Synthesis of New 4-Quinolone-type Compounds in the Benzo[*b*]thiophene Series

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Some new derivatives of 1,4-dihydro-4-oxo-3-pyridinecarboxylic acid (quinolone-type compounds) **5** and **13** have been prepared in the benzo[*b*]thiophene series. The key step was the construction of the pyridine ring starting from 2-aminobenzo[*b*]thiophene derivatives. The synthesis of amine **9**, was performed by using an original "amination" reaction.

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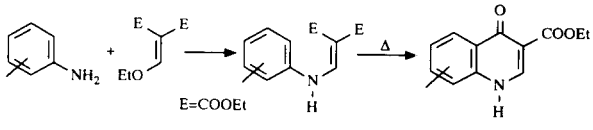
Quinolones (quinolone-types), namely derivatives of 1,4-dihydro-4-oxo-3-pyridinecarboxylic acid, are an important class of antibacterial compounds which have seen great development in the last few years [1]. A large variety of compounds have been synthesized and tested. Several methods are available for the preparation of such derivatives. Among these, one of the most widely used methods involves, in the crucial step, the condensation of diethyl ethoxymethylenemalonate with an appropriate aromatic amine [2] (Scheme 1).

Scheme 1



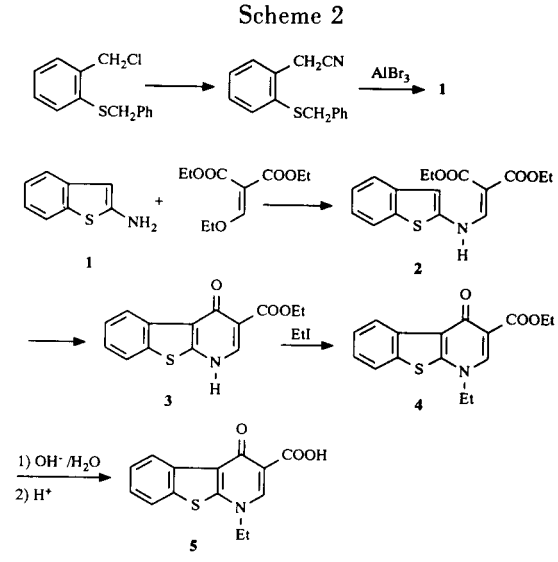
Owing to our experience in the synthesis of heterocyclic amino compounds in obtaining NADH models, we decided to use some of the same procedures for the preparation of previously undescribed (to our knowledge) "quinolone-types". According to this strategy we selected 2-aminobenzo[b]thiophene as a precursor of the quinolone-types in this series. By this means we could synthesize quinolone-type compounds bearing a rarely described tricyclic skeleton. Moreover, it could be hoped that the presence of an electron donating system fused to the pyridone would play a similar role to that played by the presence of a tertiary amine group at position 7 of some of the most efficient quinolones [3]. However, these compounds, in nearly all cases, bear a fluorine substituent at position 6 which seems to play a fundamental role in the antibacterial activity of the quinolones [4].

The purpose of this paper will be to describe the synthesis of quinolone-type compounds in the benzo[*b*]thiophene series with or without a fluorine atom at position 6.

I) Synthesis of a Simple Quinolone-type Compounds in the Benzo[*b*]thiophene Series.

The overall scheme is the following (Scheme 2).

Scheme 2



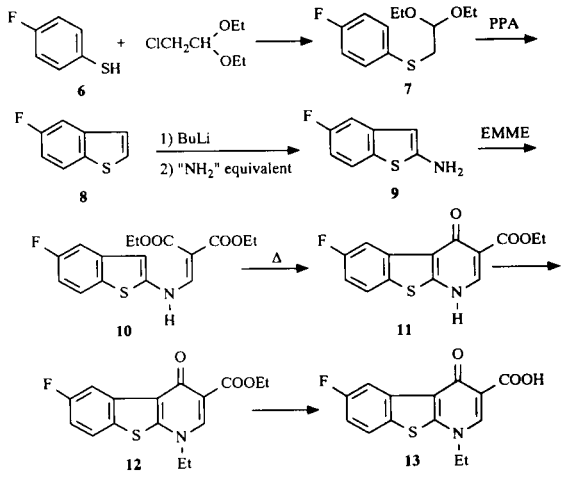
The 2-aminobenzo[*b*]thiophene **1** was obtained by using the method described by Stacy *et al.* [5] starting from 2-mercaptobenzoic acid with some modifications (see Experimental).

The crucial part is the cyclization leading to **3**. In the literature this reaction is generally carried out in diphenyl ether at 250°. In our case large amounts of tarry materials were obtained. So we used another solvent *i.e.* diethylene glycol dibutyl ether. A solution of **2** in this ether was added to another portion of the same ether warmed at 245°. After addition, the reaction mixture was quenched at low temperature to avoid degradation of **3**. The next steps of the synthesis were performed in classical conditions.

II) Synthesis of a Quinolone-type Bearing a Fluorine Atom.

By analogy with the synthesis of **5** the simplest scheme would involve the utilisation of 4-fluoro-2-mercaptobenzoic acid. However, the synthesis of this compound, by following literature information, seems to be difficult. So we decided to imagine a very different way which consisted of the introduction of an amino group at position 2 of a previously synthesized fluorobenzo[*b*]thiophene [6] (Scheme 3).

Scheme 3



The cyclization step, **7** → **8**, is difficult to perform. After several unsuccessful attempts the reaction was carried out by heating **7** under vigourous stirring with polyphosphoric acid (PPA) dispersed in dry chlorobenzene [6].

The introduction of the amine was performed in the following way: after metalation with butyllithium the benzo[*b*]thiophene derivative **8** was treated with tosyl azide and sodium pyrophosphate [7] leading to an unstable triazene salt which was reduced "*in situ*" with hydrogen sulfide. The amine was then isolated as the hydrochloride salt. Starting from this amine quinolone **13** was obtained in a similar fashion to that of compound **5**.

The pharmacology of compounds **5** and **13** is presently under study. The results of this research will be reported in an appropriate forum later.

EXPERIMENTAL

Melting points were determined on a Kofler apparatus. The ^{1}H nmr spectra were recorded on a varian EML 360 (60 MHz) or a Bruker AC 200 (200 MHz) spectrometer. Chemical shifts (δ) are given in ppm downfield from tetramethylsilane (spectra recorded in deuteriochloroform) or hexamethyldisiloxane (spectra recorded in dimethyl sulfoxide-d_6). The ir spectra were recorded on a Beckman IR 4250 spectrometer. Microanalysis were obtained from a Carlo Erba 1160 apparatus. Thin layer chromatography was carried out on Merck plates (silica gel 60 F_{254} alumina 150 F_{254}: ref 5554 and 5551). Column chromatography was carried out using silica (Merck SI 60).

2-Aminobenzo[*b*]thiophene (**1**).

This compound was obtained by the procedure described by Stacy [5]. Thiosalicyclic acid was reduced with lithium aluminium hydride to *o*-mercaptobenzyl alcohol (yield 97%). The mercapto function was protected with a benzyl group (yield 86%) and 2-benzylthiobenzyl alcohol was submitted to nucleophilic substitution leading to 2-benzylthiobenzyl chloride (yield 87%) and later to 2-benzylthiophenylacetonitrile. The procedure for this last step was modified as follows: To a solution of 5 g (0.102 mole) of sodium cyanide in 50 ml of dimethyl sulfoxide at 75° was added dropwise 20 g (0.080 mole) of 2-benzylthiobenzyl chloride. The mixture was stirred at 88° for 4.5 hours, then cooled and poured onto a mixture of 35 g of ice and 170 ml of water. The aqueous phase was extracted with 3 x 50 ml of dichloromethane. The combined organic phases were washed with 4 x 100 ml of water, then dried and concentrated. The residual red oil was purified by chromatography on silica gel (eluent, hexane/ether:80/20). 2-Benzylthiophenylacetonitrile (15 g, 0.063 mole) was obtained (yield 78%) as a pale yellow oil which crystallized slowly.

Anal. Calcd. for $C_{15}H_{13}NS$: C, 75.28; H, 5.85; N, 5.47. Found: C, 75.3; H, 5.7; N, 5.3.

The cyclization of 2-benzylthiophenylacetonitrile was carried out with aluminium tribromide [5] leading to 2-aminobenzo[*b*]-thiophene **1** (yield 80%).

2-Bisethoxycarbonylvinylaminobenzo[*b*]thiophene (**2**).

To diethyl ethoxymethylenemalonate (2.6 g, 0.012 mole) heated at 140°, 1.7 g (11.4 mmoles) of freshly prepared **1** was slowly added. Heating was maintained for 30 minutes, then the mixture was cooled slowly to room temperature. The frozen mixture was treated with 10 ml of petroleum ether, filtered and the solid washed again with 20 ml of the same solvent affording, after drying, compound **2** (93%), mp 69-70°; ir (potassium bromide): ν C=O 1690 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.2 (t, 6H), 4.1 (q, 4H), 7.2 (m, 5H), 8.1 (d, 1H), 11.05 (d, 1H).

Anal. Calcd. for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.36; N, 4.38. Found: C, 60.17; H, 5.29; N, 4.32.

Ethyl 1,4-Dihydro-4-oxobenzo[*b*]thieno[2,3-*b*]pyridine-3-carboxylate (**3**).

Compound **1**, 2 g (6.27 mmoles) was dissolved in 20 ml of diethylene glycol dibutyl ether. This solution was added, under argon with stirring, to 20 ml of the same solvent at 245°. The temperature was maintained after addition for 10 minutes and the mixture was quickly quenched by external cooling with at first, ice then dry ice. The solvent was eliminated under reduced pressure and after cooling the remaining solid was treated with 40 ml of petroleum ether, filtered and recrystallized in ethanol/water (70/30) affording 1.04 g of **3** (67%), mp 84-87°; ir (potassium bromide): ν C=O 1690 and 1710 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.3 (t, 3H), 4.3 (q, 2H), 7.5 (m, 2H), 8.0 (m, 1H), 8.5 (m, 1H), 8.7 (s, 1H).

Anal. Calcd. for $C_{14}H_{11}NO_3S$: C, 61.53; H, 4.06; N, 5.12. Found: C, 61.62; H, 3.90; N, 5.19.

Ethyl 1-Ethyl-1,4-dihydro-4-oxobenzo[*b*]thieno[2,3-*b*]pyridine-3-carboxylate (**4**).

A solution of compound **3**, 0.61 g (2.3 mmoles), 0.92 g (6.7 moles) of potassium carbonate and 0.54 g (6.7 mmoles) of ethyl iodide in 15 ml of dimethylformamide was heated at between 100-110° for 3 hours. At this time, 0.36 ml (4.6 mmoles) of ethyl iodide was added and heating continued for 2 hours. After cooling and concentration under vacuum, the residue was taken up in dichloromethane and filtered (to eliminate potassium carbonate). The solvent was evaporated and the solid recrystallized in a mixture ethanol/water (60/40). Compound **4**, 0.33 g was obtained in 49% yield, mp 167-169°; ir (potassium bromide): ν (C=O) 1720 cm^{-1}; ^{1}H nmr (dimethyl sulfoxide-d_6): δ 1.3 (m, 6H), 4.2 (m, 4H),

7.4 (m, 2H), 8.0 (m, 1H), 8.5 (s, 1H), 8.7 (s, 1H).

Anal. Calcd. for $C_{16}H_{15}NO_3S$: C, 63.72; H, 5.02; N, 4.65. Found: C, 42.46; H, 4.89; N, 4.67.

1-Ethyl-1,4-dihydro-4-oxobenzo[*b*]thieno[2,3-*b*]pyridine-3-carboxylic Acid (**5**).

A mixture of 0.5 g (2 mmoles) of compound **4**, 5 ml of 10% sodium hydroxide and 1.5 ml of ethanol was refluxed for 2 hours. The solution was cooled and poured in 25 ml of water then acidified with aqueous 10% sulphuric acid (*p*H 2). The precipitate was washed with water and compound **5** (0.38 g) was obtained in 84% yield, mp >255°; ir: ν C=O 1705 cm^{-1}; ^1H nmr (trifluoroacetic acid, the spectrum was recorded without internal reference and the chemical shifts are given with respect to the methyl signal assumed to be at 1.3 ppm as in compound **4**): δ 1.30 (t, 3H), 4.25 (q, 2H), 7.10-7.70 (m, 3H), 8.05-8.60 (m, 1H), 8.70 (s, 1H), 10.80 (s, 1H); ir: ν C=O 1705 cm^{-1}.

Anal. Calcd. for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.12. Found: C, 61.17; H, 4.00; N, 5.04.

1-(2-Diethoxyethylthio)-4-fluorobenzene (**7**).

4-Fluorothiophenol (10 g, 0.078 mole) was added to a solution of sodium ethoxide obtained from 2.5 g (0.108 mole) of sodium and 45 ml of ethanol. To this solution 16.5 g (0.108 mole) of 1-chloro-2,2-diethoxyethane was added dropwise. After addition, the mixture was refluxed for 15 hours. The ethanol was then evaporated and the residue taken up in ether and water. The organic phase was separated, washed with water and dried. After elimination of the solvent the crude product was not further purified; ^1H nmr (deuteriochloroform): δ 1.25 (t, 6H), 3.05 (d, 2H), 3.6 (m, 4H), 4.6 (t, 1H), 6.8-7.6 (m, 4H).

5-Fluorobenzo[*b*]thiophene (**8**).

In a 500 ml flask equipped with an efficient stirrer, 18 g of polyphosphoric acid and 160 ml of anhydrous chlorobenzene were introduced. The mixture was refluxed under argon and 4.88 g (0.020 mole) of the above compound **7** were added slowly. The reflux was maintained for one day. After cooling the organic phase was separated and the polyphosphoric acid phase was treated with 100 ml of water and left for one hour and then extracted with dichloromethane. The organic phases were combined, dried, and the solvents evaporated under reduced pressure. The residue was purified by column chromatography on silica, (eluent, hexane/dichloromethane: 80/20). Compound **8**, 2.91 g was obtained in 95% yield; ^1H nmr (deuteriochloroform): δ 6.8-7.9 (m, 5H).

2-Amino-5-fluorobenzo[*b*]thiophene (**9**).

In a flask flushed with argon, 1 g (6.57 mmoles) of 5-fluorobenzo[*b*]thiophene **8** and 30 ml of anhydrous ether were introduced. Butyllithium, (2.90 ml of 2.5 *M* hexane solution, 7.25 mmoles) was added at a rate to maintain a light reflux. Stirring was continued for one hour and the mixture was cooled to −70°. A solution of 1.42 g (7.23 mmoles) of sodium azide in 20 ml of anhydrous ether was then dropwise added. The mixture was stirred at −70° for 5 hours and a solution of sodium pyrophosphate (3 g dissolved in 33 ml of water) was added with vigourous stirring. The temperature was allowed to reach 20°. Stirring was continued for 15 hours. The organic phase was separated and the aqueous phase extracted with 2 x 40 ml of ether. The organic phases were washed with water, dried and the solvent evaporated. The crude product (1.54 g) was used in the next step without purification due to its instability (ir: ν N_3 2100 cm^{-1}). The azide was dissolved in 150 ml of methanol containing a few drops of piperidine. Hydrogen sulfide was bubbled into the solution for 30 minutes at 20°. Excess hydrogen sulfide was eliminated by bubbling air and then argon through the solution for 15 minutes. The sulphur was filtered out and the solvent evaporated. The residue was taken up with 25 ml of dichloromethane and hydrogen chloride was bubbled into it for 15 minutes. The hydrochloride of the amine **9** was filtered (yield 27% from **8**); ^1H nmr (dimethyl sulfoxide-d_6): δ 6.0 (m, 3H), 6.8-7.9 (m, 5H).

Anal. Calcd. for $C_8H_6FNS{\cdot}HCl$: C, 47.18; H, 3.46; N, 6.88. Found: C, 46.85; H, 3.37; N, 6.68.

2-Bisethoxycarbonylvinylamino-5-fluorobenzo[*b*]thiophene (**10**).

2-Amino-5-fluorobenzo[*b*]thiophene hydrochloride (0.64 g, 3.14 mmoles) was dissolved in 150 ml of 5% sodium bicarbonate. Ether (50 ml) was added and the mixture was stirred for 3 hours. The ethereal phase was dried, and the solvent evaporated. The residue was added in small portions to 0.71 g (3.28 mmoles) of diethyl ethoxymethylenemalonate heated to 135°. After this addition, heating was maintained 30 minutes and the reaction mixture was allowed to cool to room temperature and treated in the same manner as that described for **2**, yield 71%, mp 114-115°; ir: ν C=O 1690 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.2 (t, 6H), 4.1 (q, 4H), 7.2 (m, 2H), 7.5 (d, 1H), 7.9 (q, 1H), 8.1 (d, 1H).

Anal. Calcd. for $C_{16}H_{16}FNO_4S$: C, 56.96; H, 4.78; N, 4.15. Found: C, 57.12; H, 4.67; N, 3.85.

Ethyl 1,4-Dihydro-4-oxo-6-fluorobenzo[*b*]thieno[2,3-*b*]pyridine-3-carboxylate (**11**).

This compound was obtained by the same procedure as that used for compound **3**. The crude product was purified by column chromatography on silica gel (eluent, ethyl acetate). Compound **11** was obtained in 50% yield, mp 165-166°; ir: ν (C=O) 1700 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.3 (m, 3H), 4.3 (m, 2H), 6.5-8.7 (m, 5H).

Anal. Calcd. for $C_{14}H_{10}FNO_3S$: C, 57.72; H, 3.46; N, 4.81. Found: C, 57.50; H, 3.48; N, 4.92.

Ethyl 1-Ethyl-1,4-dihydro-4-oxo-6-fluorobenzo[*b*]thieno[2,3-*b*]pyridine-3-carboxylate (**12**).

The procedure was the same as for **4**. Compound **12** was purified by column chromatography on silica gel (eluent, ethyl acetate), yield 43%, mp 181-182°; ^1H nmr (dimethyl sulfoxide-d_6): δ 1.3 (m, 6H), 4.3 (m, 4H), 7.4 (m, 1H), 8.2 (m, 1H), 8.6 (m, 2H); ir: ν C=O 1700 cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}FNO_3S$: C, 60.18; H, 4.42; N, 4.39. Found: C, 60.00; H, 4.62; N, 4.12.

1-Ethyl-1,4-dihydro-4-oxo-6-fluorobenzo[*b*]thieno[2,3-*b*]pyridine-3-carboxylic Acid (**13**).

Alkaline hydrolysis of **12** was performed under the same conditions as for **5**, yield 37%, mp >260°; ^1H nmr (trifluoroacetic acid, no internal reference, chemical shifts with respect to the methyl group at 1.3 ppm): δ 1.3 (t, 3H), 4.2 (q, 2H), 6.7-8.1 (m, 3H), 8.7 (s, 1H), 11.0 (s, 1H); ir: ν C=O 1710 cm^{-1}.

Anal. Calcd. for $C_{14}H_{10}FNO_3S$: C, 57.72; H, 3.46; N, 4.80. Found: C, 57.70; H, 3.70; N, 4.50.

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