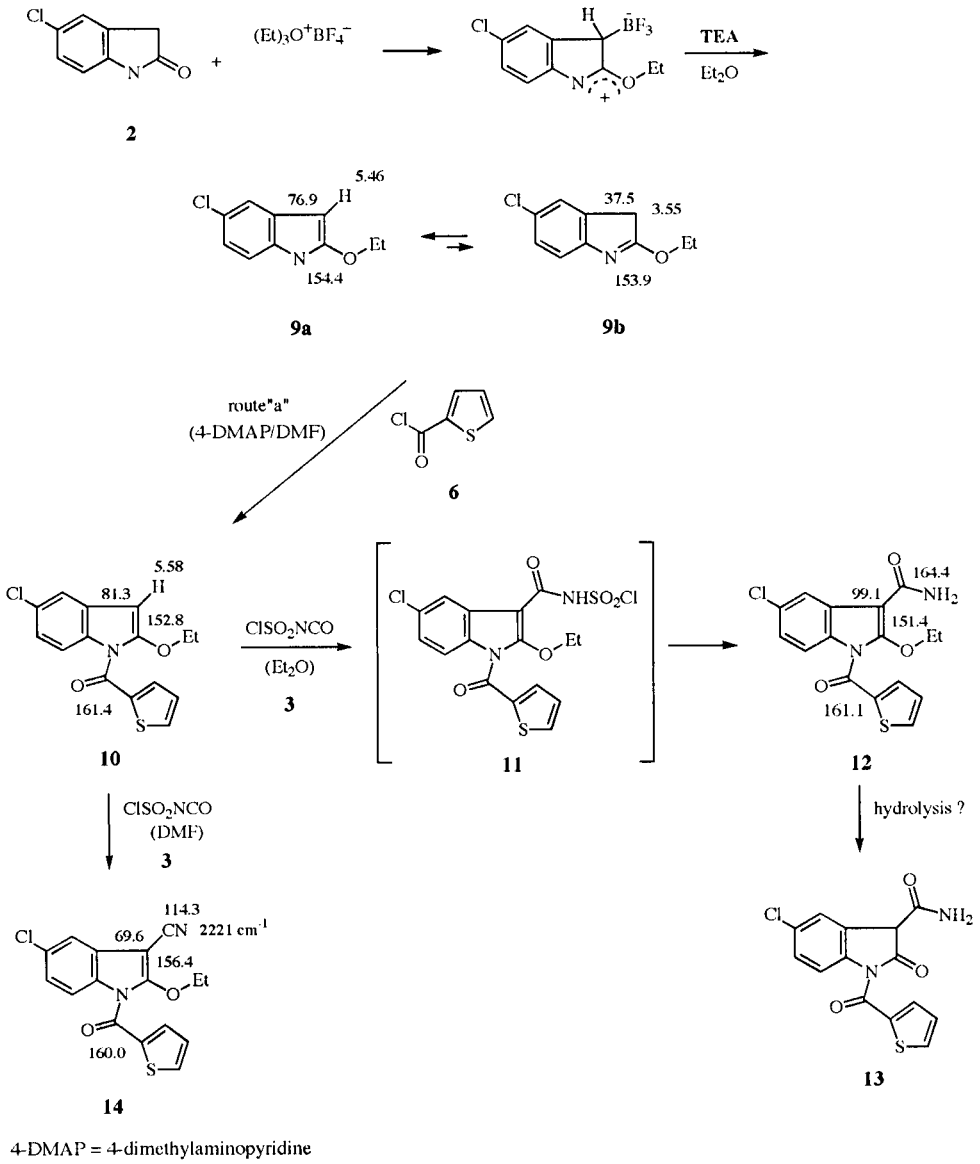


Taking into account the high selectivity of the NH-1 and CH_2-3 groups of 5-chlorooxindole (**2**) toward the acylating agents **3** and **6,** the planned synthesis was based on the conversion of 5-chlorooxindole (**2**) into 2-ethoxy-5-chloroindole (**9**) (Scheme 3) that was believed to have opposite reactivity toward acylating agents **3** and **6** (Scheme 3). The planned synthesis could be performed either through routes "a" or "b" (Schemes 3 and 4).

Scheme 2



Scheme 3



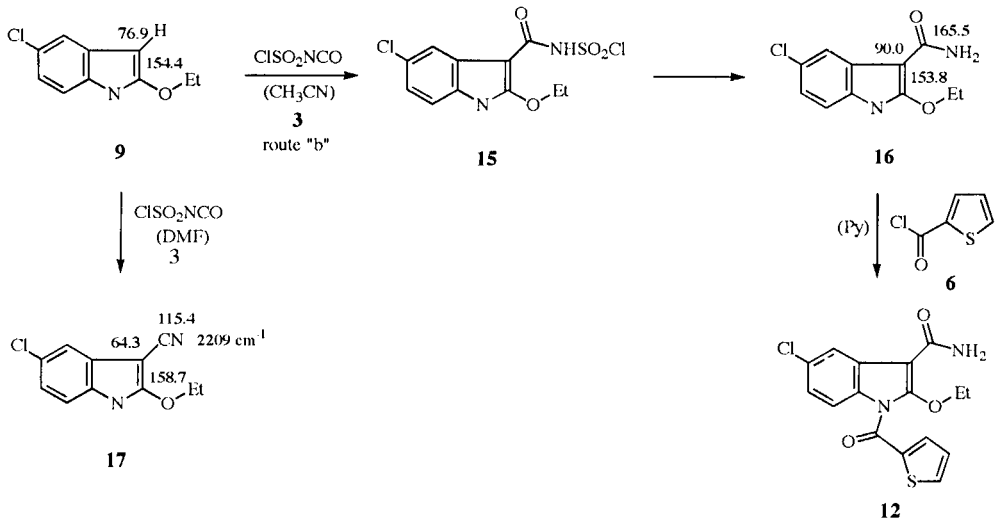
4-DMAP = 4-dimethylaminopyridine

The synthesis of 2-ethoxy-5-chloroindole (**9**) was perfomed by an analogous method of the synthesis of 2-ethoxyindole [5] starting from 5-chlorooxindole (**2**) through the corresponding trifluoroborate complex (Scheme 3). As proved by its pmr spectra compound **9** exists in deuteriochloroform solution as a 10 : 1 mixture of tautomers **9a** and **9b**.

The acylation of **9** with thiophene-2-carbonyl chloride provided in *N,N*-dimethylformamide in the presence of 4-(*N,N*-dimethylamino)pyridine base led to the expected 5-chloro-2-ethoxy-1-thienoylindole (**10**). Its structure is consistent with the practically unchanged chemical shift of proton 3 as compared with that in **9a** (5.46 and 5.52 ppm, respectively, Scheme 3) as well as having good agreement for the chemical shifts of carbons 2 and 3 of **9a** and **10**, respectively (154.4 and 76.9 versus 152.8 and 81.3 ppm, Scheme 3).

The reaction of **10** with chlorosulphonyl isocyanate carried out in ether as solvent at 5° led, through the not isolated **11**, to (5-chloro-2-ethoxy-1-thienoylindol-3-yl)carboxamide (**12**) (Scheme 3). Its structure is in agreement with the cmr spectra recorded (see the unchanged chemical shifts of the thienoyl carbonyl group and carbon atom 2 of **12** as compared with those of **10**, as well as the downfield shift of the carbon atom 3 of **12** caused by the carboxamide moiety). On the other hand, performing the above reaction in *N,N*-dimethylformamide at room temperature the (5-chloro-2-ethoxy-1-thenoylindol-3-yl)-

Scheme 4



nitrile (**14**) was isolated. Its structure is consistent with the nitrile band appearing at 2221 cm^{-1} in the ir spectra as well as with the unchanged chemical shift of the thienoyl carbonyl group as compared with those of **10** and **11**. However, as a consequence of the nitrile moiety in position 3, carbon atom 2 is shifted slightly downfield, while that of position 3 is upfield compared with those of **10**, respectively (Scheme 3).

Analogous with the selectivity of the NH-1 and CH_2-3 groups of 5-chlorooxindole (**2**) toward acylating agents **3** and **6** when **9** was acylated first with chlorosulphonyl isocyanate (**3**) in acetonitrile the 5-chloro-3-chlorosulphonyl-2-ethoxyindole (**15**) was formed. Compound **15** was hydrolysed without purification to (5-chloro-2-ethoxyindol-3-yl)acetamide (**16**). Its structure corroborates the practically unchanged chemical shift of carbon atom 2 and the downfield shift of carbon atom 3 as compared with those of **9**, respectively (Scheme 4).

However, when performing the above reaction in *N,N*-dimethylformamide, analogously to the reaction of **10** (Scheme 3) the corresponding (5-chloro-2-ethoxyindol-3-yl)nitrile (**17**) was formed as proved by the nitrile band appearing in the ir spectra at 2209 cm^{-1} and the chemical shifts of the carbon atoms 2 and 3 appearing analogously to those of **14** shifted downfield and upfield, respectively (Scheme 4).

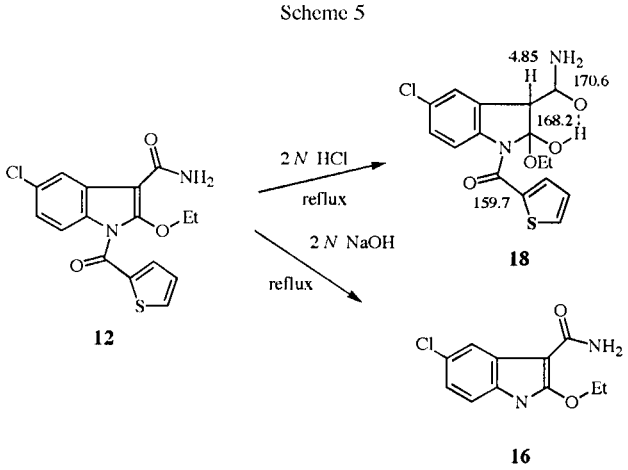
The acylation of **16** with thiophene-2-carbonyl chloride (**6**) provided in pyridine afforded (5-chloro-2-ethoxy-1-thenoylindol-3-yl)carboxamide **12**, identical with that obtained from **10** (Scheme 4).

Having in hand the key intermediate **12**, it seemed that the only thing left to do was to hydrolyse **12** to **13**. Surprisingly, using the usual acidic conditions, **12** did not hydrolyse and instead of **13** a very stable water adduct **18** was isolated (Scheme 5). The structure of **18** is consistent with the direct coupling between the H-3 proton and the corresponding carbon atom 3 observed in the Heteronuclear Single Quantum Correlation {^1H-^{13}C} experiment. The above fact proves also that during the addition of water the nucleophilic attack of the OH group occurred at carbon atom 2 of **12**.

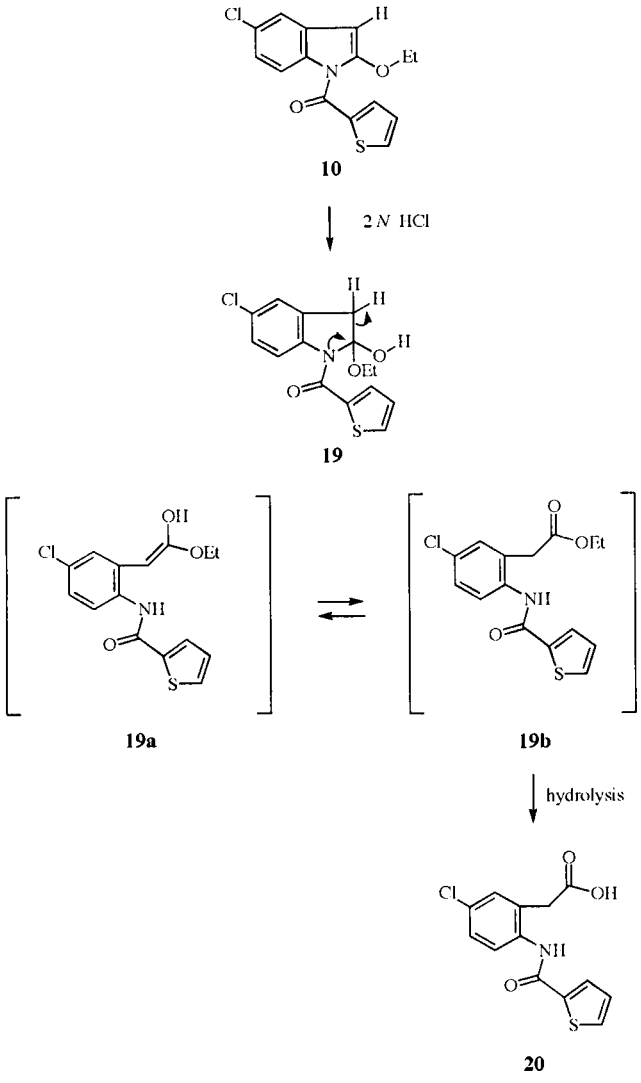
On the other hand, compound **18** stabilised by a strong intramolecular hydrogen-bond (as proved by the chemical shift of the OH proton appearing at 11.15 ppm) should exist as a mixture of *Z* and *E* diastereomers. This is in agreement with the unusually rich multiplet of the OCH_2 protons of the ethoxy group. The 1:1 ratio of the *Z* and *E* diastereomers could be deduced from the 1:1 ratio of integrals for the two well separated NH_2 groups in the pmr spectrum appearing at 7.72 and 8.07 ppm, respectively.

As a consequence of the strong intramolecular chelate hydrogen-bond **18** is stable to further hydrolysis in acidic conditions.

Scheme 5



Scheme 6



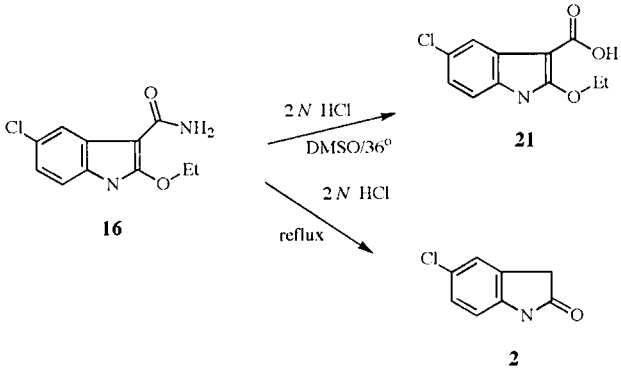
Not succeeding with the acid hydrolysis of **12** the hydrolysis was repeated in basic conditions. However, in this reaction the 2-thienoyl group was cleaved off and only **16** was isolated from the reaction mixture (Scheme 5).

From the unexpected addition of a molecule of water to **12** the question arose as to whether the unusual stability was caused by the activation of the thienoyl group or by the 3-carboxamide moiety (or both). To solve the above problem the hydrolysis of derivatives **10** and **16** was also studied (Schemes 6 and 7).

Providing the hydrolysis of **10** in refluxing 2*N* hydrochloric acid besides the addition of water to yield derivative **19** a ring opened acetic acid derivative **20** was also formed (Scheme 6). The formation of **20** from **19** could be easily explained by the ring opening of **19** to form **19a** that is in tautomeric equilibria with the ester **19b**, that after hydrolysis yields **20**. This reaction could proceed smoothly as **19** is not stabilised by an intramolecular chelate ring.

On the other hand the hydrolysis of **16** with 2*N* hydrochloric acid in dimethylsulfoxide provided at 36° led to the acid **21**, while its simple refluxing in 2*N* hydrochloric acid yielded 5-chlorooxindole (**2**) (Scheme 7).

Scheme 7



The above reactions indicate that the unusual stability of water addition to **10** and **12** is caused preferably by steric and electronic factors of the thienoyl group.

EXPERIMENTAL

Melting points were determined on a Koffler-Boëtius micro apparatus and are not corrected. The infrared spectra were obtained as potassium bromide pellets using a Perkin-Elmer 577 spectrophotometer. The pmr and cmr measurements were performed using Varian Gemini-2000 (200 MHz) and Varian Inova-400 (400 MHz) instruments. To confirm the assignment in some cases standard Varian HSQC and HMQC 2D-nmr programs were used. Mass spectra were taken with a KRATOS MS 25 RFA double focusing instrument in EI and CI mode. The dry-column flash chromatographies were performed according to [6]. As adsorbents aluminium oxide G (Merck 1090 for thin layer chromatography) and Kieselgel 60H (Merck 7736 for thin layer chromatography) were used.

5-Chloro-2-ethoxyindole (**9**).

To a mixture of 18 g (0.09 mole) of triethyloxonium tetrafluoroborate [7] in 100 ml of chloroform 13.4 g (0.08 mole) of 5-chlorooxindole (Aldrich) was added in small portions with stirring below 24°. The mixture was stirred at 32° for 15 minutes during which the 5-chlorooxindole was dissolved. The solution was allowed to cool, with stirring, to room temperature. After two hours of stirring the crystals that precipitated were filtered off and washed thoroughly with ethyl acetate to yield 12.8 g (54%) of 5-chloro-2-ethoxyindole 3-trifluoroborate complex, mp 148-152°. This was suspended with stirring in 200 ml of ether, to the suspension 10 ml of triethylamine and 20 ml of water was added, the phases were separated, the ether layer was washed with 100 ml of 25% sodium chloride solution, treated with charcoal, dried and filtered. After passing the ether layer through a short silica gel

column and evaporation of the appropriate fractions 9.2 g (98%, overall yield 53%) of 5-chloro-2-ethoxyindole (**9**) was obtained, mp 122-124°; ir: ν NH = 3364 cm^{-1}, ν ArC=C = 1578 cm^{-1}; pmr (deuteriochloroform): δ, ppm tautomeric form **9a**: 1.43 [t (J = 7.8 Hz), 3H, CH_3], 4.14 [q (J = 7.8 Hz), 2H, CH_2], 5.46 [d (J = 2.1 Hz), 1H, H-3], 6.97 [dd (J = 8.5 and 2.0 Hz), 1H, H-6], 7.03 [d (J = 8.5 Hz), 1H, H-7], 7.34 [d (J = 2.1 Hz), 1H, H-4], 7.63 (bs, 1H, NH); tautomeric form **9b**: 1.42 (t 0.3H, CH_3], 4.44 (q, 0.2H, CH_2], 3.55 (s, 0.2H, CH_2-3); ratio of **9a** and **9b** approximately 10:1 deduced from the ratios of integrals of the CH_2 quartets and the CH_2-3 and CH-3 singlets, respectively; cmr (deuteriochloroform): δ, ppm tautomeric form **9a**: 14.6 (CH_3), 66.3 (OCH_2), 76.9 (C-3), 110.6 (C-4), 118.1 (C-7), 119.7 (C-6), 125.4 (C-8a), 129.2 (C-3a), 129.8 (C-5), 154.4 (C-2); tautomeric form **9b**: 14.3 (CH_3), 37.5 (CH_2-3), 65.5 (OCH_2), 110.6 (C-4), 118.8 (C-6 and 7), 123.6 (C-3a), 127.8 (C-8a), 133.3 (C-5), 153.9 (C-2);

Anal. Calcd. for $C_{10}H_{10}ClNO$ (MW 195.65): C, 61.39; H, 5.15; N, 7.16; Cl, 18.12. Found: C, 61.33; H, 5.21; N, 7.06; Cl, 18.09.

5-Chloro-2-ethoxy-1-thienoylindole (**10**).

To a solution of 4.89 g (0.025 mole) of 5-chloro-2-ethoxyindole (**9**) in 50 ml of dimethylformamide 6.0 g (0.048 mole) of 98% 4-dimethylaminopyridine (Fluka) was added at room temperature. The solution obtained was cooled to 6° and at this temperature 3.5 ml (4.8 g, 0.032 mole) of 97% thiophene-2-carbonyl chloride (**6**) (Fluka) was added dropwise with stirring over a period of 90 minutes. During addition a yellow material crystallised from the reaction mixture. The mixture was allowed to warm to the room temperature and was poured into a mixture of 250 ml of ice and 19 ml of concentrated hydrochloric acid. The oil that separated crystallised upon stirring the reaction mixture for one hour. The crystals were filtered off and washed thoroughly with water to yield 8.0 g of crude product. The crystals were dissolved in 200 ml of ether, and the solution was extracted with 100 ml of 25% sodium chloride solution, filtered, and evaporated *in vacuo* at ambient temperature to a small volume. The residue crystallised after addition of a small amount of methanol and cooling. The crystals were separated and washed with methanol to yield 5.6 g (73%) of 5-chloro-2-ethoxy-1-thienoylindole (**10**), mp 78-79°; ir: ν C=O = 1656 cm^{-1}, ArC=C = 1582 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.22 [t (J = 7.0 Hz), 3H, CH_3], 4.08 [q (J = 7.0 Hz), 2H, CH_2], 5.58 (s, 1H, H-3), 7.07 [dd (J = 8.7 and 2.0 Hz), 1H, H-6], 7.10 [dd (J = 5.0 and 3.8 Hz), 1H, H-4'], 7.32 [d (J = 2.0 Hz), 1H, H-4], 7.57 [dd (J = 3.8 and 1.2 Hz), 1H, H-5'], 7.66 [d (J = 8.7 Hz), 1H, H-7], 7.68 [dd (J = 5.0 and 1.1 Hz), 1H, H-3']; cmr (deuteriochloroform): δ, ppm 14.0 (CH_3), 67.1 (CH_2), 81.3 (C-3), 114.6 (C-4), 118.5 (C-7), 121.8 (C-6), 127.2 (C-4'), 128.5 (C-7a), 130.0 (C-3a), 130.8 (C-5), 133.7 and 134.7 (C-3' and 5'), 137.8 (C-2'), 152.8 (C-2), 161.4 (C=O); ms (CI): $(M+1)^+$ = 306.

Anal. Calcd. for $C_{15}H_{12}ClNO_2S$ (MW 305.79): C, 58.92; H, 3.96; N, 4.58; S, 10.49; Cl, 11.59. Found: C, 59.06; H, 4.11; N, 4.52; S, 10.33; Cl, 11.66.

(5-Chloro-2-ethoxy-1-thienoylindol-3-yl)carboxamide (**12**).

To a solution of 0.886 g (0.0029 mole) of 5-chloro-2-ethoxy-1-thenoylindole (**10**) in 20 ml of ether 0.36 ml (0.58 g, 0.0041 mole) of chlorosulphonyl isocyanate (**3**) (Fluka) was added at 5° dropwise while stirring the reaction mixture over a period of 15 minutes. The stirring was continued at 5° for 1 hour then 8 ml of water was added to the reaction mixture and stirred for a further hour. The crystals that precipitated were filtered off and washed thoroughly with water, ether and ethyl acetate, respectively, to yield 0.80 g (79%) of (5-chloro-2-ethoxy-1-thienoylindol-3-yl)carboxamide (**12**), mp 174-175°; ir: ν NH_2 = 3467 and 3277 cm^{-1}, ν C=O (thenoyl) 1669 cm^{-1}, ν C=O (carboxamide) 1609 cm^{-1}, ν ArC=C = 1573 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.03 [t (J = 7.0 Hz), 3H, CH_3], 4.14 [q (J = 7.0 Hz), 2H, CH_2], 7.15 (bs, 2H, NH_2), 7.25 [dd (J = 8.8 and 2.1 Hz), 1H, H-6], 7.30 [dd (J = 5.0 and 3.8 Hz), 1H, H-4'], 7.53 [d (J = 8.8 Hz), 1H, H-7], 7.83 [dd (J = 3.8 and 1.1 Hz), 1H, H-5'], 8.07 [d (J = 2.1 Hz), 1H, H-4], 8.24 [dd (J = 5.0 and 1.1 Hz), 1H, H-3']; cmr (DMSO-d_6): δ, ppm 14.6 (CH_3), 73.3 (CH_2), 99.1 (C-3), 114.7 (C-4), 120.4 (C-7), 123.7 (C-6), 127.5 (C-4'), 128.1 (C-7a), 129.0 (C-3a), 129.9. (C-5), 136.0 (C-5'), 137.6 and 137.7 (C-2' and 3'), 151.4 (C-2), 161.1 (C=O thenoyl), 164.4 (C=O carboxamide); ms (CI): $(M+1)^+$ = 349.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_3S$ (MW 348.81): C, 55.10; H, 3.76; N, 8.03; S, 9.19; Cl, 10.16. Found: C, 55.20; H, 3.88; N, 7.99; S, 9.12; Cl, 10.23.

(5-Chloro-2-ethoxy-1-thienoylindol-3-yl)carboxamide (**12**) from **16**.

To a solution of 0.238 g (0.001 mole) of (5-chloro-2-ethoxyindol-3-yl)carboxamide (**16**) in 5 ml of pyridine 0.132 ml (0.181 g, 0.0012 mole) of 97% thiophene-2-carbonyl chloride (**6**) (Fluka) was added dropwise with cooling and stirring below 5°. The reaction mixture was alowed to warm with stirring to room temperature and then decomposed with 20 ml of water. The product that crystallised was filtered off and washed thoroughly with ether to yield 0.29 g (83%) of crude (5-chloro-2-ethoxy-1-thienoylindol-3-yl)carboxamide (**12**), mp 168-170°. This was dissolved in 2 ml of dimethylformamide, to the solution obtained 0.2 ml of water was added and allowed to crystallise. The crystals that precipitated were filtered off and washed with water and ether to yield 0.23 g (66%) of pure **12**, mp 174-175°. The product is identical (mixed mp, ir) with that of obtained above.

(5-Chloro-2-ethoxy-1-thienoylindol-3-yl)carbonitrile (**14**).

To a solution of 0.85 g (0.00278 mole) of 5-chloro-2-ethoxy-1-thienolylindole (**10**) in 4.5 ml of dimethylformamide 0.36 ml (0.58 g, 0.0041 mole) of chlorosulphonyl isocyanate (**3**) (Fluka) was added dropwise with stirring at room temperature over a period of 5 minutes. The reaction mixture was stirred at room temperature for 2 hours, then decomposed by addition of a mixture of 1 ml acetic acid and 9 ml of water and stirred for a further hour. The crystals that precipitated were filtered off and washed thoroughly with ether to yield 0.61 g (66%) of (5-chloro-2-ethoxy-1-thienoylindol-3-yl)carbonitrile (**14**), mp 160-162°. An analytical sample was recrystallised from ethyl acetate, mp 162-163°; ir: ν CN = 2221 cm^{-1}, ν C=O = 1690 cm^{-1}, ν ArC=C = 1580 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.31 [t (J = 7.2 Hz), 3H, CH_3), 4.70 [q (J = 7.2 Hz), 2H, CH_2], 7.19 [dd (J = 4.8 and 4.0 Hz), 1H, H-4'], 7.21 [dd (J = 8.8 and 2.2 Hz), 1H, H-6], 7.46 [d (J = 8.8 Hz), 1H, H-7], 7.54 [d (J = 2.2 Hz), 1H, C-4], 7.62 [dd (J = 4.0 and 1.1 Hz), 1H, H-5'], 7.82 [dd (J = 4.8 and 1.1 Hz), 1H, H-3']; pmr (deuteriochloroform): δ, ppm 14.5 (CH_3), 69.6 (C-3), 70.2 (CH_2), 114.3 (CN), 114.4 (C-4), 118.1 (C-7), 124.4 (C-6), 127.5 (C-4'), 128.0 (C-7a), 129.0 (C-3a), 130.0 (C-5), 135.9 (two peaks, C-3' and 5'), 136.7 (C-2'), 156.4 (C-2), 160.0 (C=O); ms (CI): $(M+1)^+$ = 331.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2S$ (MW 330.80): C, 58.10; H, 3.35; N, 8.47; S, 9.69; Cl, 10.72. Found: C, 58.16; H, 3.45; N, 8.55; S, 9.65; Cl, 10.82.

(5-Chloro-2-ethoxyindol-3-yl)carboxamide (**16**).

To a solution of 1.56 g (0.008 mole) of 5-chloro-2-ethoxyindole (**9**) in 30 ml of acetonitrile 0.87 ml (1.41 g, 0.01 mole) of chlorosulphonyl isocyanate (**3**) (Fluka) was added at room temperature dropwise while stirring the reaction mixture. After stirring at room temperature for 1 hour 230 ml of ether was added to the reaction mixture, the crystals that precipitated were filtered off and washed with acetonitrile and ether to yield 2.36 g (87%) of raw 5-chloro-2-ethoxy-3-chlorosulphonylaminocarbonylindole (**15**), mp 147-150°. To this material 20 ml of acetic acid was added and heated with stirring at 60° for 5 minutes. After cooling the crystals that precipitated were filtered off and washed with water and acetonitrile to yield 1.5 g (78%) of (5-chloro-2-ethoxyindol-3-yl)carboxamide (**16**), mp 248-250°; ir: ν NH_2 =3508 and 3393 cm^{-1}, ν C=O = 1620 cm^{-1}, ν ArC=C = 1593 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.44 [t (J = 7.2 Hz), 3H, CH_3], 4.45 [q (J = 7.2 Hz), 2H, CH_2], 6.45 [bs, 1H, NH-"out"), 6.95 (bs, 1H, NH-"in"), 7.02 [dd (J = 8.5 and 2.2 Hz), 1H, H-6], 7.25 [d (J = 8.5 Hz), 1H, H-7], 8.01 [d (J = 2.2 Hz), 1H, H-4], 11.9 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm 14.8 (CH_3), 68.0 (CH_2), 90.0 (C-3), 112.2 (C-4), 119.1 (C-7), 120.1 (C-6), 125.5 (C-9a), 128.3 (C-3a), 129.1 (C-5), 153.8 (C-2), 165.5 (C=O).

Anal. Calcd. for $C_{11}H_{11}ClN_2O_2$ (MW 238.68): C, 55.36; H, 4.65; N, 11.74; Cl, 14.85. Found: C, 55.39; H, 4.85; N, 11.68; Cl, 14.90.

(5-Chloro-2-ethoxyindol-3-yl)carboxamide (**16**) by Alkaline Hydrolysis of **12**.

A mixture of 0.3 g (0.00086 mole) of (5-chloro-2-ethoxy-1-thienoylindol-3-yl)carboxamide (**12**) and 15 ml of 2*N* sodium hydroxide solution was refluxed with stirring for 4 hours. The yellow solution obtained was allowed to cool, filtered and made acidic (p*H* = 5) with acetic acid. The crystals that precipitated were filtered off and washed thoroughly with water to yield, after drying, 0.19 g (92%) of (5-chloro-2-ethoxyindol-3-yl)carboxamide (**16**), mp 248-250° (dec) that was identical (mixed mp, ir) with that of **16** obtained above.

(5-Chloro-2-ethoxyindol-3-yl)carbonitrile (**17**).

To a solution of 0.98 g (0.005 mole) of 5-chloro-2-ethoxyindole (**9**) in 5 ml of dimethylformamide 0.52 ml (0.85 g, 0.006 mole) of chlorosulphonyl isocyanate (**3**) (Fluka) was added dropwise with stirring at room temperature within 5 minutes. The stirring was continued for a further hour, then the reaction mixture was decomposed with a mixture of 0.7 ml of concentrated hydrochloric acid and 15 ml of water and stirred at room temperature for a further hour. The crystals that precipitated were filtered off and washed thoroughly with water and a slight amount of acetonitrile to yield 0.65 g (59%) of (5-chloro-2-ethoxyindol-3-yl)carbonitrile (**17**), mp 250-253°; ir: ν CN = 2209 cm^{-1}, ν ArC=C = 1572 cm^{-1}; pmr (DMSO-d_6): δ, ppm 1.46 [t (J = 7.0 Hz), 3H, CH_3], 4.56 [q (J = 7.0 Hz), 2H, CH_2], 7.14 [dd (J = 8.5 and 2.0 Hz), 1H, H-6], 7.31 [d (J = 8.5 Hz), 1H, H-7], 7.37 [d (J = 2.0 Hz), 1H, H-4], 12.2 (bs, 1H, NH); cmr (DMSO-d_6): δ, ppm 14.6 (CH_3), 64.5 (C-3), 68.1 (CH_2), 113.0 (C-4), 115.4 (CN), 116.1 (C-7), 121.6 (C-6), 126.1 (C-7a), 127.7 (C-3a), 128.7 (C-5), 158.7 (C-2).

Anal. Calcd. for $C_{11}H_9ClN_2O$ (MW 220.66): C, 59.88; H, 4.11; N, 12.70; Cl, 16.07. Found: C, 60.01; H, 4.35; N, 12.67; Cl, 15.91.

(5-Chloro-2-ethoxy-2-hydroxy-1-thienoylindolin-3-yl)carboxamide (**18**).

A mixture of 0.5 g (0.0014 mole) of (5-chloro-2-ethoxy-1-thienoylindol-3-yl)carboxamide (**12**) and 20 ml of 2*N* hydrochloric acid was refluxed with stirring for 2 1/2 hours. After cooling the crystals that precipitated were filtered off and washed thoroughly with water and methanol to yield 0.3 g (57%) of (5-chloro-2-ethoxy-2-hydroxy-1-thenoylindolin-3-yl)carboxamide (**18**), melting at 183-185°. An analytical sample was recrystallised form 2-propanol to yield **18** melting at 185-186°; ir: : ν NH_2 = 3471 cm^{-1}, ν OH = 3351 cm^{-1}, ν CO (carboxamide) 1722 cm^{-1}, ν CO (thienoyl) = 1680 cm^{-1}; pmr (DMSO-d_6): , ppm 0.99 [t (J = 7.1 Hz), 3H, CH_3], 3.98 (m, 2H, OCH_2), 4.85 (s, 1H, H-3), 7.23 [dd (J = 5.0 and 3.8 Hz), 1H, H-4'], 7.44 (m, 2H, H-4 and H-6], 7.69 (bs, 1H, NH_2-*Z*), 7.78 [d (J = 8.3 Hz), 1H, H-7], 7.79 [dd (J = 3.8 and 1.1 Hz), 1H, H-3'], 7.87 [dd (J = 5.0 and 1.1 Hz), 1H, H-5'], 8.07 (bs, 1H, NH_2-*E*], 11.15 (bs, 1H, OH); cmr (DMSO-d_6): δ, ppm 13.8 (CH_3), 55.5 (C-3), 61.4 (OCH_2), 127.0 (C-7), 128.3 (C-6 and C-4'), 128.7 (C-5), 128.9 (C-3'), 130.2 (C-7a), 130.9 (C-4), 132.2 (C-5'), 136.0 (C-3a), 139.6 (C-2'), 159.7 (C=O thienoyl), 168.3 (C-2), 170.6 (C=O carboxamide). Assignment confirmed by HSQC and HMQC; ms (EI): $(M+1)^+$ = 367

Anal. Calcd. for $C_{16}H_{15}ClN_2O_4S$ (MW 366.83): C, 52.39; H, 4.12; N, 7.64; S, 8.74; Cl, 9.66. Found: C, 52.51; H, 4.26; N, 7.58; S, 8.64; Cl, 9.75.

5-Chloro-2-ethoxy-2-hydroxy-1-thenoylindoline (**19**) and 3-Chloro-6-thienoylaminophenylacetic Acid (**20**).

A mixture of 3.05 g (0.01 mole) of 5-chloro-2-ethoxy-1-thienoylindole (**10**) and 100 ml of 2*N* hydrochloric acid was refluxed for 1 hour and then stirred at room temperature for further 7 hours. During this time the oily product that separated partly crystallised. The solvent was decanted from the partly crystalline brown material and the residue was dissolved in 5 ml of dimethylformamide. After addition of water to the solution obtained it crystallised upon standing. The crystals were filtered off to yield 1.95 g of a product mixture melting at 145-147°. The mother liquor crystallised again upon standing at room temperature to yield after filtering a second crop (0.45 g, mp 100-110° sinters, 153-155° melts) of the above material. The two raw crystals were combined and recrystallised twice from acetonitrile to yield 0.6 g (20%) of 3-chloro-6-thienoylaminophenylacetic acid (**20**), mp 157-158°; ir: ν CO (acid) 1713 cm^{-1}, ν CO (thenoyl) = 1643 cm^{-1}; pmr (DMSO-d_6): δ, ppm 3.68 (s, 2H, CH_2), 7.20 [dd (J = 5.0 and 3.8 Hz), 1H, H-4'], 7.37 [dd (J = 8.6 and 2.6 Hz), 1H, H-4], 7.43 [d (J = 2.6 Hz), 1H, H-2], 7.44 [d (J = 8.6 Hz), 1H, H-5], 7.85 [dd (J = 5.0 and 1.0 Hz), 1H, H-5'], 7.92 [dd (J = 3.8 and 1.0 Hz), 1H, H-3'], 10.0 (s, 1H, NH), 12.4 (b, 1H, OH); cmr (DMSO-d_6): δ, ppm 37.2 (CH_2), 127.2 (C-4), 128.18 (C-4'), 128.22 (C-5), 129.6 (d, C-3'), 130.9 (C-2), 131.9 (C-6 and C-5'), 133.3 (C-3), 135.4 (C-2'), 139.4 (C-1), 160.1 (C=O), 172.2 (COOH). Assignment confirmed by HSQC; ms (EI) : M^+ = 295.

Anal. Calcd. for $C_{13}H_{10}ClNO_3S$ (MW 295.75): C, 52.80; H, 3.41; N, 4.74; S, 10.84; Cl, 11.99. Found: C, 52.88; H, 3.45; N, 4.71; S, 10.78; Cl, 11.86.

The combined mother liquors were evaporated *in vacuo* to dryness and the residue was chromatographed on a silica gel column (eluent: different mixtures of toluene and chloroform of continuously increasing polarity) to yield after evaporation of the appropriate fractions *in vacuo* 0.3 g (9.3%) of 5-chloro-2-ethoxy-2-hydroxy-1-thienoylindoline (**19**) that after recrystallisation from 2-propanol melted at 97-98°; ir: ν OH = 3315 cm^{-1}, ν CO = 1699 and 1665 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.31 [t (J = 7.1 Hz), 3H, CH_3], 3.64 (s, 2H, H-3), 4.22 [q (J = 7.1 Hz), 2H, OCH_2], 7.13 [dd (J = 5.0 and 3.8 Hz), 1H, H-4'], 7.23 [d (J = 2.4 Hz), 1H, H=4], 7.31 [dd (J = 8.7 and 2.4 Hz), 1H, H-6], 7.55 [dd (J = 5.0 and 1.1 Hz), 1H, H-5'], 7.77 [dd (J = 3.8 and 1.1 Hz), 1H, H-3'], 7.97 [d (J = 8.7 Hz), 1H, H-7], 9.72 (s, 1H, OH); cmr (deuteriochloroform): δ, ppm 14.0 (CH_3), 39.0 (CH_2-3), 62.0 (OCH_2), 125.8 (C-7), 127.0 (C-3a), 127.9 (C-4'), 128.5 (C-6), 128.6 (C-3'), 130.1 (C-5), 130.6 (C-4), 131.1 (C-5'), 135.4 (C-7a), 139.5 (C-2'), 160.2 (C=O), 172.7 (C-2). Assignment confirmed by HMQC and HSQC; ms (EI) : M^+ = 323.

Anal. Calcd. for $C_{15}H_{14}ClNO_3S$ (MW 323.80): C, 55.64; H, 4.36; N, 4.33; S, 9.90; Cl, 10.95. Found: C, 55.58; H, 4.37; N, 4.30; S, 9.87; Cl, 10.86.

Continuing the chromatography a further 1.3 g (44%) of 3-chloro-6-thienoylaminophenylacetic acid (**20**) was obtained increasing its yield to 64 %.

(5-Chloro-2-ethoxyindol-3-yl)carbonic acid (**21**) by Acidic Hydrolysis of **16** at 36° in Dimethyl Sulfoxide Solution.

To a solution of 0.48 g (0.002 mole) of (5-chloro-2-ethoxyindol-3-yl carboxamide (**16**) in 6 ml of dimethylformamide 15 ml of 2*N* hydrochloric acid was added at room temperature and the reaction mixture was stirred at room temperature for 3 hours. The crystals that precipitated were filtered off and washed thoroughly with water to yield 0.3 g (63%) of crude (5-chloro-2-ethoxyindol-3-yl)carbonic acid (**21**), mp 140-142°. This was chromatographed on a short silica-gel column (eluent dichloromethane) to yield after evaporation of the appropriate fractions *in vacuo* 0.21 g (44 %) of pure **21**, mp 153-155°. ir: ν C=O = 1757 and 1732 cm^{-1}; pmr (deuteriochloroform): δ, ppm 1.25 [t (J = 7.1 Hz), 3H, CH_3], 4.28 (m, 2H, OCH_2), 6.95 [d (J = 8.4 Hz), 1H, H-7], 7.32 [dd (J = 8.4 and 2.1 Hz), 1H, H-6], 7.40 [d (J = 2.1 Hz), 1H, C-4], 9.2 (bs, 1H, NH); cmr (deuteriochloroform): δ, ppm 13.9 (CH_3), 64.1 (OCH_2), 77.0 (C-3), 112.3 (C-4), 125.5 (C-7), 128.5 (C-6), 129.5 (C-5), 131.1 (C-7a), 139.4 (C-3a), 154.9 (C-2), 164.4 (C=O).

Anal. Calcd. for $C_{11}H_{10}ClNO_3$ (MW 239.66): C, 55.13; H, 4.21; N, 5.84; Cl, 14.79. Found: C, 55.23; H, 4.35; N, 5.80; Cl, 14.66.

5-Chorooxindole (**2**) by Acidic Hydrolysis of **16** at Reflux Temperature.

A suspension of 0.42 g (0.002 mole) of (5-chloro-2-ethoxyindol-3-yl carboxamide (**16**) in 30 ml of 2*N* hydrochloric acid was refluxed for 3 hours. After cooling the crystals that precipitated were filtered off and washed thoroughly with water and ether to yield 0.19 g (57%) of 5-chorooxindole (**2**), mp 195-196° that was identical (mixed mp, ir) with an authentic sample.

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