# Heteroarene-fused Benzodiazepines. Part 1. Synthesis of Thieno-[2,3-*b*][1,5]-, -[3,2-*b*][1,5]-, and -[3,4-*b*][1,5]-benzodiazepinones

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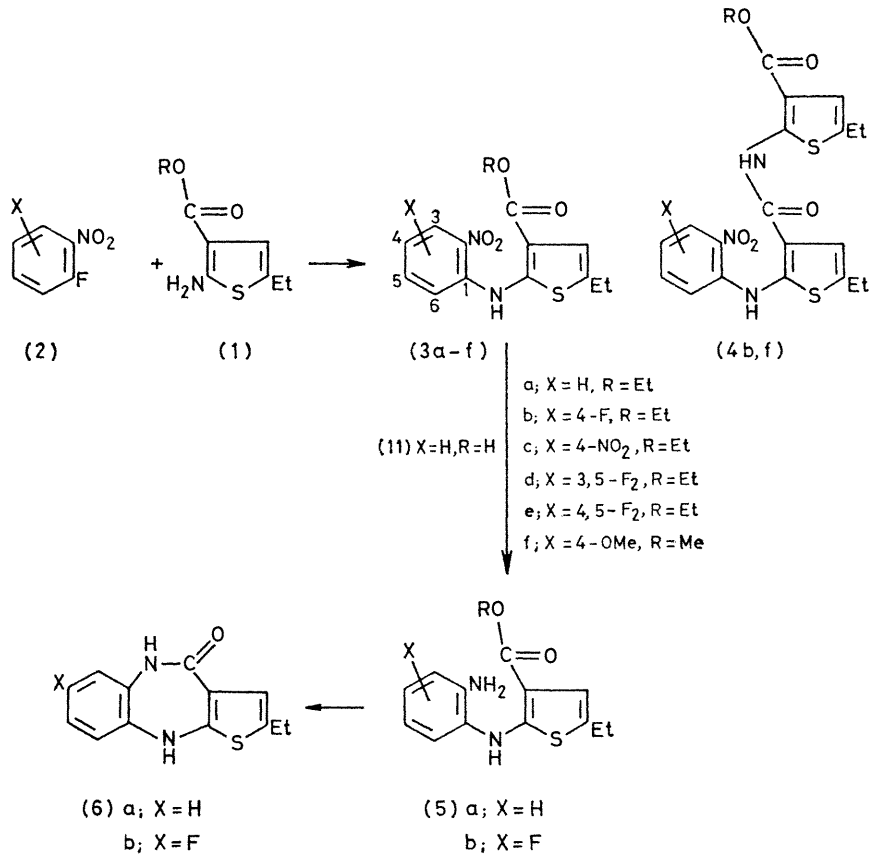
The synthesis of the 4*H*-thieno-[2,3-*b*][1,5]-, -[3,2-*b*][1,5]-, and -[3,4-*b*][1,5]-benzodiazepinone ring systems is described. Sodium methylsulphinylmethanide was used for the intramolecular cyclisation of the intermediate amino-esters (5), (9), and (14). However, attempted cyclisation of ethyl 2-(2-amino-4-fluoroanilino)-5-ethylthiophen-3-carboxylate (5b) with sodium hydride at a higher temperature caused rearrangement to a benzimidazolone (12).

A NUMBER of antipsychotic agents, developed during recent years, possess a tricyclic dibenzodiazepine system. Electron transfer reactions have been often implicated in reversible attachment of drugs at a biological receptor site. The electronic character of these tricyclic systems can be altered by appropriate substituents. Although various modifications of nuclear substitution have been made, very little attention has been given to the replacement of one or both benzene rings with other heteroarene groups. We now describe the synthesis of three isomeric thieno[1,5]benzodiazepinones. The reaction of ethyl 2-(2-amino-4-fluoroanilino)-5-ethylthiophen-3-carboxylate (5b) with sodium hydride in dimethyl sulphoxide leading to an unexpected rearrangement product, 5-fluoro-1-(5-ethyl-2-thienyl)-1,3-dihydrobenzimidazol-2*H*-one (12), is also described.

The general synthetic route to the thieno[2,3-*b*][1,5]-benzodiazepine system (6) is outlined in the Scheme.




SCHEME

Since all three *o*-aminothiophen esters are readily available,[1-3] it seemed appropriate to examine the reactions of these with 1-fluoro-2-nitrobenzene. This was expected to provide the starting materials for the preparation of the three isomeric ring systems. Our initial study of the reaction of ethyl 2-amino-5-ethyl-

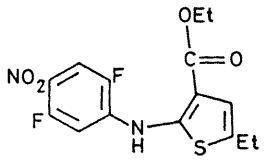
[1] K. Gewald, E. Schinke, and H. Böttcher, *Chem. Ber.*, 1966, **99**, 94.
[2] H. Fiesselmann, *Angew. Chem.*, 1959, **71**, 377.
[3] B. R. Baker, J. P. Joseph, R. E. Schaub, F. J. McEvoy, and J. H. Williams, *J. Org. Chem.*, 1953, **18**, 138; R. B. Woodward and R. H. Eastman, *J. Amer. Chem. Soc.*, 1946, **68**, 2229.

thiophen-3-carboxylate with 1-fluoro-2-nitrobenzene under normal displacement reaction conditions met with little success. This is probably due to the poor nucleophilicity of this amino-group. The difficulty, however, was overcome by generating an anion at the amino-function using n-butyl-lithium at −20 to −50 °C. The addition of the anion to a solution of 1-fluoro-2-nitrobenzene in THF at 20—30 °C gave consistent and satisfactory yields (35—50%) of the required products. Variation of conditions (temperature, use of reactants in excess) did not improve the yields. The gradual appearance and persistence of a deep blue colour, presumably due to the generated anion, was noticed. A similar colour appeared when n-butyl-lithium was added to the product. This suggests that an anion exchange takes place between the starting amino-ester (1) and the product nitro-ester (3) and also explains the fact that yields were no greater than 50%.

The reaction proceeded well with various (4-H, 4-F, 4-$NO_2$, 3,5-$F_2$) 1-fluoro-2-nitrobenzenes. The nature and position of these groups seemed to have no appreciable effect on the displacement, which always occurred as expected at the 1-position. With 1-fluoro-2,4-dinitrobenzene a marked increase in yield (50%) was obtained. However with 1,2,4-trifluoro-5-nitrobenzene, the displacement occurred *para* as well as *ortho* to the nitro-group resulting in two products [(7) and (3e)], while with 1,3,5-trifluoro-2-nitrobenzene the fluorine at the *ortho*-position only was displaced. The inductive effect of the neighbouring fluoro-group enhanced the displacement at the *para*-position in the former case.

Similarly, methyl 3-aminothiophen-2-carboxylate was treated with 1,4-difluoro-2-nitrobenzene to give a similar yield of the product (8).

It was also found that the displacement reaction between 1,4-difluoro-2-nitrobenzene and ethyl 2-amino-5-ethylthiophen-3-carboxylate can be effected in good yield in dimethyl sulphoxide solution in the presence



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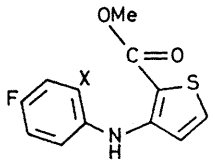
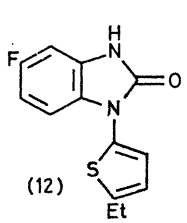


(8) X = $NO_2$
(9) X = $NH_2$

of anhydrous potassium carbonate at elevated temperatures (*ca.* 95—100 °C). Although this reaction gives better yields than those obtained in the former case, the products are always contaminated with by-products, such as the amide (4b) (*ca.* 2—11%). Higher temperatures and excess of the aminothiophen ester seem to increase the yield of this amide. With 1-fluoro-4-methoxy-2-nitrobenzene, even when the reaction was carried out under normal conditions, the formation of the corresponding amide (4f) was enhanced and constituted one third of the isolated products. On the other hand, the reaction with the lithium thienylamide always produced clean products. In view of the reported multistage alkylation [4] of ethyl 2-aminothiophen-3-carboxylate, which required prior activation of the amino-function either by tosylation or benzoylation, the process described here provides a convenient one-step arylation at this nitrogen atom.



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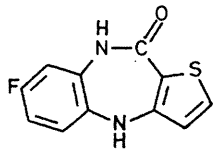

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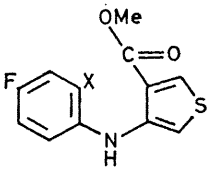
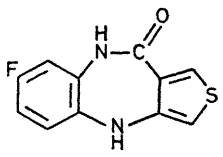


(13) X = $NO_2$
(14) X = $NH_2$



(15)

The reaction of methyl 4-aminothiophen-3-carboxylate with 1,4-difluoro-2-nitrobenzene was effected in dimethyl sulphoxide solution in the presence of triethylamine to give the nitro-ester (13).

On catalytic reduction, the nitro-esters (3a and b) gave essentially quantitative yields of the corresponding amino-esters (5a and b). Attempted cyclisation by various means [reflux in xylene with molecular sieve or toluene-*p*-sulphonic acid; NaOMe–MeOH; $NaOBu^t$–$Bu^tOH$; $MNH_2$–dioxan (M = Na or Li)] did not produce any satisfactory result. The nitro-ester (3a) was hydrolysed to the nitro-acid (11), which was catalytically reduced to the amino-acid. This acid, which appeared less stable than its corresponding ester, was used directly for cyclisation by means of dicyclohexylcarbodi-imide (DCC) to give the desired diazepinone (6a) in 37% yield.

Metal amides, generated by treating primary or secondary amines with metal hydrides, have been used for the aminolysis of esters.[5] Attempted cyclisation of the amino-ester (5b) with sodium hydride in dimethyl sulphoxide at temperatures ⩾80 °C led exclusively to an unexpected rearrangement product, an *N*-thienylbenzimidazolone (12). The structure is assigned on the basis of spectral evidence. T.l.c. indicated that the benzodiazepinone (6b), initially formed at lower temperature, undergoes ring contraction to give the benzimidazolone (12) at higher temperatures. This has been further confirmed by the reaction of the benzodiazepinone (6b) under similar conditions at high temperatures.

[4] R. F. Koebel, L. L. Needham, and C. D. Blanton, jun., *J. Medicin. Chem.*, 1975, **18**, 192.

[5] B. Singh, *Tetrahedron Letters*, 1971, 321; Kim-Wenn Yang, J. G. Cannon, and J. G. Rose, *ibid.*, 1970, 1791.

The reaction of arene-1,2-diamines with a β-oxo-ester is known to give unpredictable products (benzodiazepinone, benzimidazolone, and benzimidazole) depending on the conditions and the relative reactivities of the reagents. The fused diazepinones formed in these reactions undergo thermal rearrangement at high temperatures to give *N*-alkenyl arene-fused imidazolones.[6] The reaction of 1,2-diaminobenzene with methyl 4-oxotetrahydrothiophen-3-carboxylate in boiling xylene to give predominantly a mixture of two isomeric dihydrothienylbenzimidazolones has also been reported recently.[7] Thus, the facility with which the present rearrangement occurs, particularly under basic conditions, to give exclusively *N*-thienylbenzimidazolone is remarkable and the reaction may well represent a useful synthetic route.

The intermediacy of the diazepinone in the above reaction prompted us to use preformed sodium methylsulphinylmethanide for this intramolecular cyclisation. The amino-esters (5a and b), with 3 equiv. of this reagent at 65—70 °C, smoothly underwent ring closure to give the lactams (6a and b) in good yields. The rearrangement leading to the benzimidazolone tends to occur at higher temperatures than those required for the formation of the diazepinone.

Similarly, the amino-esters (9) and (14) in the other two series were also cyclised to give the diazepinones (10) and (15).* The use of methylsulphinylmethanide for the aminolysis of esters has not previously been reported. The reagent may well prove of use for the general synthesis of amides.

## EXPERIMENTAL

M.p.s were determined with a Köfler hot-stage apparatus. Unless otherwise stated, i.r. spectra were measured for potassium bromide discs with a Perkin-Elmer 457 instrument and u.v. spectra for solutions in methanol using 10 mm cells in a Unicam SP 800 spectrophotometer. $^1$H N.m.r. spectra were measured for solutions in deuteriochloroform ($Me_4Si$ as internal reference) with either a Varian A-60A or a Brüker WH90 instrument. The latter was also used to measure the $^{13}$C n.m.r. spectra (at 22.63 MHz under both broad-band and off-resonance continuous wave decoupling conditions). Mass spectra were obtained with an LKB-9000S spectrometer (ionising beam energy 20 eV). Unless mentioned otherwise, the drying agent used was magnesium sulphate.

*Ethyl 5-Ethyl-2-(4-fluoro-2-nitroanilino)thiophen-3-carboxylate* (3b) (*Method A*).—To a stirred solution of ethyl 2-amino-5-ethylthiophen-3-carboxylate [1] (40 g, 0.2 mol) in tetrahydrofuran (150 ml; distilled from lithium aluminium hydride) under nitrogen, was added n-butyl-lithium (125.6 ml, 0.2 mol) in n-hexane, the temperature being kept between −20 and −40 °C. A solution of 1,4-difluoro-2-nitrobenzene (31.8 g, 0.2 mol) in dry tetrahydrofuran (50 ml) was added and the mixture was allowed to attain room temperature. As the temperature reached 5 °C a deep ink-blue colour developed. The stirring was continued for 2 h, and then the mixture was poured onto iced water (1 l), the solution turning orange-red. The solution was extracted with ethyl acetate and the extract was washed with water, dried, and evaporated to leave a red oil, which was crystallised from ethanol to yield the *ester* (3b) (17.5 g, 26%), m.p. 90°; $\nu_{max.}$ 1 680 cm$^{-1}$; $\lambda_{max.}$ 332 and 450 nm (log ε 4.02 and 3.70); δ 1.3 (3 H, t, Me), 1.38 (3 H, t, Me), 2.71 (2 H, q, $CH_2$Me), 4.34 (2 H, q, $CO_2CH_2$Me), 6.85 (1 H, t, thiophen-4-H), 7.3—7.95 (3 H, m, anilino), and 11.52 (1 H, s, NH) (Found: C, 53.5; H, 4.75; N, 8.2; F, 5.7; S, 9.8. $C_{15}H_{15}FN_2O_4S$ requires C, 53.3; H, 4.45; N, 8.3; F, 5.6; S, 9.5%).

The reaction, when carried out as above gave inconsistent yields (5—26%). A more consistent yield (30—35%) was obtained if the cold lithiated amino-ester was transferred through an inverted U-tube under nitrogen pressure to a solution of 1,4-difluoro-2-nitrobenzene in dry tetrahydrofuran maintained at 20—40 °C.

The following compounds were similarly prepared by the reverse addition technique.

*Ethyl 5-ethyl-2-(2-nitroanilino)thiophen-3-carboxylate* (3a), yield 32%, had m.p. 66—68° (ethanol); $\nu_{max.}$ 1 675 cm$^{-1}$; $\lambda_{max.}$ 331 and 434 nm (log ε 4.05 and 3.71); δ 1.31 (3 H, t, Me), 1.38 (3 H, t, Me), 2.77 (2 H, q, $CH_2$Me), 4.40 (2 H, q, $CO_2CH_2$Me), 6.95—8.25 (5 H, m, aryl), and 11.75 (1 H, s, NH) (Found: C, 56.1; H, 5.15; N, 8.8; S, 9.7. $C_{15}H_{16}N_2O_4S$ requires C, 56.2; H, 5.05; N, 8.7; S, 10.0%).

*Ethyl 2-(2,4-dinitroanilino)-5-ethylthiophen-3-carboxylate* (3c), yield 50%, had m.p. 148° (ethanol); $\nu_{max.}$ 1 680 cm$^{-1}$; $\lambda_{max.}$ 390 nm (log ε 4.16); δ 1.32 (3 H, t, Me), 1.38 (3 H, t, Me), 2.80 (2 H, q, $CH_2$Me), 4.40 (2 H, q, $CO_2CH_2$Me), 7.03 (1 H, s, thiophen H-4), 7.89—9.2 (3 H, m, anilino), and 12.18 (1 H, s, NH) (Found: C, 49.1; H, 4.1; N, 11.3; O, 26.2; S, 8.6. $C_{15}H_{15}N_3O_6S$ requires C, 49.3; H, 4.15; N, 11.5; O, 26.3; S, 8.8%).

*Ethyl 2-(3,5-difluoro-2-nitroanilino)-5-ethylthiophen-3-carboxylate* (3d), yield 35%, had m.p. 74—75° (ethanol); $\nu_{max.}$ 1 685 cm$^{-1}$; $\lambda_{max.}$ 330 and 404 nm (log ε 4.08 and 3.64); δ 1.3 (3 H, t, Me), 1.37 (3 H, t, Me), 2.75 (2 H, q, $CH_2$Me), 4.39 (2 H, q, $CO_2CH_2$Me), 6.5—7.32 (3 H, m, aryl), and 11.18 (1 H, s, NH) (Found: C, 50.8; H, 4.0; F, 10.9; N, 8.1; S, 9.0. $C_{15}H_{14}F_2N_2O_4S$ requires C, 50.6; H, 3.95; F, 10.7; N, 7.9; S, 9.0%).

*Reaction of Ethyl 2-Amino-5-ethylthiophen-3-carboxylate with 1,2,4-Trifluoro-5-nitrobenzene.*—Ethyl 2-amino-5-ethylthiophen-3-carboxylate (11.3 g, 0.056 mol) was treated with n-butyl-lithium and 1,2,4-trifluoro-5-nitrobenzene (10 g, 0.056 mol) as in method A. Crystallisation from cyclohexane separated the isomer *ethyl 2-(2,5-difluoro-4-nitroanilino)-5-ethylthiophen-3-carboxylate* (7) (1.3 g), m.p. 186°, $\delta_H$ 1.37 (3 H, t, Me), 1.42 (3 H, t, Me), 2.82 (2 H, q, $CH_2$Me), 4.37 (2 H, q, $CO_2CH_2$Me), 6.93 (1 H, t, thiophen H-4), 7.33 (1 H, dd, anilino H-6), and 7.93 (1 H, dd, anilino H-3); $\delta_C$ 148.5 and 160.0 [d, C(5)F], and 140.9 and 151.4 [d, C(2)F]; $\lambda_{max.}$ 391 nm (log ε 4.35) (Found: C, 50.7; H, 3.95; N, 7.5; F, 10.5; S, 8.9. $C_{15}H_{14}F_2N_2O_4S$ requires C, 50.6; H, 3.95; N, 7.9; F, 10.7; S, 9.0%).

* Since the original report [8] of our work a publication [7] describing the preparation of 4,9-dihydro-10*H*-thieno[3,4-*b*][1,5]-benzodiazepin-10-one has come to our notice. We also accomplished an alternative synthesis of this compound using a route essentially similar to that described by these authors.

[6] M. Israel and L. C. Jones, *J. Heterocyclic Chem.*, 1973, **10**, 201; A. Rossi, A. Hunger, J. Kebrle, and K. Hoffmann, *Helv. Chim. Acta*, 1960, **43**, 1298.

[7] O. Hromatka, D. Binder, and K. Eichinger, *Monatsh.*, 1975, **106**, 375.

[8] J. K. Chakrabarti and D. E. Tupper, B.P. Appl. 51,240/1974; Belg. P. 835,932/1976.

The mother liquors from the above crystallisation were chromatographed on a column of Sorbsil U30 silica eluted with xylene to give the other isomer *ethyl* 2-(4,5-*difluoro*-2-*nitroanilino*)-5-*ethylthiophen*-3-*carboxylate* (3e) (2.7 g), m.p. 105°, $\delta_H$ 1.30 (3 H, t, Me), 1.37 (3 H, t, Me), 2.74 (2 H, q, $CH_2$Me), 4.32 (2 H, q, $CO_2CH_2$Me), 6.93 (1 H, t, thiophen H-4), 7.62 (1 H, dd, anilino H-6), and 8.08 (1 H, dd, anilino H-3); $\delta_C$ 148.7, 149.7, 160.5, 161.1 [dd, C(5)F], and 137.1, 137.7, 148.3, and 148.9 [dd, C(4)F]; $\lambda_{max.}$ 333 and 429 nm (log ε 3.99 and 3.80) (Found: C, 50.8; H, 4.1; N, 8.1; F, 10.9; S, 8.8. $C_{15}H_{14}F_2N_2O_4S$ requires C, 50.6; H, 3.95; N, 7.9; F, 10.7; S, 9.0%).

*Reaction of* 1,4-*Difluoro*-2-*nitrobenzene with Ethyl* 2-*Amino*-5-*ethylthiophen*-3-*carboxylate* (*Method B*).—A mixture of 1,4-difluoro-2-nitrobenzene (8.4 g, 0.052 8 mol) and ethyl 2-amino-5-ethylthiophen-3-carboxylate (10.52 g, 0.052 8 mol) in dimethyl sulphoxide (40 ml) was stirred and heated to 65 °C and anhydrous $K_2CO_3$ (7.29 g, 0.052 8 mol) was added. The mixture was heated at *ca.* 96 °C for 6 h with stirring, and then cooled and poured into water. The resulting solid was filtered off, washed with water, and dried at 50 °C under vacuum (17.2 g). Recrystallisation from ethanol gave the ester (3b) (12.6 g, 66.5%). Alternatively, the above crude solid was chromatographed on silica (methylene chloride as eluant) to afford (3b) as the main product. A minor component (2%), *ethyl* 5-*ethyl*-2-[5-*ethyl*-2-(4-*fluoro*-2-*nitroanilino*)-3-*thienylcarboxamido*]-*thiophen*-3-*carboxylate* (4b) was also isolated, m.p. 158—159°, $\nu_{max.}$ 3 275, 2 975, 1 660, 1 635, 1 585, 1 560, and 1 520 cm$^{-1}$; δ 1.05—1.65 (9 H, m, 3 × Me), 2.48—3.00 (4 H, q, 2 × $CH_2$Me), 4.23 (2 H, q, $CO_2CH_2$Me), 6.80—6.98 (2 H, q, 2 × thiophen H-4), 7.0—7.88 (3 H, m, anilino), 11.25 (1 H, NH), and 11.75 (1 H, CONH) (Found: C, 53.6; H, 4.75; F, 4.0; N, 8.5; S, 12.8. $C_{22}H_{22}FN_3O_5S_2$ requires C, 53.8; H, 4.5; F, 3.9; N, 8.6; S, 13.1%).

*Reaction of Methyl* 2-*Amino*-5-*ethylthiophen*-3-*carboxylate with* 1-*Fluoro*-4-*methoxy*-2-*nitrobenzene*.—The reaction was carried out as described under method B. The crude product was found (t.l.c.) to consist of two major components. These were separated by column chromatography (Sorbsil M60; methylene chloride as eluant) to give (a) *methyl* 5-*ethyl*-2-[5-*ethyl*-2-(4-*methoxy*-2-*nitroanilino*)-3-*thienylcarboxamido*]*thiophen*-3-*carboxylate* (4f) (17.1%), m.p. 160—163°, $\nu_{max.}$ 1 665 cm$^{-1}$; δ 1.23 (6 H, t, 2Me), 2.68 (4 H, q, 2$CH_2$Me), 3.72 (6 H, s, $OCH_3$, $CO_2$Me), 6.7—7.68 (5 H, m, Ar), 11.48 (2 H, s, NH, CONH); *m/e* 489 ($M^+$), 459 ($M$ — NO), 457 [$M$ — ($CH_3O$ + H)], 305 ($M$ — $C_8H_{10}SO_2S$), 274 [$M$ — ($C_8H_{10}NO_2S$ + $OCH_3$)], 259 [$M$ — ($C_8H_{10}NO_2S$ + $NO_2$)] (Found: C, 53.9; H, 4.95; N, 8.4; O, 19.4; S, 13.3. $C_{22}H_{23}N_3O_6S_2$ requires C, 54.0; H, 4.75; N, 8.6; O, 19.6; S, 13.1%); and (b) *methyl* 5-*ethyl*-2-(4-*methoxy*-2-*nitroanilino*)*thiophen*-3-*carboxylate* (3f) (33%), m.p. 125—127° (ethanol), $\nu_{max.}$ 1 675 cm$^{-1}$; $\lambda_{max.}$ 336 nm (log ε 4.34); δ 1.30 (3 H, t, Me), 2.71 (2 H, q, $CH_2$Me), 3.82 (3 H, s, OMe or $CO_2$Me), 3.85 (3 H, s, OMe or $CO_2$Me), 6.72 (1 H, s, thiophen H-4), 7.18—7.75 (3 H, anilino), and 11.7 (1 H, s, NH) (Found: C, 53.6; H, 4.9; N, 8.4; O, 23.5; S, 9.5. $C_{15}H_{16}N_2O_5S$ requires C, 53.6; H, 4.8; N, 8.3; O, 23.8; S, 9.5%).

*Ethyl* 2-(2-*Amino*-4-*fluoroanilino*)-5-*ethylthiophen*-3-*carboxylate* (5b).—A solution of the ester (3b) (1.0 g) in ethanol (100 ml) was hydrogenated at 60 lb in$^{-2}$ over 10% Pd–C (100 mg). The catalyst was filtered off and the solvent removed under vacuum. Crystallisation from hexane and treatment with carbon gave the *amino-ester* (5b) (0.75 g, 84%), m.p. 80—83°, $\nu_{max.}$ 3 440, 3 350, 3 260, and 1 640 cm$^{-1}$; $\lambda_{max.}$ 318 nm (log ε 3.99); δ 1.20 (3 H, t, Me), 1.32 (3 H, t, Me), 2.56 (2 H, q, $CH_2$Me), 3.88 (2 H, s, $NH_2$), 4.22 (2 H, q, $CO_2CH_2$Me), 6.15—7.15 (4 H, aryl), and 8.51 (1 H, s, NH) (Found: C, 58.3; H, 5.6; F, 6.3; N, 9.0; S, 10.4. $C_{15}H_{17}FN_2O_2S$ requires C, 58.4; H, 5.55; F, 6.2; N, 9.1; S, 10.4%).

*Ethyl* 2-(2-*aminoanilino*)-5-*ethylthiophen*-3-*carboxylate* (5a), similarly prepared by reduction of (3a) (88% yield), had m.p. 50—52° (n-hexane), $\nu_{max.}$ 3 420, 3 360, 3 260, and 1 640 cm$^{-1}$; $\lambda_{max.}$ 326 nm (log ε 4.00); δ 1.23 (3 H, t, Me), 1.35 (3 H, t, Me), 2.59 (2 H, q, $CH_2$Me), 3.73 (2 H, s, $NH_2$), 4.26 (2 H, q, $CO_2CH_2$Me), 6.5—7.28 (5 H, aryl), and 8.88 (1 H, s, NH) (Found: C, 62.3; H, 6.41; N, 9.4; O, 11.3; S, 11.1. $C_{15}H_{18}N_2O_2S$ requires C, 62.1; H, 6.24; N, 9.6; O, 11.0; S, 11.0%).

2-*Ethyl*-7-*fluoro*-5,10-*dihydro*-4H-*thieno*[2,3-b][1,5]*benzodiazepin*-4-*one* (6b).—Sodium methylsulphinylmethanide (0.17 mol, 3 equiv.) was prepared by treating sodium hydride (9.1 g, 0.17 mol) with dimethyl sulphoxide (100 ml) at 70 °C under nitrogen (until evolution of hydrogen ceased). The amino-ester (5b) (18.2 g, 0.059 mol) in dimethyl sulphoxide (50 ml) was added slowly, the temperature of the exothermic reaction being kept below 80 °C. The mixture was stirred for 15 min and was then poured onto ice–water (800 ml). The precipitate was filtered off, washed with water, and dried under vacuum at 60 °C. Crystallisation from ethyl acetate gave the pure *lactam* (6b) (11.5 g, 75%), m.p. 210—212°, $\nu_{max.}$ 3 280 and 1 645 cm$^{-1}$; $\lambda_{max.}$ 228 and 248 nm (log ε 4.45 and 4.27); δ 1.23 (3 H, t, Me), 2.58 (2 H, q, $CH_2$Me), 6.3—6.8 (4 H, m, aryl), 8.13 (1 H, s, CONH), and 8.57 (1 H, s, NH); *m/e* 262 ($M^+$), 247 ($M$ — 15), 233 ($M$ — 29), and 219 ($M$ — 43) (Found: C, 59.4; H, 4.25; F, 7.4; N, 10.5; S, 12.0. $C_{13}H_{11}FN_2OS$ requires C, 59.5; H, 4.25; F, 7.2; N, 10.7; S, 12.2%).

2-*Ethyl*-5,10-*dihydro*-4H-*thieno*[2,3-b][1,5]*benzodiazepin*-4-*one* (6a), similarly prepared from (5a) (83% yield), had m.p. 218—220°, $\nu_{max.}$ 3 290, 3 200, and 1 640 cm$^{-1}$; $\lambda_{max.}$ 227 and 257 nm (log ε 4.33 and 4.19); δ 1.20 (3 H, t, Me), 2.60 (2 H, q, $CH_2$Me), 6.70 (1 H, s, thiophen), 6.84 (4 H, s, benzo), 8.34 (1 H, s, NH), and 8.44 (1 H, s, CONH); *m/e* 244 ($M^+$), 229 ($M$ — 15), 205, 201 ($M$ — 43), 149, 143, and 119 (Found: C, 63.6; H, 5.05; N, 11.4; O, 6.7; S, 13.0. $C_{13}H_{12}N_2OS$ requires C, 63.9; H, 4.95; N, 11.5; O, 6.5; S, 13.1%).

*Reaction of Ethyl* 2-(2-*Amino*-4-*fluoroanilino*)-5-*ethylthiophen*-3-*carboxylate* (5b) *with Sodium Hydride*.—A solution of the amino-ester (5b) (0.2 g) in dimethyl sulphoxide (5 ml) was treated with sodium hydride (50% dispersion in oil) (0.05 g, *ca.* 3 equiv.) and warmed on a steam-bath. T.l.c. ($SiO_2$; diethyl ether) after 2 min showed a mixture of starting material, the diazepinone (6b), and a slightly more polar component. After 10 min there was no starting material or diazepinone left. The mixture was poured onto ice and extracted with methylene chloride, and the extracts were washed with water, dried, and evaporated. Crystallisation of the residue from n-hexane and treatment with carbon gave 5-*fluoro*-1-(5-*ethyl*-2-*thienyl*)-1,3-*dihydro*-2H-*benzimidazol*-2-*one* (12) (50 mg), m.p. 162—164°, $\nu_{max.}$ 1 710 cm$^{-1}$; $\lambda_{max.}$ 227 and 281 nm (log ε 4.10 and 3.92); δ 1.38 (3 H, t, $CH_2Me$), 2.83 (2 H, q, $CH_2$Me), 6.4—7.1 (5 H, m, aryl), and 11.45 (1 H, s, NH); *m/e* 262 ($M^+$), 247 ($M$ — 15), 187, 111 ($M$ — 151), 108, and 85 (Found: C, 59.3; H, 4.2; F, 7.5; N, 10.4; S, 12.0. $C_{13}H_{11}FN_2OS$ requires C, 59.5; H, 4.25; F, 7.2; N, 10.7; S, 12.2%).

5-*Ethyl*-2-(2-*nitroanilino*)*thiophen*-3-*carboxylic Acid* (11).

—Ethyl 5-ethyl-2-(2-nitroanilino)thiophen-3-carboxylate (3a) (6.0 g) in ethanol (100 ml) and water (50 ml) was heated to 60 °C with stirring. Sodium hydroxide (5N; 50 ml) was then added and the temperature maintained at 60 °C for 16 h. The mixture was cooled, acidified, and diluted with water, and the solid filtered off and crystallised from ethyl acetate to yield the *acid* (11) (5.5 g, *ca.* 100%), m.p. 189—191° (Found: C, 53.2; H, 4.25; N, 9.4; O, 22.3; S, 10.8. $C_{13}H_{12}N_2O_4S$ requires C, 53.4; H, 4.15; N, 9.6; O, 21.9; S, 11.0%).

2-*Ethyl*-5,10-*dihydro*-4H-*thieno*[2,3-b][1,5]*benzodiazepin*-4-*one* (6a).—The nitro-acid (11) (8.0 g, 0.027 mol) in ethanol (150 ml) was reduced over 10% Pd–C (0.9 g) at 60 lb $in^{-2}$. The catalyst was filtered off, and the solvent removed under vacuum to give 2-(2-aminoanilino)-5-ethylthiophen-3-carboxylic acid, which, without further purification, was dissolved in tetrahydrofuran (200 ml; distilled from $LiAlH_4$). To the solution was added dicyclohexylcarbodi-imide (5.7 g, 0.027 mol) and the mixture was stirred under nitrogen for 16 h. The solid was filtered off, and the filtrate evaporated. The residue was crystallised from carbon tetrachloride to give the lactam (6a) (2.5 g, 37%).

*Methyl* 3-(4-*fluoro*-2-*nitroanilino*)*thiophen*-2-*carboxylate* (8), prepared from methyl 3-aminothiophen-2-carboxylate [2] and 1,4-difluoro-2-nitrobenzene as in method A (yield 36.5%), had m.p. 174—175°, $\nu_{max.}$ 1 675 $cm^{-1}$; δ 3.92 (3 H, s, $CO_2Me$), 7.2—8.0 (5 H, m, aryl), 10.8 (1 H, s, NH) (Found: C, 45.1; H, 3.0; N, 8.9. $C_{12}H_9FN_2O_4S$ requires C, 45.1; H, 3.05; N, 8.5%).

*Methyl* 3-(2-*amino*-4-*fluoroanilino*)*thiophen*-2-*carboxylate* (9), prepared by catalytic reduction of (8) as described earlier (yield 95%), had m.p. 111—113° (Found: C, 54.1; H, 4.15; F, 7.2; N, 10.5; S, 12.0. $C_{12}H_{11}FN_2O_2S$ requires C, 54.1; H, 4.15; F, 7.1; N, 10.5; S, 12.0%).

7-*Fluoro*-4,9-*dihydro*-10H-*thieno*[3,2-b][1,5]*benzodiazepin*-10-*one* (10), prepared by cyclisation of (9) with methylsulphinylmethanide as described in earlier examples (yield 66%), had m.p. 228—230°, $\nu_{max.}$ 3 280 and 1 640 $cm^{-1}$; δ 6.3—7.23 (5 H, m, aryl), 7.97 (1 H, s, NH), and 8.73 (1 H, s, CONH); *m/e* 234 ($M^+$) and 205 ($M$ − 29) (Found: C, 56.2; H, 3.05; F, 8.2; N, 11.8; S, 13.4. $C_{11}H_7FN_2OS$ requires C, 56.4; H, 3.0; F, 8.1; N, 12.0; S, 13.7%).

*Methyl* 4-(4-*Fluoro*-2-*nitroanilino*)*thiophen*-3-*carboxylate* (13).—The freshly generated base from methyl 4-aminothiophen-3-carboxylate hydrochloride [3] (48.5 g, 0.25 mol) was dissolved in dry dimethyl sulphoxide (100 ml). To the stirred solution at 100 °C, under nitrogen, were added 1,4-difluoro-2-nitrobenzene (40 g, 0.25 mol) and triethylamine (35 ml). After 1 h more triethylamine (35 ml) was added, and the heating continued for 40 h. The mixture was chilled and poured onto saturated brine and ethyl acetate. The organic phase was washed with brine, dried, and evaporated. The resulting gum was dissolved in ethyl acetate and the solution filtered through a pad of Florisil. Crystallisation from ethanol gave the *nitro-ester* (13) (9.7%), m.p. 164°, δ 3.93 (3 H, s, $CO_2Me$), 6.97 (1 H, d, thiophen H-5, *J ca.* 3 Hz), 8.12 (1 H, d, thiophen H-2, *J ca.* 3 Hz), 7.0—8.0 (3 H, m, anilino), and 10.75 (1 H, NH, exchanged in $D_2O$) (Found: C, 48.5; H, 2.95; F, 6.6; N, 9.3; S, 10.8. $C_{12}H_9FN_2O_4S$ requires C, 48.6; H, 3.05; F, 6.4; N, 9.5; S, 10.8%).

7-*Fluoro*-4,9-*dihydro*-10H-*thieno*[3,4-b][1,5]*benzodiazepin*-10-*one* (15).—The nitro-ester (13) was catalytically reduced to the amino-ester (14) which, without further purification, was cyclised using methylsulphinylmethanide as described earlier, to give the *diazepinone* (15) in 41.7% yield, m.p. 238° (decomp.), $\nu_{max.}$ 3 300, 1 643, 1 600, and 1 530 $cm^{-1}$; δ[$CDCl_3$–$(CD_3)_2SO$] 6.38 (1 H, d, thiophen H-3, *J ca.* 3 Hz), 7.90 (1 H, d, thiophen H-1, *J ca.* 3 Hz), 6.39—7.05 (3 H, m, benzo), and 9.35 (1 H, NH); *m/e* 234 ($M^+$) and 205 ($M$ − 29) (Found: C, 56.1; H, 3.4; F, 8.5; N, 11.6. $C_{11}H_7FN_2OS$ requires C, 56.4; H, 3.0; F, 8.1; N, 12.0%).

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