Thieno[2,3-*b*]indole. The Unsubstituted Ring System

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Methyl thieno[2,3-*b*]indolecarboxylate (**2**) was prepared from methyl 1-benzylthieno[2,3-*b*]indolecarboxylate by debenzylation with aluminium trichloride in toluene. Compound **2** was in one step saponified and decarboxylated by heating in morpholine to give the previously unreported parent heterocycle thieno[2,3-*b*]indole.

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In connection with our work on β-carbolines [1-2], the non classical benzodiazepine receptor ligands, we became interested in investigating other annulated ring systems in which an ester functional group is located at the same distance relative to the indole nitrogen atom as in the methyl β-carboline-3-carboxylate ring system.

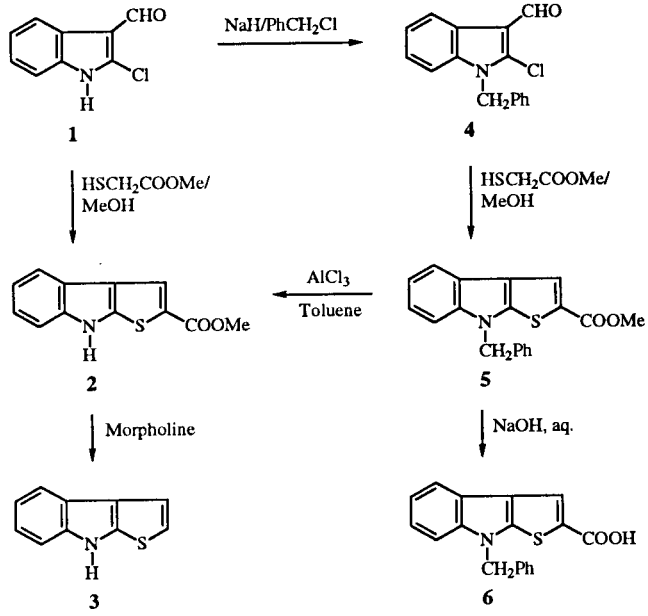
According to molecular models methyl thieno[2,3-*b*]-indole-3-carboxylic acid (**2**) would fulfil this criterion. The thieno[2,3-*b*]indole ring system is only briefly described in the literature [3-5] and only recently thienodoline, 6-chlorothieno[2,3-*b*]indole-2-carboxamide, has been discovered as a new plant growth-regulating substance produced by a *Streptomycete* strain [6]. In this paper we present a facile synthesis for methyl thieno[2,3-*b*]indole-2-carboxylate (**2**) as well as the parent ring system thieno[2,3-*b*]indole (**3**).

Analogues to methods described for the synthesis of thieno[2,3-*d*]imidazoles [7], annulation reactions of 2-chloroindole-3-carbaldehyde [8] with methyl thioglycolate to obtain methyl thieno[2,3-*b*]indolecarboxylate (**2**) were investigated, but the yields of the reaction were in general low with an optimum yield of only 10% of **2**, when the reaction was performed in methanol with dry potassium carbonate as the base.

Starting from the protected compound 1-benzyl-2-chloroindole-3-carbaldehyde (**4**) [8] under similar reaction conditions resulted in a nearly quantitative yield of methyl 8-benzyl-2-chlorothieno[2,3-*b*]indole-2-carboxylate (**5**), indicating that the acidic proton of the indole ring impeded the annulation reaction.

Attempts to deprotect compound **5** by catalytic hydrogenation were unsuccessful, whereas aluminium trichloride in toluene at reflux for 10 minutes gave methyl thieno[2,3-*b*]indole-3-carboxylate (**2**) in 40% yield [8]. As a byproduct 8-benzylthieno[2,3-*b*]indole carboxylic acid (**6**) was isolated in 25% yield.

Attempts to convert methyl thieno[2,3-*b*]indole-3-carboxylate to the morpholino amide by heating in morpholine gave thieno[2,3-*b*]indole (**3**) as the only isolated product. The reaction was followed by thin layer chromatography. No intermediates were observed and it seems as if the saponification and decarboxylation take place in one step. The unprotected nitrogen atom in the indole ring



is involved in the reaction *via* a proton abstraction by morpholine, since the benzyl protected compound **5** upon heating in morpholine only results in starting material.

The target compound methyl thieno[2,3-*b*]indole-2-carboxylate **2** did not show any affinity to the benzodiazepine receptors as measured by [^{3}H]-Flunitrazepam displacement studies, which show that the pyridine nitrogen is essential for the affinity of the β-carbolines to the benzodiazepine receptors.

The reaction path to methyl thieno[2,3-*b*]indole-2-carboxylate **2** could serve as a route to the new plant growth-regulating substance thienodoline, 6-chlorothieno[2,3-*b*]-indole-2-carboxamide and analogues thereof.

Although the substituted thieno[2,3-*b*]indole ring system previously has been reported [2-4], this is the first report for the synthesis of the parent thieno[2,3-*b*]indole ring system.

EXPERIMENTAL

Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. The ^{1}H nmr spectra

were recorded at 60 MHz on a Hitachi Perkin Elmer R-248 spectrometer and mass spectra were recorded with a Finnigan 5100 mass spectrometer. Column chromatography was performed on silica gel 60 (70-230 mesh, ASTM Merck). Elemental analyses were performed by Preben Hansen microanalytical laboratory, University of Copenhagen. No particular attempt was made to optimize reaction conditions for most of the reactions described.

Methyl 8-Benzylthieno[2,3-*b*]indole-2-carboxylate (**5**).

To a solution of **4**, (27.00 g, 0.10 mole) in methanol (200 ml) was added powdered potassium carbonate (15.4 g, 0.11 mole) and methyl thioglycolate (11.7 g, 0.11 mole). The reaction mixture was stirred under nitrogen at 60° for 4 hours. After cooling, ice water was added and the precipitated compound filtered. The crude compound was dried and recrystallized from a toluene/methanol mixture giving the title compound in 25.0 g (79%) yield, mp 159-161°; ^{1}H nmr (60 MHz, deuteriochloroform): δ 3.85 (s, 3H), 5.25 (s, 2H), 7.1-7.3 (m, 8H), 7.6-7.9 (m, 1H), 8.1 (m, 1H).

Anal. Calcd. for $C_{19}H_{15}O_2NS$ (321.40): C, 71.00; H, 4.70; N, 4.36; S, 9.98. Found C, 71.02; H, 4.71; N, 4.32; S, 9.89.

Methyl Thieno[2,3-*b*]indole-2-carboxylate (**2**).

To a suspension of aluminium trichloride (4.0 g, 30 mmoles) in toluene (50 ml) was added **5** (4.8 g, 15 mmoles) in one portion. The reaction mixture was heated at reflux for 10 minutes. After cooling to room temperature the reaction mixture was poured in ice water (200 ml). The phases were separated and the aqueous solution was extracted further with ethyl acetate (3 x 100 ml). The combined organic extracts were washed with 0.5 *N* sodium hydroxide solution (2 x 100 ml) and water (2 x 100 ml). The organic solution was dried, and the solvent was removed under reduced pressure. The residue was crystallized from toluene to give compound **2** in 1.3 g (38%) yield, mp 201-209°; ^{1}H nmr (60 MHz, DMSO-d_6): δ 3.85 (s, 3H), 7.1-7.8 (m, 4H), 8.2 (s, 1H), 11.9 (s, 1H, broad).

Anal. Calcd. for $C_{12}H_9O_2NS$ (231.27): C, 62.32; H, 3.92; N, 6.06; S, 13.86. Found: C, 62.45; H, 3.89; N, 5.97; S, 13.68.

The basic washings of the organic extracts were combined and acidified with concentrated hydrochloric acid. The precipitated crystals were filtered giving compound **6** in 26% (1.2 g) yield.

Thieno[2,3-*b*]indole (**3**).

Methyl thieno[2,3-*b*]indolecarboxylate (**2**) (1.0 g, 4.3 mmoles) was dissolved in morpholine (5 ml) and heated at 120° for 20 hours. After cooling, water (40 ml) was added and the precipitated crystals filtered. The crude material was purified by column chromatography on silica gel using petroleum ether/dichloromethane (1:1) as the eluent. The fractions containing the title compound were evaporated and triturated with petroleum ether. The separated compound was filtered and dried giving the title compound in 67% (0.5 g) yield, mp 210-211°; ^{1}H nmr (deuteriochloroform): δ 6.8 (d, 1H), 7.0-7.5 (m, 4H), 7.1-7.4 (m, 1H), 11.1 (s, 1H, broad); ms: m/2 173 (M^+).

Anal. Calcd. for $C_{10}H_7NS$ (173.24): C, 69.33; H, 4.07; N, 8.09; S, 18.51. Found: C, 69.21; H, 4.02; N, 8.04; S, 18.38.

8-Benzylthieno[2,3-*b*]indole-2-carboxylic Acid (**6**).

Potassium hydroxide (10 g) was dissolved in methanol/water 1:1 (159 ml). Methyl 8-benzylthieno[2,3-*b*]indole-2-carboxylate (**5**) (9.1 g, 30 mmoles) was added and the mixture heated at reflux for 2 hours. After cooling the reaction mixture was acidified with acetic acid. The precipitated compound was filtered and dried. Recrystallization from a toluene/ethanol mixture gave the title compound in 8.6 g (94%) yield, mp 194-195°; ^{1}H nmr (DMSO-d_6): δ 5.5 (s, 2H), 7.1-8.0 (m, 9H), 8.2 (s, 1H), 12.5 (s, 1H, broad).

Anal. Calcd. for $C_{18}H_{13}O_2NS$ (307.28): C, 70.34; H, 4.26; N, 4.56; S, 10.43. Found: C, 70.47; H, 4.24; N, 4.47; S, 10.55.

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