FLUORINATED TRICYCLIC NEUROLEPTICS: SYNTHESIS AND PHARMACOLOGY OF 8-FLUORO-4-(4-METHYLPIPERAZINO)-4,5-DIHYDROTHIENO[2,3-*b*]-1-BENZOTHIEPIN*

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Received February 26th, 1979

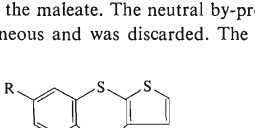
A reaction of (4-fluoro-2-iodophenyl)acetic acid with 2-thiophenethiol gave the acid *V* which was cyclized to 8-fluorothieno[2,3-*b*]-1-benzothiepin-4(5*H*)-one (*VII*); two further steps led to 4-chloro-8-fluoro-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin (*IX*). A substitution reaction with 1-methylpiperazine resulted in the title compound which showed a very strong central depressant and cataleptic activity, being at the same time almost inactive in the test of inhibition of apomorphine stereotypies in rats. Ethyl 2-amino-5-ethylthiophene-3-carboxylate (*X*) was transformed by multi-step procedures to the acids *XV*, *XIX* and *XXVI* out of which only the first one could be cyclized to a tricyclic ketone, *i.e.* 2-ethyldithieno[2,3-*b*; 3',2'-*e*]thiopyran-4-one (*XX*).

In a previous communication of this series[1], we described the synthesis and pharmacology of 4-(4-methylpiperazino)-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin (*I*) which proved a very potent tranquilizer with a mild cataleptic activity. This activity was increased on the one hand by introduction of an atom of chlorine to position 2 (ref.[2]), on the other by introduction of an additional double bond to the position 4(5) (ref.[3]). In connection with our systematic efforts in the field of fluorinated tricyclic neuroleptics[4,5], the present paper deals with the synthesis and pharmacology of the title compound *II*. The purpose of this investigation was to get information on the influence of fluorination in the mentioned position on the intensity and duration of the central depressant and cataleptic activity; the pair of compounds *I* and *II* represents a direct thiophene analogy of the pair of compounds *III* and *IV*, the comparison of which has recently been described[6]. In agreement with the Parent Compound Handbook[7], we prefer for the tricyclic system of compounds *I* and *II* the presently used name to the name used previously[1-3].

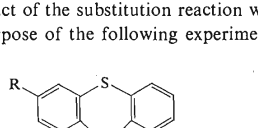
The starting compound of our synthesis was (4-fluoro-2-iodophenyl)acetic acid[6] which was reacted with 2-thiophenethiol[8] in a boiling potassium hydroxide solution in the presence of copper yielding the acid *V*. The same result was obtained if (2-bro-

* Part CXXXIV in the series Neurotropic and Psychotropic Agents; Part CXXXIII: This Journal *44*, 2987 (1979).

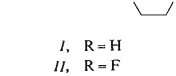
mo-4-fluorophenyl)acetic acid[9] was used but the reaction with 2-thiophenethiol[8] had to be carried out in boiling dimethylformamide in the presence of potassium carbonate and copper. (2-Bromo-4-fluorophenyl)acetic acid[9] was transformed by treatment with ethyl chloroformate and triethylamine in chloroform (for the method, *cf*[9,10]) to the ethyl ester *VI* which, however, proved unsuitable for our purpose: it does not react with 2-thiophenethiol in the presence of potassium carbonate and copper at 130°C. Cyclization of the acid *V* was carried out with phosphorus pentoxide in boiling toluene resulting in 8-fluorothieno[2,3-*b*]-1-benzothiepin-4(5*H*)-one (*VII*). Reduction of this ketone with sodium borohydride in ethanol gave the alcohol *VIII* affording by treatment with hydrogen chloride in benzene 4-chloro-8-fluoro-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin (*IX*). The substitution reaction with 1-methylpiperazine in boiling chloroform yielded about 60% of the base *II* which was transformed to the maleate. The neutral by-product of the substitution reaction was very inhomogeneous and was discarded. The purpose of the following experiments was



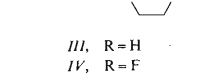
I, R = H
II, R = F



III, R = H
IV, R = F



V



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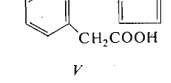
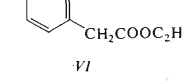


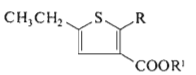
VII

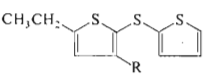


VIII, R = OH
IX, R = Cl

to use the easily accessible ethyl 2-amino-5-ethylthiophene-3-carboxylate (*X*) (ref.[11]) to the synthesis of new potential neurotropic agents in the series of the tricyclic thieno systems. Because of experimental difficulties, these investigations were discontinued in the stage of intermediates. The first necessary step was the substitution

of the amino group in compound *X* with an atom of bromine. An attempt at a direct replacement by diazotization and the following Sandmeyer reaction was unsuccessful and a different way was necessary. The amino group was first eliminated by diazotization and reduction of the diazonium salt with hypophosphorous acid in the presence of ethanol. The ester *XII* was formed which was brominated in the second step by bromine in acetic acid giving the ester *XIII*, the structure of which was confirmed by the ^{1}H-NMR spectrum. Alkaline hydrolysis of the ester *X* gave the new acid *XI* which, however, did not find further synthetic use.



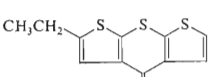


X, R = NH_2, R^1 = C_2H_5
XI, R = NH_2, R^1 = H
XII, R = H, R^1 = C_2H_5
XIII, R = Br, R^1 = C_2H_5

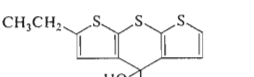
XIV, R = $COOC_2H_5$
XV, R = COOH
XVI, R = CH_2OH

XVII, R = CH_2Cl
XVIII, R = CH_2CN
XIX, R = CH_2COOH

The ester *XIII* was used in three synthetic experiments. The first one was directed towards the ethyldithieno analogue of prothixene with the very little known system of dithieno[2,3-*b*; 3′,2′-*e*]thiopyran[12,13]. A reaction of the bromo ester *XIII* with 2-thiophenethiol[8] at 135°C in the presence of potassium carbonate and copper gave the ester *XIV* in a yield of 70%; the following alkaline hydrolysis led to the acid *XV*. Cyclization with polyphosphoric acid in the presence of boiling toluene resulted in 2-ethyldithieno[2,3-*b*; 3′,2′-*e*]thiopyran-4-one (*XX*), obtained in a moderate yield and characterized by spectra. A reaction of this ketone with 3-dimethylaminopropylmagnesium chloride[14] in tetrahydrofuran afforded the tertiary alcohol *XXI*. This compound is very unstable in the presence of acids; it decomposes already during chromatography on a thin layer of silica gel. For this reason, the attempt at its acid-catalyzed dehydration did not yield the olefinic amine but only decomposition products. We mentioned a similar result of an attempt at the acid catalyzed dehydration of 9-(3-dimethylaminopropyl)-9*H*-thieno[3,2-*b*]-1-benzothiopyran-9-ol[15].



XX

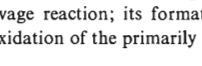


XXI

The second attempt was oriented towards the unknown system of dithieno-[2,3-*b*; 3′,2′-*f*]thiepin. The ester *XIV* was reduced with lithium aluminium hydride

in ether to the alcohol *XVI*. Its treatment with thionyl chloride in benzene gave the crude chloride *XVII* which was transformed by reaction with sodium cyanide in dimethylformamide to the nitrile *XVIII*. Alkaline hydrolysis afforded 5-ethyl--2-(2-thienylthio)thiophene-3-acetic acid (*XIX*). An attempt at its cyclization with phosphorus pentoxide in boiling toluene gave about 50% of an inhomogeneous neutral product which was chromatographed without obtaining, however, any characterized product.

The goal of the last attempt was the synthesis of 2-ethylthieno[2,3-*b*]-1-benzothiepin-5(4*H*)-one. Reaction of the ester *XIII* with thiophenol at 130°C in the presence of potassium carbonate and copper gave the ester *XXII* which was transformed like in the preceding case *via* the alcohol *XXIII*, chloride *XXIV* and nitrile *XXV* to 5-ethyl-2-(phenylthio)thiophene-3-acetic acid (*XXVI*). An attempt at cyclization of this acid by treatment with polyphosphpric acid in boiling toluene gave a neutral product which was identified as diphenyl disulfide[16]. With regard to the fact that this compound was obtained in the theoretical yield, the cleavage reaction took completely place instead of the desired cyclization. Diphenyl disulfide seems to be the primary product of this cleavage reaction; its formation hardly can be explained by a secondarily proceeding oxidation of the primarily formed thiophenol.



XXII, R = $COOC_2H_5$ *XXIV*, R = CH_2Cl
XXIII, R = CH_2OH *XXV*, R = CH_2CN
XXVI, R = CH_2COOH

Compound *II* was pharmacologically evaluated in the form of the maleate and compared with compounds *I*, *III* and *IV*, used likewise in the form of salts; the doses given were calculated for bases. The compounds were administered orally to mice and rats; their acute toxicity in mice was estimated (LD_{50}), further the incoordinating activity in the rota-rod test in mice (medium effective doses ED_{50} bringing about ataxia), inhibition of locomotor activity in the photo-cell method of Dews (medium effective doses D_{50}) and finally the cataleptic activity in rats (medium effective doses ED_{50}). The results are summarized in Table I.

Values in the Table show that the substance *II* has similar acute toxicity like the compounds under comparison, it has higher central depressant activity (incoordinating and locomotor inhibiting activity) and by far, it is the most active in the test of catalepsy. The very high cataleptic activity is a surprise because the compound lacks the „neuroleptic" substituent in position 2 of the skeleton. In the test of antiapomorphine effects in rats, the compound inhibited only the agitation which is, however, another feature of the central depressant activity; the apomorphine chewing was not

influenced: an oral dose of 5 mg/kg decreased the agitation from 100% (control value) to 66% (with statistical significance), the chewing was decreased only to 97%. The lack of activity towards the apomorphine-elicited stereotypies (chewing) indicates that the compound is not a true neuroleptic. We are dealing here with an interesting separation of cataleptic and antiapomorphine activity. The substitution of a benzene ring in perathiepin *III* by a thiophene ring (compound *I*) is connected with an increase of cataleptogenic activity; the simultaneous fluorination leads to an extreme raise of this type of activity. It is interesting to note that in the benzene series (compounds *III* and *IV*), the fluorination alone has an opposite effect.

The effects of compound *II* were also followed from the point of view of their duration, *i.e.* with respect to a possible prolongation. After doses higher than the ED_{50}, the cataleptic and incoordinating activity persists after 24 h only in 20% animals; the locomotor inhibiting and antiapomorphine (agitation) effects disappear within 24 h. The effects do not show any significant prolongation.

EXPERIMENTAL

The melting points of analytical preparations were determined in a Kofler's block and are not corrected; the samples were dried *in vacuo* at 70 Pa over PaO_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (film unless stated otherwise) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$) with a Tesla BS 487C (80 MHz) spectrometer and ^{19}F-NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

TABLE I

Pharmacology of 8-Fluoro-4-(4-methylpiperazino)-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin (*II*) (doses in mg/kg orally)

Compound[a]	Ref.	Name or code number	Acute toxicity LD_{50}	Ataxia ED_{50}	Locomotoric activity D_{50}	Catalepsy ED_{50}
I	1, 2	Peradithiepin	86	2·1	[b]	30
II	—	VÚFB-12·351	80	0·36	0·24	1·4
III	17	Perathiepin	63	2·4	2·4[c]	45
IV	6	VÚFB-12·326	61	0·55	0·48	>50

[a] The compounds were tested in the form of the salts described. [b] D_{50} = 0·065 mg/kg *i.v.* [c] D_{50} = = 0·156 mg/kg *i.v.*

[4-Fluoro-2-(2-thienylthio)phenyl]acetic Acid (*V*)

A. 2-Thiophenethiol[8] (4·2 g), 10·0 g (4-fluoro-2-iodophenyl)acetic acid[6] and 0·4 g "molecular" copper were successively added to a stirred solution of 6·6 g KOH in 30 ml H_2O and the mixture was refluxed for 5·5 h. It was diluted with H_2O, filtered and the filtrate was acidified with hydrochloric acid. The separated product was extracted with chloroform, the extract was dried with Na_2SO_4, filtered with charcoal and evaporated *in vacuo*. The residue was crystallized from 12 ml benzene; 6·0 g (62%) crude acid, m.p. 125–136°C. Analytical sample, m.p. 129–131·5°C (benzene). IR spectrum (Nujol): 712, 849 (Ar—H of thiophene), 800, 870 (2 adjacent and solitary Ar—H of benzene), 931, 1240, 1710, 2540, 2570, 2640, 2740 (COOH), 1483, 1580, 1592, 1604, 3030, 3100 cm^{-1} (Ar). For $C_{12}H_9FO_2S_2$ (268·3) calculated: 53·71% C, 3·38% H, 7·08% F, 23·90% S; found: 54·02% C, 3·44% H, 7·22% F, 23·64% S.

B. A mixture of 23·3 g (2-bromo-4-fluorophenyl)acetic acid[9], 12·8 g 2-thiophenethiol[8], 18 ml dimethylformamide, 2 g Cu and 42 g K_2CO_3 was stirred for 5 h az 160°C (bath temperature). After cooling, it was dissolved in H_2O, filtered with charcoal and the filtrate acidified with hydrochloric acid. The product was isolated by extraction with chloroform. Processing of the extract gave 26 g crude oily acid *V* which was used without purification for further work.

Ethyl (2-Bromo-4-fluorophenyl)acetate (*VI*)

A solution of 29 g (2-bromo-4-fluorophenyl)acetic acid[9] and 12·8 g triethylamine in 125 ml chloroform was stirred and treated at 3–5°C over 15 min with a solution of 13·5 g ethyl chloroformate in 25 ml chloroform, added dropwise. The mixture was stirred for 1 h at room temperature, washed with 200 ml H_2O, 200 ml 2% NaOH and 200 ml H_2O, dried with Na_2SO_4 and distilled; 28·7 g (88%), b.p. 180°C/2·7 kPa. IR spectrum: 672 (C—Br), 860, 890 (2 adjacent and solitary Ar—H), 1160, 1235, 1740 (COOR), 1492, 1590, 1600, 3080 cm^{-1} (Ar). For $C_{10}H_{10}BrFO_2$, (261·1) calculated: 46·00% C, 3·86% H, 30·61% Br, 7·28% F; found: 45·89% C, 3·94% H 30·27% Br, 7·02% F.

8-Fluorothieno[2,3-*b*]-1-benzothiepin-4(5*H*)-one (*VII*)

A mixture of 7·2 g P_2O_5 and a solution of 5·5 g *V* in 40 ml toluene was refluxed for 5·5 h. The toluene solution was separated by decantation, the residue washed with toluene, the combined toluene solutions were washed with 10% NaOH, dried with K_2CO_3 and evaporated; 4·0 g (78%) crude ketone *VII*, m.p. 158–164°C. Analytical sample, m.p. 165–167°C (ethanol). UV spectrum: λ_{max} 257 nm (log ε 4·01), 312 nm (3·66). IR spectrum (Nujol): 800, 815, 829, 869 (2 adjacent and solitary Ar—H), 1480, 1503, 1592 (Ar), 1669 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 7·50 and 7·08 (2 d, J = 5·0 Hz, 2 H, 2,3-H_2), 6·90–7·40 (m, 3 H, 6,7,9-H_3), 4·18 (s, 2 H, $ArCH_2CO$). For $C_{12}H_7FOS_2$ (250·3) calculated: 57·57% C, 2·82% H, 7·59% F, 25·62% S; found: 57·26% C, 2·95% H, 7·49% F, 25·40% S.

8-Fluoro-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin-4-ol (*VIII*)

A stirred suspension of 4·0 g *VII* in 40 ml ethanol was slowly treated with 0·8 g $NaBH_4$ and the solution formed was allowed to stand for 2 h at room temperature. It was then evaporated *in vacuo*, the residue was decomposed with H_2O and extracted with chloroform. The extract was dried with K_2CO_3 and evaporated; 3·8 g (94%) crude *VIII*, m.p. 108–110·5°C. Analytical sample, m.p. 110–111°C (benzene–light petroleum). IR spectrum (Nujol): 789, 841, 878 (2 adjacent and solitary Ar—H), 1036, 1051 (CHOH in a cycle), 1484, 1580, 1599, 3060, 3087 (Ar),

3 330, 3 380 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·70—7·50 (m, 5 H, Ar—H), 4·85 (m, after D_2O dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·58 and 3·30 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·00 (d, J = 8·0 Hz, disappears after D_2O, 1 H, OH). ^{19}F-NMR spectrum: δ —115·6 (dt). For $C_{12}H_9FOS_2$ (252·3) calculated: 57·12% C, 3·59% H, 7·53% F, 25·42% S; found: 57·21% C, 3·61% H, 7·72% F, 25·60% S.

4-Chloro-8-fluoro-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin (*IX*)

A solution of 5·2 g *VIII* in 50 ml benzene was saturated with anhydrous HCl at room temperature in the presence of 3·0 g $CaCl_2$. After standing for 1 h, the mixture was filtered and the filtrate evaporated *in vacuo*; 5·5 g (98%), m.p. 135—140°C. Analytical sample, m.p. 135—140°C (cyclohexane). For $C_{12}H_8ClFS_2$ (270·8) calculated: 53·22% C, 2·98% H, 13·10% Cl, 23·69% S; found: 53·16% C, 2·97% H, 13·31% Cl, 23·48% S.

8-Fluoro-4-(4-methylpiperazino)-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin (*II*)

A mixture of 5·0 g *IX*, 4·7 g 1-methylpiperazine and 25 ml chloroform was refluxed for 4 h. After cooling, it was washed with H_2O and the product was extracted into an excess of 10% H_2SO_4. The acid solution was separated, made alkaline with NH_4OH and the base isolated by extraction with chloroform. The extract was dried with K_2CO_3 and evaporated *in vacuo*; 3·5 g (57%), m.p. 122—125°C. Analytical sample, m.p. 124—126°C (80% ethanol). ^{1}H-NMR spectrum: δ 6·80 to 7·30 (m, 5 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·69 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3). ^{19}F-NMR spectrum: δ —116·8 (dt). For $C_{17}H_{19}FN_2S_2$ (334·5) calculated: 61·04% C, 5·72% H, 5·68% F, 8·38% N, 19·18% S; found: 61·33% C, 5·93% H, 5·85% F, 8·45% N, 19·20% S.

Maleate, m.p. 151—153°C (ethanol–ether). For $C_{21}H_{23}FN_2O_4S_2$ (450·6) calculated: 55·98% C, 5·14% H, 4·22% F, 6·22% N, 14·24% S; found: 56·09% C, 5·31% H, 4·35% F, 6·17% N, 14·06% S.

2-Amino-5-ethylthiophene-3-carboxylic Acid (*XI*)

A solution of 6·0 g *X* (ref.[11]) in 10 ml ethanol was treated with a solution of 3·4 g KOH in 3·5 ml H_2O and the mixture was refluxed for 1 h. Ethanol was evaporated *in vacuo*. The residue was diluted with H_2O, the solution filtered and the filtrate acidified with dilute hydrochloric acid. The precipitated product was filtered, washed with H_2O and dried *in vacuo*; 4·5 g (87%), m.p. 92—94°C with decomposition. Analytical sample, m.p. 97°C decomp. (benzene). For $C_7H_9NO_2S$ (171·2) calculated: 49·10% C, 5·30% H, 8·18% N, 18·73% S; found: 49·63% C, 5·25% H, 8·00% N, 18·12% S.

Ethyl 2-Ethylthiophene-4-carboxylate (*XII*)

A solution of 60 g *X* (ref.[11]) in a mixture of 450 ml ethanol and 450 ml hydrochloric acid was cooled to —2° and under stirring diazotized with a solution of 25 g $NaNO_2$ in 60 ml H_2O. The suspension formed was stirred for 1 h at —2°C and then treated with a cold solution of 159 g $NaH_2PO_2.H_2O$ in 300 ml H_2O. The mixture was stirred for 2 h at —2°C, allowed to stand overnight at 0°C, diluted with 2 l H_2O and extracted with benzene. The extract was dried with $MgSO_4$, filtered with charcoal and the filtrate evaporated *in vacuo*; 24·3 g (44%), b.p. 86°C/0·1 kPa. IR spectrum: 739 and 856 (C—H of thiophene), 1 235, 1 720 (C=C—COOR), 1 550, 3 110 cm^{-1} (C=C—H of thiophene). ^{1}H-NMR spectrum: δ 7·95 (mcs, J = 2·0 Hz, 1 H, 5-H), 7·25

(m, 1 H, 3-H), 4·28 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 2·77 (q, J = 7·0 Hz, 2 H, CH_2 adjacent to thiophene), 1·32 (t, J = 7·0 Hz, 3 H, CH_3 of the ester ethyl), 1·27 (t, J = 7·0 Hz, 3 H, remaining CH_3). For $C_9H_{12}O_2S$ (184·3) calculated: 58·66% C, 6·57% H, 17·40% S; found: 59·10% C, 6·55% H, 17·39% S.

Ethyl 2-Bromo-5-ethylthiophene-3-carboxylate (*XIII*)

A stirred solution of 50 g *XII* in 150 ml acetic acid was treated dropwise over 30 min with a solution of 50 g bromine in 50 ml acetic acid. The mixture was stirred for 1 h, diluted with 800 ml H_2O and extracted with ether. The extract was washed with 2·5% NaOH and H_2O, dried with Na_2SO_4 and distilled; 65·1 g (91%), b.p. 114°C/40 Pa. ^{1}H-NMR spectrum: δ 7·05 (mct, J = 1·0 Hz, 1 H, 4-H), 4·31 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 2·75 (mcq, J = 7·0; 1·0 Hz, 2 H, CH_2 adjacent to thiophene), 1·38 (t, J = 7·0 Hz, 3 H, CH_3 of the ester ethyl), 1·29 (t, J = = 7·0 Hz, 3 H, remaining CH_3). For $C_9H_{11}BrO_2S$ (263·2) calculated: 41·07% C, 4·21% H, 30·37% Br, 12·19% S; found: 41·59% C, 4·22% H, 29·99% Br, 12·01% S.

Ethyl 5-Ethyl-2-(2-thienylthio)thiophene-3-carboxylate (*XIV*)

A mixture of 41·5 g *XIII*, 16·2 g 2-thiophenethiol[8], 0·9 g Cu and 19 g K_2CO_3 was stirred and heated for 4 h to 125—135°C (bath temperature). The melt was then stirred with 70 ml chloroform, filtered with charcoal and the filtrate distilled; 25·3 g (71%), b.p. 174—178°C/40 Pa. For analysis, a sample was redistilled, b.p. 174°C/40 Pa. UV spectrum: λ_{max} 228·5 nm (log ε 4·39), 250 nm (4·10), 310 nm (3·93). IR spectrum: 704, 770, 845 (C—H of thiophene), 1 228, 1 700 cm^{-1} (ArCOOR). ^{1}H-NMR spectrum: δ 7·53 and 7·35 (2 mcd, J = 5·5; 1·0 and 3·5; 1·0 Hz, 2 H, 3,5-H_2 of thienylthio), 7·05 (dd, J = 5·5; 3·5 Hz, 1 H, 4-H of thienylthio), 6·98 (mct, J = 0·5 Hz, 1 H, 4-H), 4·30 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 2·58 (q, J = 6·0 Hz, 2 H, CH_2 adjacent to thiophene), 1·36 (t, J = 7·0 Hz, 3 H, CH_3 of ester ethyl). 1·17 (t, J = 6·0 Hz, 3 H, remaining CH_3). For $C_{13}H_{14}O_2S_3$ (298·5) calculated: 52·31% C, 4·73% H, 32·24% S; found: 51·81% C, 4·96% H, 31·67% S.

Ethyl 5-Ethyl-2-(phenylthio)thiophene-3-carboxylate (*XXII*)

A mixture of 5·2 g *XIII*, 2·2 g thiophenol, 0·3 g Cu and 2·8 g K_2CO_3 was stirred and heated for 4 h to 120—130°C. Processing like in the preceding case gave 4·0 g (69%) product boiling at 154 to 157°C/13 Pa. For analysis, a sample was redistilled, b.p. 154°C/0·1 Torr. UV spectrum: λ_{max} 223 nm (log ε 4·29), infl. 244·5 nm (4·03), 314 nm (3·87). IR spectrum (KBr): 688, 747 (C_6H_5), 847 (C—H of thiophene), 1 170, 1 224, 1 694 (ArCOOR), 1 544, 1 578 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·20—7·80 (m, 5 H, C_6H_5), 7·05 (mct, J = 1·0 Hz, 1 H, 4-H), 4·32 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 2·65 (mcq, J = 7·0; 1·0 Hz, 2 H, CH_2 adjacent to thiophene), 1·38 (t, J = 7·0 Hz, 3 H, CH_3 of ester ethyl), 1·20 (t, J = 7·0 Hz, 3 H, remaining CH_3). For $C_{15}H_{16}O_2S_2$ (292·4) calculated: 61·61% C, 5·52% H; found: 61·58% C, 5·53% H.

5-Ethyl-2-(2-thienylthio)thiophene-3-carboxylic Acid (*XV*)

A mixture of 23·2 g *XIV*, 12·4 g KOH and 23 ml ethanol was refluxed for 2 h. After cooling, it was diluted with H_2O, the solution was acidified with hydrochloric acid and the product extracted with chloroform. The extract was dried with $MgSO_4$ and evaporated. Crystallization of the residue from 40 ml benzene gave 16·8 g (81%) product, m.p. 142·5—144·5°C. Analytical sample, m.p. 146—150°C (benzene). UV spectrum: λ_{max} 228 nm (log ε 4·33), infl. 244·5 nm (4·10),

304 nm (3·88). IR spectrum (KBr): 707, 835 (C—H of thiophene), 923, 1252, 1655, 2580 (ArCOOH), 1545 cm^{-1} (C=C—H of thiophene). For $C_{11}H_{10}O_2S_3$ (270·4) calculated: 48·86% C, 3·73% H, 35·58% S; found: 49·16% C, 3·74% H, 35·24% S.

2-Ethyldithieno[2,3-*b*; 3′,2′-*e*]thiopyran-4-one (*XX*)

A mixture of 30 g polyphosphoric acid and a solution of 5·0 g *XV* in 50 ml toluene was refluxed for 2·5 h under vigorous stirring. After cooling, it was decomposed with 100 ml H_2O and extracted with benzene. The extract was washed with 2·5% NaOH and H_2O, dried with K_2CO_3, filtered with charcoal and evaporated *in vacuo*. The residue (2·8 g) was crystallized from 15 ml ethanol; 1·8 g (39%), m.p. 96·5—100°C. Analytical sample, m.p. 97—98·5°C (ethanol). UV spectrum: λ_{max} 266 nm (log ε 4·49), 304 nm (3·90), 335 nm (3·90). IR spectrum (KBr): 725, 740, 763, 818, 845 (C—H of thiophene), 1064, 1093, 1252 (C—O), 1420 (C=C—H of thiophene), 1610 cm^{-1} (thiophene-CO-thiophene). ^{1}H-NMR spectrum: δ 7·76 (d, J = 5·0 Hz, 1 H, 6-H), 7·43 (mcs, 1 H, 3-H), 7·30 (d, J = 5·0 Hz, 1 H, 5-H), 2·85 (mcq, J = 7·0 Hz, 2 H, CH_2), 1·30 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{11}H_8OS_3$ (252·4) calculated: 52·35% C, 3·19% H, 38·12% S; found: 52·51% C, 3·31% H, 38·38% S.

2-Ethyl-4-(3-dimethylaminopropyl)dithieno[2,3-*b*; 3′,2′-*e*]-thiopyran-4-ol (*XXI*)

A suspension of 1·8 g *XX* in 10 ml tetrahydrofuran was added dropwise to a stirred solution of the Grignard reagent, prepared from 1·7 g 3-dimethylaminopropyl chloride and 0·4 g Mg in 6 ml tetrahydrofuran (ref.[14]). The mixture was stirred for 1 h at room temperature, decomposed under cooling with a solution of 3·0 g NH_4Cl in 12 ml H_2O and extracted with benzene. The extract was dried with K_2CO_3, filtered with charcoal and evaporated. The residue (2·3 g) was crystallized from 15 ml acetone; 1·4 g (58%), m.p. 110—118°C. Analytical sample, m.p. 109—115°C (benzene–light petroleum). UV spectrum: λ_{max} 280 nm infl. (log ε 3·96), 300 nm (4·05). IR spectrum (Nujol): 700, 756, 816, 846 (C—H of thiophene), 1026, 1031, 1059 (C—OH in a cycle), 2700, 2775, 2820 (dimethylamino), 3069, 3090 (C=C—H of thiophene), infl. 3200 cm^{-1} (OH···N). ^{1}H-NMR spectrum: δ 7·18 (s, 2 H, 5,6-H_2), 6·90 (mcs, 1 H, 3-H), 6·40 (bs, 1 H, OH), 2·80 (q, J = 7·0 Hz, 2 H, CH_2 adjacent to thiophene), 2·10 (s, 6 H, CH_3NCH_3), 2·12 and 2·40 (2 t, 4 H, CH_2—C—CH_2N), 1·30 (t, J = 7·0 Hz, 3 H, C—CH_3), *c.* 1·30 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{16}H_{21}NOS_3$ (339·6) calculated: 56·59% C, 6·23% H, ·13% N, 28·33% S; found: 56·63% C, 6·25% H, 4·14% N, 28·38% S.

5-Ethyl-2-(2-thienylthio)thiophene-3-methanol (*XVI*)

A solution of 6·2 g *XIV* in 15 ml ether was added dropwise to a stirred suspension of 0·9 g $LiAlH_4$ in 60 ml ether. The mixture was refluxed for 2 h, cooled, decomposed with 2 ml H_2O and 28 ml 1 : 4 dilute hydrochloric acid. The organic layer was separated, washed with H_2O. dried with K_2CO_3 and distilled; 4·4 g (80%), b.p. 166°C/30 Pa. IR spectrum: 700, 842 (C—H of thiophene), 1050 (CH_2OH), 1218 (C—O), 3350 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·22 and 7·08 (2 mcd, J = 5·5; 1·0 and 3·5; 1·0 Hz, 2 H, 3,5-H_2 of thienylthio), 6·89 (dd, J = 5·0; 3·5 Hz, 1 H, 4-H of thienylthio), 6·75 (mct, J = 0·5 Hz, 1 H, 4-H), 4·70 (s, 2 H, CH_2O), 2·71 (q, J = 6·0 Hz, 2 H, CH_2 of ethyl), 2·00 (s, 1 H, OH), 1·25 (t, J = 6·0 Hz, 3 H, CH_3). For $C_{11}H_{12}OS_3$ (256·4) calculated: 51·52% C, 4·72% H, 37·52% S; found: 51·10% C, 4·84% H, 37·66% S.

5-Ethyl-2-(phenylthio)thiophene-3-methanol (*XXIII*)

XXII (27·0 g) was reduced with 3·5 g $LiAlH_4$ in 300 ml ether like in the preceding case. Processing gave 20·8 g (90%), b.p. 155–160°C/13 Pa. IR spectrum: 687, 738 (C_6H_5), 841 (C—H of thiophene), 1022, 1056 (CH_2OH), 1479, 1581 (Ar), 3350 cm^{-1} (OH). For $C_{13}H_{14}OS_2$ (250·4) calculated: 62·36% C, 5·64% H, 25·62% S; found: 62·82% C, 5·76% H, 25·33% S.

3-(Chloromethyl)-5-ethyl-2-(2-thienylthio)thiophene (*XVII*)

A stirred solution of 20·0 g *XVI* in 45 ml benzene was treated dropwise with 14·5 g $SOCl_2$ at 70°C. The mixture was refluxed for 1 h and evaporated *in vacuo*. The oily residue (21·9 g, almost 100%) was used for further work without purification.

3-(Chloromethyl)-5-ethyl-2-(phenylthio)thiophene (*XXIV*)

The reaction of 12·5 g *XXIII* and 9·0 g $SOCl_2$ in 30 ml benzene was carried out like in the preceding case. The crude product obtained was distilled; 10·6 (79%), b.p. 156°C/50 Pa. IR spectrum 685, 738 (C_6H_5), 837 (C—H of thiophene), 1479, 1582, 3070 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·14 (m, 5 H, C_6H_5), 6·89 (mct, J = 0·5 Hz, 1 H, 4-H), 4·58 (s, 2 H, CH_2Cl), 2·78 (mcq: J = 7·0; 0·5 Hz, 2 H, CH_2 of ethyl), 1·28 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{13}H_{13}ClS_2$ (268·8), calculated: 58·08% C, 4·87% H, 13·19% Cl, 23·86% S; found: 58·46% C, 4·82% H, 13·23% Cl, 23·49% S.

5-Ethyl-2-(2-thienylthio)thiophene-3-acetonitrile (*XVIII*)

A solution of 21·9 g crude *XVII* in 30 ml dimethylformamide was treated with 5·9 g NaCN and the mixture was stirred for 2 h at room temperature. After standing overnight, it was diluted with 200 ml H_2O and extracted with chloroform. The extract was dried with K_2CO_3 and distilled; 15·3 g (72%), b.p. 170°C/80 Pa. ^{1}H-NMR spectrum: δ 7·28 (mcd, J = 5·0 Hz, 1 H, 5-H of thienylthio), 7·12 (mcd, J = 3·5 Hz, 1 H, 3-H of thienylthio), 6·90 (dd, J = 5·0; 3·5 Hz, 1 H, 4-H of thienylthio), 6·80 (mcs, 1 H, 4-H), 3·80 (s, 2 H, CH_2CN), 2·76 (mcq, J = 7·5 Hz, 2 H, CH_2 of ethyl), 1·26 (t, J = 7·5 Hz, 3 H, CH_3). For $C_{12}H_{11}NS_3$ (265·4) calculated: 54·30% C, 4·18% H, 5·28% N, 36·24% S; found: 54·30% C, 4·30% C, 5·43% N, 36·48% S.

5-Ethyl-2-(phenylthio)thiophene-3-acetonitrile (*XXV*)

The reaction of 10·3 g *XXIV* and 2·8 g NaCN in 15 ml dimethylformamide was carried out like in the preceding case. Processing gave 8·5 g (86%) oil, b.p. 168°C/50 Pa. IR spectrum: 683, 736 (C_6H_5), 830 (C—H of thiophene), 1478, 1542, 1580 (Ar), 2253 cm^{-1} (R—CN). ^{1}H-NMR spectrum: δ *c.* 7·15 (m, 5 H, C_6H_5), 6·90 (mcs, J = 0·5 Hz, 1 H, 4-H), 3·55 (s, 2 H, CH_2CN), 2·80(mcq, J = 7·0; 0·5 Hz, 2 H, CH_2 of ethyl), 1·29 (t, J — 7·0 Hz, 3 H, CH_3). For $C_{14}H_{13}NS_2$ (259·4) calculated: 64·82% C, 5·05% H, 5·40% N, 24·73% S; found: 65·02% C, 5·10% H, 5·08% N, 24·52% S.

5-Ethyl-2-(2-thienylthio)thiophene-3-acetic Acid (*XIX*)

A mixture of 15·3 g *XVIII*, 17·0 g KOH, 4 ml H_2O and 20 ml ethanol was stirred and refluxed for 3 h. It was then dissolved in H_2O, the solution was filtered and the filtrate acidified with hydrochloric acid. The product. was isolated by extraction with chloroform. Processing of the extract and crystallization of the crude product from 60 ml cyclohexane gave 14·5 g (89%) solid

melting at 71—76·5°C. Analytical sample, m.p. 75—78°C (cyclohexane). ^{1}H-NMR spectrum: δ 10·65 (bs, 1 H, COOH), 7·14 (mcd, J = 5·0; 1·2 Hz, 1 H, 5-H of thienylthio), 7·01 (mcd, J = = 3·5; 1·2 Hz, 1 H, 3-H of thienylthio), 6·56 (dd, J = 5·0; 3·5 Hz, 1 H, 4-H of thienylthio), 6·60 (mcs, 1 H, 4-H), 3·75 (s, 2 H, CH_2CO), 2·68 (q, J = 7·0 Hz, 2 H, CH_2 of ethyl), 1·20 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{12}H_{12}O_2S_3$ (284·4) calculated: 50·67% C, 4·25% H, 33·83% S; found: 50·66% C, 4·34% H, 33·48% S.

5-Ethyl-2-(phenylthio)thiophene-3-acetic Acid (*XXVI*)

A mixture of 8·2 g *XXV*, 8·5 g KOH, 5 ml H_2O and 10 ml ethanol was processed like in the preceding case. There were obtained 7·6 g (86%) product melting at 73—75°C (cyclohexane). IR spectrum (Nujol): 690, 740 (C_6H_5), 836 (C—H of thiophene), 923, 1227, 1714, 3180 (COOH), 1480, 1582 cm^{-1} (Ar). For $C_{14}H_{14}O_2S_2$ (278·4) calculated: 60·40% C, 5·07% H, 23·04% S; found: 60·41% C, 5·12% H, 22·78% S.

In an attempt to cyclize the acid *XXVI*, a mixture of 3·0 g *XXVI*, 40 ml toluene and 22 g polyphosphoric acid was refluxed for 7 h. After cooling and decomposition with H_2O, it was extracted with toluene. The extract was washed with 10% NaOH and H_2O, dried and evaporated. The residue (1·1 g, 100%) was identified as diphenyl disulfide, m.p. 64—66°C (methanol). For $C_{12}H_{10}S_2$ (218·3) calculated: 66·01% C, 4·62% H, 29·37% S; found: 66·16% C, 4·69% H, 28·90% S. The literature[16] reported for diphenyl disulfide a m.p. of 60—61°C.

The authors are indebted to Drs J. Holubek and E. Svátek (Department of physical chemistry of this institute) for recording and interpreting the spectra reported, and to Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech, Mrs J. Kropáčová and Mrs A. Slaviková (Department of analytical chemistry of this institute) for carrying out the analyses.

REFERENCES

1. Rajšner M., Metyšová J., Protiva M.: Farmaco, Ed. Sc. (Pavia) *23*, 140 (1968).
2. Rajšner M., Metyšová J., Protiva M.: This Journal *35*, 378 (1970).
3. Šindelář K., Metyšová J., Protiva M.: This Journal *36*, 3404 (1971).
4. Protiva M.: Conf. Org. Chem. *Biologically Active Compounds*, Smolenice, April 1976; Proc. Conf., p. 72, (Pub. 196).
5. Protiva M.: Pharmazie *34*, 274 (1979).
6. Protiva M., Šindelář K., Šedivý Z., Metyšová J.: This Journal *44*, 2108 (1979).
7. *Parent Compound Handbook*, Ring Parents I, GSLGY. Chemical Abstracts Service, August 1976.
8. Houff W. H., Schuetz R. D.: J. Amer. Chem. Soc. *75*, 6316 (1953).
9. Rajšner M., Svátek E., Metyšová J., Bartošová M., Mikšík F., Protiva M.: This Journal *42*, (1977).
10. Rajšner M., Mikšík F., Protiva M.: This Journal *43*, 1276 (1978).
11. Gewald K., Schinke E., Böttcher H.: Chem. Ber. *99*, 94 (1966).
12. Apitzsch H.: Ber. Deut. Chem. Ges. *41*, 4047 (1908).
13. Grol C. J.: Tetrahedron *30*, 3621 (1974).
14. Protiva M., Rajšner M., Adlerová E., Seidlová V., Vejdělek Z. J.: This Journal *29*, 2161 (1964).
15. Rajšner M., Metyš J., Kakáč B., Protiva M.: This Journal *40*, 2905 (1975).
16. Rosenmund K. W., Harms H.: Ber. Deut. Chem. Ges. *53*, 2226 (1920).
17. Šindelář K., Metyšová J., Protiva M.: This Journal *34*, 3801 (1969).

Translated by the author (M.P.).