FLUORINATED ANALOGUES OF THE TRICYCLIC NEUROLEPTICS; 7-FLUORO AND 7-TRIFLUOROMETHYL DERIVATIVE OF 10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN*

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Reaction of 3-fluorothiophenol with (2-iodophenyl)acetic acid gave the acid *VIII* which was cyclized with polyphosphoric acid to the ketone *XII*. The first title compound *VI* was prepared *via* the intermediates *XV* and *XVIII*. Treatment of the ketone *XII* with 1-methylpiperazine in the presence of titanium tetrachloride resulted in the enamine *XXIII*. The similarly prepared acid *IX* was cyclized to the ketone *XIII*. By-products were the di-acid *X* and the enol-lactone *XXIV*, affording by alkaline hydrolysis the keto acid *XXV*. The synthesis of the second title compound *VII* was carried out from the ketone *XIII via* the intermediates *XVI* and *XIX*. 10,11-Dihydrodibenzo[*b*,*f*]thiepin-3,11-diol (*XVII*) gave by treatment with methanesulfonyl chloride and by the following reaction with 1-methylpiperazine the salt of 1-methylpiperazine with dibenzo[*b*,*f*]thiepin-3-ol (*XXII*) and 1-methyl-4-(methylsulfonyl)piperazine (*XXVI*). Whereas the compound *VI* has low central depressant and cataleptic activity, the corresponding enamine *XXIII* is very potent in both lines. The trifluoromethyl derivative *VII* has the character of a neuroleptic but its depressant and cataleptic activity are ten times lower than those of the 8-trifluoromethyl isomer.

After the discovery of the neuroleptic activity of perathiepin (*I*) (ref.[1-3]) and especially its 8-chloro derivative clorothepin (*II*) (ref.[1,4,5]), all of the possible Ar-monochloro derivatives of perathiepin were prepared[6-8] and it was found that in addition to the 8-chloro compound only the 7-chloro derivative *V* has a clear cataleptic activity. The interest of the position 7 for localization of a substituent in neuroleptic derivatives of perathiepin (*I*) was also shown by some 2,7- and 7,8-disubstituted, and 3,7,8-trisubstituted derivatives[9-12]. In these cases, indeed, in which the 7-substituent was mostly the fluorine atom it was not possible to evaluate precisely its active contribution to the overall effect of the compounds with respect to the presence of further substituents. This was the reason for carrying out the present investigation. We are describing here the synthesis and pharmacology of three 7-monosubstituted compounds: fluoro derivative *VI*, the corresponding enamine

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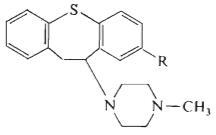
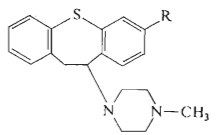
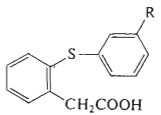
XXIII and the trifluoromethyl derivative *VII*. The activity of the present compounds may be compared with that of the following isomers, described in the preceding communications of this series: 2-fluoro[9], 3-fluoro[13], 6-fluoro[14], 8-fluoro (*III*) (ref.[4,10]), 2-trifluoromethyl[15] and 8-trifluoromethyl (*IV*) (ref.[16]). Out of the 7-monosubstituted derivatives of perathiepin (*I*), only the 7-methoxy derivative[17] was prepared in addition to the chloro compound *V*; unsuccessfull attempts at preparing the 7-hydroxy compound were described[18].



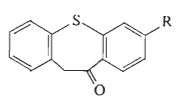
I, R = H
II, R = Cl
III, R = F
IV, R = CF_3



V, R = Cl
VI, R = F
VII, R = CF_3



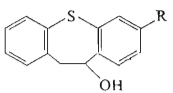
VIII, R = F
IX, R = CF_3
X, R = COOH
XI, R = OCH_3



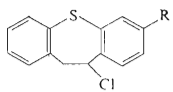
XII, R = F
XIII, R = CF_3
XIV, R = COOH

In the synthesis of the 7-fluoro derivatives *VI* and *XXIII* we started from the reaction of 3-fluorothiophenol[19] with (2-iodophenyl)acetic acid[20] in a boiling aqueous solution of potassium hydroxide in the presence of copper resulting in [2-(3-fluorophenylthio)phenyl]acetic acid (*VIII*). Its cyclization with polyphosphoric acid at 125°C gave in a high yield a homogeneous product which was identified as the desired 7-fluoro ketone *XII*; the formation of the isomeric 9-fluoro ketone was not observed at all (*cf.*[6,10]). Reduction of the ketone *XII* with sodium borohydride in aqueous ethanol afforded the alcohol *XV* which was transformed by treatment with hydrogen chloride in benzene at room temperature to the chloro compound

XVIII. Its substitution reaction with 1-methylpiperazine in boiling chloroform resulted in the desired base *VI* in a yield of 68%; 3-fluorodibenzo[*b*,*f*]thiepin (*XX*) (ref.[13]) was isolated in a small amount as the by-product, formed by the simultaneous elimination reaction. The ketone *XII* was treated with 1-methylpiperazine and titanium tetrachloride in boiling benzene and the enamine *XXIII* was obtained. All of the reactions mentioned are analogies of procedures commonly used in this series[2,4,9–16].



XV, R = F
XVI, R = CF_3
XVII, R = OH



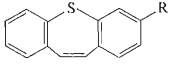
XVIII, R = F
XIX, R = CF_3

The synthesis of the trifluoromethyl derivative *VII* was started some time ago but discontinued because of the low yield in the step of cyclization[16]. Difficulties in the cyclization reactions of the trifluoromethyl compounds with polyphosphoric acid are common in this series and their reason is the hydrolysis of the trifluoromethyl group to carboxyl, followed by further side reactions[11,15,21]. The starting acid *IX*, the preparation of which was described[16] from 2-(3-trifluoromethylphenylthio)benzoic acid by a four-step homologization procedure, has now been obtained directly from (2-iodophenyl)acetic acid[20] and 3-trifluoromethylthiophenol[16,22–24]. In an attempt to cyclize the acid *IX* with phosphoric acid at 140–150°C, the dicarboxylic acid *X* was obtained as the main product; only the hydrolysis of the trifluoromethyl group took place. When 1,2-dichlorobenzene was used as the medium, it was possible to heat the mixture with polyphosphoric acid to 180°C without effecting the hydrolysis of the trifluoromethyl and the ketone *XIII* was obtained in a yield of 73%. The dicarboxylic acid *X* could also be cyclized in 1,2-dichlorobenzene by treatment with polyphosphoric acid and at 100°C, the keto acid *XIV* resulted as the main product, described already in our previous paper[16]. Both cyclization reactions produce the same minor by-product, an orange-coloured compound having according to the mass spectrum and analysis the composition $C_{15}H_{18}O_2S$. The IR spectrum identified an unsaturated γ-lactone carbonyl (ν(C=O) 1738 cm^{-1}) and the UV spectrum indicated a strong conjugation. The compound has evidently the structure of the enol-lactone *XXIV* which was proven by its alkaline hydrolysis to the keto acid *XXV*, isomeric with the acid *XIV*. Compounds *XXIV* and *XXV* are remarkable by the presence of a substituent in the unusual position 9 of the dibenzo[*b*,*f*]thiepin skeleton. We are dealing here with a precise analogy

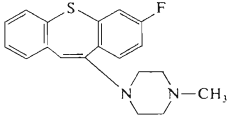
of phenomena observed already in the cyclization of 2-[2-(4-chloro-3-trifluoromethylphenylthio)phenyl]acetic acid[11]. The formation of the lactone *XXIV* in the cyclization of the dicarboxylic acid *X* shows that this acid affords surprisingly in addition to the expected product *XIV* also the isomeric 9-substituted product *XXV*, cyclizing smoothly to the enol-lactone. The possibilities of formation of enol-lactones of the present type were discussed in detail in connection with the mentioned chlorinated product[11]. The ketone *XIII* was transformed like in the preceding case *via* the intermediates *XVI* and *XIX* to the base *VII*. 3-Trifluoromethyldibenzo[*b*,*f*]thiepin (*XXI*) was the by-product of the final substitution reaction.

We already mentioned the unsuccessful attempts to prepare the 7-hydroxy derivative of perathiepin which is a potential metabolite of this psychotropic agent[18]: attempts to demethylate the 7-methoxy derivative of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin with boron tribromide led to the elimination of 1-methylpiperazine. Recently, we have described a method for preparing the phenolic derivatives of the 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin series where the demethylation is carried out in the stage of stable intermediates, *i.e.* methoxy ketones[25]; we have tried now to apply this method to the present case. The starting acid *XI* (ref.[17]) was prepared similarly like in the preceding cases, *i.e.* by a reaction of (2-iodophenyl)acetic acid[20] with 3-methoxythiophenol[26]. This acid was transformed in four steps by a described procedure[17] to 10,11-dihydrodibenzo[*b*,*f*]thiepin-3,11-diol (*XVII*). This was subjected to the treatment with methanesulfonyl chloride in dichloromethane in the presence of triethylamine. The formation of the dimethanesulfonate was supposed which, however, was not isolated and characterized, but used in crude state for the reaction with 1-methylpiperazine. Substitution in position 11 and the aminolysis in position 3 were expected. For preventing the cleavage of the unstable product in the usual isolation procedures, the reaction mixture was only diluted with benzene and the solution was chromatographed on alumina. 1-Methyl-4-(methylsulfonyl)piperazine (*XXVI*) (ref.[27,28]) was eluted first as the least polar product; we are dealing here with a product of the expected aminolysis. A rather polar compound was obtained as the main product; its analysis corresponds to $C_{19}H_{22}N_2OS$ which is in agreement with the composition of the desired product. The mass spectrum, however, did not confirm the presence of the expected molecular ion (326); on the contrary, molecular ions with *m*/e 226 and 100 are present. The substance appears thus as a mixture of dibenzo[*b*,*f*]-thiepin-3-ol (*XXII*) and 1-methylpiperazine. The ^{1}H-NMR spectrum led to the same conclusion: the olefinic protons in positions 10 and 11 (compound *XXII*) were clearly identified. With regard to the fact that the substance behaves like a chemical individual, it is necessary to conclude that we are dealing here with a salt of phenol *XXII* with 1-methylpiperazine. Treatment of this salt with maleic acid in solution led to anion exchange and 1-methylpiperazine bis(hydrogen maleate) was obtained. The decomposition of the salt with ammonium hydroxide enabled the isolation of the

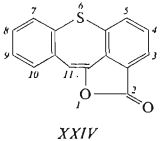
free phenol *XXII*. A new attempt to synthesize the 7-hydroxy derivative of perathiepin was thus unsuccessful again. It is not clear in which stage the cleavage occurred because the product of the reaction of the diol *XVII* with methanesulfonyl chloride was not characterized. The most probable explanation is that this product was not the expected dimesylate and that already in this step the elimination took place and for further reaction only the methanesulfonate of *XXII* was used.



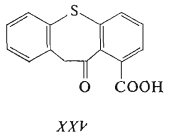
XX, R = F
XXI, R = CF_3
XXII, R = OH



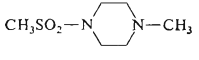
XXIII



XXIV



XXV



XXVI

Compounds *VI*, *VII* and *XXIII* were evaluated pharmacologically as potential neuroleptics. The described salts were used for testing but the doses given were calculated for bases. The basic results are summarized in Table I which includes compounds *I*–*V* for the sake of comparison. The acute toxicity in mice after oral or intravenous administration (LD_{50} values) is given in the first line. The rota-rod test was used as a criterion of the central depressant action indicating disturbances of the motor coordination; the medium effective doses (after oral or intravenous administration) bringing about ataxia (in the interval of maximum activity) are given. Finally, the cataleptic activity in rats after oral or intraperitoneal administration was estimated; the indicated medium effective doses ED_{50} bring about catalepsy in 50% animals.

The following conclusions may be drawn from the data given in the table: *a*) all the three new 7-substituted perathiepin derivatives have cataleptic activity, *b*) the 7-fluoro derivative of perathiepin (*VI*) is 2–3 times less toxic and in both of the tests used

less active than the 8-fluoro isomer (*III*), *c*) a direct comparison of the fluoro compound *VI* with the chloro analogue *V* is not possible with regard to the different way of administration used, *d*) the 7-trifluoromethyl derivative *VII* is only slightly less toxic but in both tests 10 times less active than the 8-trifluoromethyl isomer *IV*, *e*) out of the new compounds, the enamine *XXIII* is the most active one being 4 times more active than clorothepin (*II*) in the test of catalepsy. In general, in the perathiepin series (10,11-dihydro compounds), the 8-substitution is more favourable than the 7-substitution with regard to the activities. In the series of enamines, this relation is less clear[10].

Compound *VI* was also tested with regard to the possible prolongation of effects. It was found, however, that 24 hours after the administration, the effects disappeared practically. Compound *VII* was tested for the antihistamine effect. In the test of histamine aerosol in guinea-pigs, the medium effective dose protecting 50% animals from the effect of histamine, PD_{50} = 0·45 mg/kg intraperitoneally. In the test of detoxication of the parenterally administered histamine in guinea-pigs, a subcutaneous dose of 10 mg/kg compound *VII* rendered protection to 40% animals from the toxic

TABLE I

Pharmacological Effects of the 7-Substituted 10-(4-Methylpiperazino)dibenzo[*b*,*f*]thiepins and Standards (doses in mg/kg)

Compound[a]	Code number or generic name	Administration[b]	Acute toxicity LD_{50}	Ataxia ED_{50}	Catalepsy ED_{50}
I (ref.[3])	Perathiepin	*p.o.*	62·7	2·4	45
I (ref.[3])	Perathiepin	*i.v./i.p.*	42·3	0·19	10
II (ref.[5])	Clorothepin	*p.o.*	78	2·2	4·3
II (ref.[5])	Clorothepin	*i.v./i.p.*	46·3	0·06	2·4
III (ref.[10])	Fluothepin	*p.o.*	102	3·3	20
III (ref.[29])	Fluothepin	*i.v./i.p.*	42	0·12	2·7
IV (ref.[16])	Trifluthepin	*i.v./i.p.*	32	0·09[c]	0·68
V (ref.[6])	VÚFB- 5.921	*i.v./i.p.*	70	2·0	4·5
VI	VÚFB-12.297	*p.o.*	200	9·2	50
VII	VÚFB-12·493	*i.v./i.p.*	51	0·85	6·4
XXIII	VÚFB-12.287	*p.o.*	190	1·3	0·95

[a] The compounds were tested in the form of salts described in the Experimental or in the indicated papers. [b] Intraperitoneal administration relates only to the test of catalepsy. [c] In reference[16] this value was erroneously given as being 86 mg/kg instead of 86 μg/kg.

effect of histamine. In both tests, the compound is about 10 times weaker than dithiadene[30]. A similar activity was reported earlier for the 7-methoxy derivative of perathiepin[17].

Compounds *VI*, *VII* and *XXIII* were also tested for antimicrobial activity *in vitro* (Dr J. Turinová and Dr A. Čapek, bacteriological department of this Institute). The used microorganisms, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *VI* 25, *VII* 12·5, *XXIII* 25; *Streptococcus faecalis*, *VI* 50, *VII* 12·5, *XXIII* 50; *Staphylococcus pyogenes aureus*, *VI* 100, *VII* 12·5, *XXIII* 25; *Escherichia coli*, *VII* 12·5; *Proteus vulgaris*, *VI* 100; *Mycobacterium tuberculosis* H37Rv, *VI* 6·25, *VII* 3·12; *XXIII* 12·5; *Saccharomyces pasterianus*, *VI* 50, *VII* 12·5, *XXIII* 50; *Trichlophyton mentagrophytes*, *VI* 50, *VII* 25, *XXIII* 25.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler block and are not corrected; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were registered with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) were produced 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 mass spectra were recorded on a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

[2-(3-Fluorophenylthio)phenyl]acetic Acid (*VIII*)

A solution of 10 g KOH in 100 ml water was successively treated with 6·4 g 3-fluorothiophenol[19], 13·0 g (2-iodophenyl)acetic acid[20] and 1 g "molecular copper". The mixture was refluxed under stirring for 7 h, cooled to 35°C and filtered. The filtrate was acidified with 3M-HCl and the product filtered after 3 h of standing at room temperature, washed with water and dried *in vacuo*; 10·0 g (77%), m.p. 101—104°C. Analytical sample, m.p. 103—105°C (cyclohexane). IR spectrum: 750, 770, 780, 862, 876, 884 (4 and 3 adjacent and solitary Ar-H), 950, 1218, 1245, 1710, 2570, 2640, 2750 (COOH), 1479, 1580, 1600 cm^{-1} (Ar). For $C_{14}H_{11}FO_2S$ (262·3) calculated: 64·10% C 4·23% H, 7·24% F, 12·22% S; found: 64·04% C, 4·22% H, 7·26% F, 12·14% S.

[2-(3-Trifluoromethylphenylthio)phenyl]acetic Acid (*IX*)

A mixture of 40 g KOH in 370 ml water, 34 g 3-trifluoromethylthiophenol[16,22–24], 48 g (2-iodophenyl)acetic acid[20] and 1·5 g Cu was refluxed for 14 h and filtered with charcoal while hot. The filtrate was acidified with hydrochloric acid, the crude product filtered and crystallized from 50 ml 85% aqueous ethanol; 31·3 g (55%), m.p. 90—92°C. Analytical sample, m.p. 91—92°C (benzene–light petroleum). IR spectrum: 700, 763, 805, 898 (4 and 3 adjacent and solitary Ar—H), 920, 1242, 1718, 2565, 2640, 2740, 3140 (COOH), 1140, 1160, 1327 ($ArCF_3$), 1586, 1600, 3072 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 10·95 (bs, 1 H, COOH), 7·00—7·50 (m, 8 H, Ar—H), 3·80 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR: δ —63·6 (s, 3 F). For $C_{15}H_{11}F_3O_2S$ (312·3) calculated: 57·68% C, 3·55% H, 18·25% F, 10·27% S; found: 57·61% C, 3·62% H, 18·56% F, 10·54% S. This acid was prepared earlier[16] by hydrolysis of the nitrile and obtained in the form of a hemihydrate melting at 68·5—70·5°C.

[2-(3-Methoxyphenylthio)phenyl]acetic Acid (*XI*)

Was prepared similarly like in the preceding case from 52 g 3-methoxythiophenol[26], 92 g (2-iodophenyl)acetic acid[20], 80 g KOH in 710 ml water and 2 g Cu; 73 g (76%), m.p. 61—63°C. A sample was crystallized from a mixture of benzene and light petroleum, m.p. 63—64°C. For this product, prepared differently, we reported[17] a m.p. of 65—66°C.

7-Fluorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XII*)

A mixture of 113 g *VIII* and 570 g polyphosphoric acid was stirred and heated for 5 h to 125 to 130°C. After standing overnight, it was decomposed with 1 kg mixture of ice and water and the product was extracted with benzene. The extract was washed with water, 5% NaOH and water, dried with $MgSO_4$ and evaporated under reduced pressure; 102 g (98%) crude ketone, m.p. 111—113°C. Analytical sample, m.p. 114—115°C (ethanol). UV spectrum: λ_{max} 245 nm (log ε 4·26) 263 nm (4·00), infl. 271 nm (3·90), 319 nm (3·56). IR spectrum: 749, 770, 824, 888, 900 (4 and 2 adjacent and solitary Ar—H), 1211, 1242 (CO), 1569, 1599, 3080 (Ar), 1678 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 8·15 (dd, J_{H-H} = 8·0 Hz; J_{H-F} = 6·0 Hz, 1 H, 9-H), 6·80—7·70 (m,6 H, remaining Ar—H), 4·30 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR: δ —106·0 (m.) For $C_{14}H_9FOS$ (244·3) calculated: 68·83% C, 3·71% H, 7·78% F, 13·13% S; found: 68·78% C, 3·62% H, 7·93% F, 12·93% S.

[2-(3-Carboxyphenylthio)phenyl]acetic Acid (*X*)

A mixture of 25 g 100% H_3PO_4 and 5·0 g *IX* was stirred and heated for 5 h to 140—150°C, and decomposed with water. The precipitated solid was filtered and crystallized from a mixture of benzene and acetone; 4·5 g (98%), m.p. 180—193°C. Analytical sample, m.p. 205—206°C (acetic acid). UV spectrum: λ_{max} 225 nm (log ε 4·27), 250 nm (4·05), infl. 275 nm (3·77), infl. 310 nm (3·18). IR spectrum (KBr): 712, 749, 764 (Ar-H), 956, 1300, 1700, 2555 (COOH), 1476, 1576, 1591 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·70 (m, 2 H, Ar—H adjacent to the benzoic acid carboxyl), 7·30 (m, 6 H, remaining Ar—H), 3·70 (s, 2 H, $ArCH_2CO$). For $C_{15}H_{12}O_4S$ (288·3) calculated: 62·49% C, 4·20% H, 11·12% S; found: 62·48% C, 4·26% H, 10·88% S.

7-Trifluoromethyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIII*)

A mixture of polyphosphoric acid (prepared from 120 g P_2O_5 and 60 ml 85% H_3PO_4), 15 g *IX* and 300 ml 1,2-dichlorobenzene was stirred and refluxed for 6 h (bath of 190°C). After partial cooling, it was decomposed with water, filtered, the organic layer was separated, washed with 5% NaOH and water, dried with $MgSO_4$ and evaporated. The residue was dissolved in light petroleum and a small amount of an orange-coloured solid was filtered off. The filtrate was evaporated and the residue crystallized; 10·3 g (73%) *XIII*, m.p. 92—93·5°C. For this ketone, prepared differently, we reported[16] a m.p. of 89—91°C.

The undissolved orange substance was recrystallized from a mixture of benzene and light petroleum; 20 mg [1]benzothiepino[4,3,2-*cd*]isobenzofuran-2-one (*XXIV*) (*cf.*[31]), m.p. 132 to 135°C, then resolidification and a second melting at 142—143°C. Mass spectrum, *m/e*: 252 (M^+, corresponds to $C_{15}H_8O_2S$). UV spectrum: λ_{max} 257 nm (log ε 4·33), 278 nm (4·31), 288 nm (4·31), 322 nm (4·07), 400 nm (3·49). IR spectrum (KBr): 711, 741, 753, 770 (4 and 3 adjacent Ar—H), 881 (olefinic CH=C), 999, 1220 (C—O), 1478, 1599, 1600, 3020, 3045, 3073 (Ar), 1738 cm^{-1} (CO of an unsaturated γ-lactone). ^{1}H-NMR spectrum: δ 7·00—7·70 (m, 7 H, Ar—H), 6·54 (s, 1 H, Ar—CH=C—O). For $C_{15}H_8O_2S$ (252·3) calculated: 71·41% C, 3·20% H, 12·71% S; found: 71·51% C, 3·42% H, 12·70% S.

11-Oxo-10*H*-dibenzo[*b*,*f*]thiepin-3-carboxylic Acid (*XIV*)

A mixture of polyphosphoric acid (prepared from 30 g P_2O_5 and 15 ml 85% H_3PO_4), 80 ml 1,2-dichlorobenzene and 3·5 g *X* was heated for 7 h to 100°C. It was decomposed with water and the precipitated solid was filtered off; 3·0 g (91%) crude *XIV*, m.p. 215—225°C and 233 to 236°C with decomposition. Analytical sample, m.p. 226—229°C, then resolidification and a second melting at 238—239°C (aqueous acetic acid). Mass spectrum, *m/e*: 270 (M^+, corresponds to $C_{15}H_{10}O_3S$), 241, 237, 225, 209, 197. UV spectrum: λ_{max} 246·5 nm (log ε 4·35), 345 nm (3·56). IR spectrum: 740, 756, 771, 870 (Ar—H), 1122, 1232, 1331, 3140 (COOH), 1551, 1602 (Ar), 1642 (ArCO···HO), 1728 cm^{-1} (ArCOOH). IR spectrum ($CHCl_3$): 1680 (ArCO), 1715 cm^{-1} (ArCOOH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 8·07 (mcs, 1 H, *J* = 1·5 Hz, 4-H), 8·06 (d, *J* = 8·0 Hz, 1 H, 1-H), 7·82 (mcd, *J* = 8·0; 1·5 Hz, 1 H, 2-H), 7·10—7·75 (m, 4 H, 6,7,8,9-H_4), 4·29 (s, 2 H, $ArCH_2CO$). For $C_{15}H_{10}O_3S$ (270·3) calculated: 66·65% C, 3·73% H, 11·86% S; found: 66·32% C, 3·90% H, 11·75% S. For the acid *XIV*, prepared differently, we reported[16] earlier a m.p. of 215—219°C.

The filtrate was separated, the organic layer was washed with 5% Na_2CO_3, dried with $MgSO_4$, evaporated *in vacuo*, and the residue crystallized from a mixture of benzene and light petroleum; 0·23 g (8%) orange-coloured crystals of the enol-lactone *XXIV*, m.p. 142—144°C.

11-Oxo-10*H*-dibenzo[*b*,*f*]thiepin-1-carboxylic Acid (*XXV*)

A mixture of 170 mg *XXIV*, 10 ml 10% NaOH and 5 ml ethanol was refluxed for a short time, ethanol was evaporated, the residue cooled and acidified with hydrochloric acid; 170 mg, m.p. 179—184°C. Analytical sample, m.p. 184—186°C (benzene). Mass spectrum, *m/e*: 270 (M^+, corresponds to $C_{15}H_{10}O_3S$), 196. UV spectrum: λ_{max} 244 nm (log ε 4·12), 333 nm (3·80). IR spectrum (KBr): 710, 764, 820 (Ar—H), 929, 1209, 1255, 2580 (COOH), 1567, 1575 (Ar), 1670 (ArCO), 1696 cm^{-1} (ArCOOH), For $C_{15}H_{10}O_3S$ (270·3) calculated: 66·65% C, 3·73% H, 11·86% S; found: 66·67% C, 3·75% H, 11·87% S.

7-Fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XV*)

A mixture of 12·2 g *XII* and 200 ml ethanol was stirred and treated at 70°C over 5 min with a solution of 0·7 g $NaBH_4$ in 7 ml water, containing 0·1 ml 20% NaOH. The mixture was then refluxed for 3 h, ethanol was evaporated under reduced pressure, the residue was diluted with 100 ml water and extracted with benzene. The extract was washed with 3% NaOH and water, dried with $MgSO_4$, filtered with charcoal and the filtrate evaporated. The residue was crystallized from a mixture of 25 ml benzene and 45 ml light petroleum; 10·6 g (86%), m.p. 69—71°C. Analytical sample, m.p. 72—74°C (benzene–light petroleum). IR spectrum: 746, 809, 860, 891, 907 (4 and 2 adjacent and solitary Ar—H), 1050 (CHOH in a cycle), 1207, 1250 (C—O), 1482, 1566, 1600 (Ar), 3230 cm^{-1} (OH). For $C_{14}H_{11}FOS$ (246·3) calculated: 68·27% C, 4·50% H, 7·71% F, 13·02% S; found: 68·14% C, 4·58% H, 7·59% F, 12·78% S.

7-Trifluoromethyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XVI*)

A solution of 8·2 g *XIII* in 50 ml ethanol and 50 ml dioxane was treated with a solution of 1·1 g $NaBH_4$ in 3 ml water containing 1 drop 20% NaOH and the mixture was stirred for 5 h at room temperature. After standing overnight, the solvents were evaporated under reduced pressure, the residue was diluted with water and extracted with benzene. Processing of the extract gave 7·7 g (93%) product, m.p. 86—87·5°C. Analytical sample, m.p. 86—87·5°C (benzene–light

petroleum). IR spectrum: 749, 760, 837, 910 (4 and 2 adjacent and solitary Ar—H), 1120, 1172, 1330 ($ArCF_3$), 1568, 3068 (Ar), 3320, 3380 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·00—7·80 (m, 7 H, Ar—H), 5·31 (dt, 1 H, Ar—CH—O), 3·70 and 3·30 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·24 (d, J = 8·0 Hz, 1 H, OH). ^{19}F-NMR: δ —63·4 (s, 3 F). For $C_{15}H_{11}F_3OS$ (296·3) calculated: 60·80% C, 3·74% H, 19·24% F, 10·82% S; found: 60·94% C, 3·85% H, 19·46% F, 10·80% S.

10,11-Dihydrodibenzo[*b,f*]thiepin-3,11-diol (*XVII*)

A solution of 34·4 g 7-acetoxydibenzo[*b,f*]thiepin-10(11*H*)-one[17] in 360 ml dioxane was reduced with 7·25 g $NaBH_4$ in 35 ml water according to our published procedure[17]. There were obtained 22·2 g (75%) crude *XVII*, m.p. 152—155°C. Analytical sample, m.p. 153—155°C (benzene–acetone). Mass spectrum, *m/e* (%): 244 (M^+, corresponds to $C_{14}H_{12}O_2S$, 50), 226 (100), 211 (30), 194 (33), 181 (12), 165 (62), 152 (25). For $C_{14}H_{12}O_2S$ (244·3) calculated: 68·83% C, 4·95% H, 13·12% S; found: 68·97% C, 5·13% H, 13·00% S. For the compound, prepared in a similar way, we reported a m.p. of 140—144°C[17].

11-Chloro-3-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin (*XVIII*)

A solution of 10·0 g *XV* in 90 ml benzene was saturated for 5 h at 20°C with hydrogen chloride in the presence of 8·0 g $CaCl_2$. After standing overnight, charcoal was added and the mixture filtered. The filtrate was evaporated under reduced pressure; 10·3 g (96%), m.p. 80—82°C. Analytical sample, m.p. 82—83°C (benzene–light petroleum). ^{1}H-NMR spectrum: δ 6·70—7·60 (m, 7 H, Ar—H), 5·65 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·92 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_{10}ClFS$ (264·7) calculated: 63·51% C, 3·82% H, 13·39% Cl, 7·17% F, 12·11% S; found: 64·06% C, 3·88% H, 13·40% Cl, 7·10% F, 11·83% S.

11-Chloro-3-trifluoromethyl-10,11-dihydrodibenzo[*b,f*]thiepin (*XIX*)

A solution of 7·6 g *XVI* in 100 ml benzene was treated with HCl similarly like in the preceding case and gave 7·9 g (98%) product, m.p. 61—63°C. Analytical sample, m.p. 62—63°C (light petroleum). ^{1}H-NMR spectrum: δ 7·00—7·80 (m, 7 H, Ar—H), 5·75 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 4·00 and 3·65 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). For $C_{15}H_{10}ClF_3S$ (314·8) calculated: 57·23% C, 3·20% H, 11·26% Cl, 18·11% F, 10·19% S; found: 57·54% C, 3·22% H, 11·39% Cl, 18·34% F, 10·51% S.

3-Fluoro-11-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*XXIII*)

A solution of 10·0 g *XII* and 20·5 g 1-methylpiperazine in 80 ml benzene was stirred and treated over 5 min with a solution of 4·1 g $TiCl_4$ in 25 ml benzene, added dropwise. The mixture was then refluxed for 24 h. After cooling, it was stirred and slowly treated with 120 ml water, the precipitated solid was filtered off and washed with benzene. The filtrate was separated, the benzene layer was washed with water, dried with $MgSO_4$ and evaporated. The residue crystallized from light petroleum; 9·4 g (70%), m.p. 115—117°C. Analytical sample, m.p. 120—122°C (methanol). UV spectrum: λ_{max} 269 nm (log ε 4·11), 305 nm (3·93). ^{1}H-NMR spectrum: δ 7·58 (dd, J_{H-H} = 8·0 Hz, J_{H-F} = 6·0 Hz, 1 H, 1-H), 6·80—7·50 (m, 6 H, remaining Ar—H), 6·28 (s, 1 H, Ar—CH=C), 2·95 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·28 (s, 3 H, NCH_3). ^{19}F-NMR: δ —113·4 (dt). For $C_{19}H_{19}FN_2S$

(326·4) calculated: 69·91% C, 5·87% H, 5·82% F, 8·58% N, 9·82% S; found: 70·13% C, 6·03% H, 5·96% F, 8·38% N, 9·78% S.

Maleate, m.p. 241—242°C (aqueous ethanol). For $C_{23}H_{23}FN_2O_4S$ (442·5) calculated: 62·43% C, 5·24% H, 4·29% F, 6·33% N, 7·25% S; found: 62·88% C, 5·39% H, 3·93% F, 6·25% N, 7·74% S.

3-Fluoro-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]-thiepin (*VI*)

A solution of 9·5 g *XVIII* and 10·8 g 1-methylpiperazine in 15 ml chloroform was refluxed for 7 h. After standing overnight, chloroform was evaporated, the residue was diluted with 50 ml 10% NaOH and extracted with benzene. The extract was washed with water and then shaken with an excess of 1·25M-H_2SO_4. The aqueous layer was separated, made alkaline with NH_4OH and the base isolated by extraction with benzene. Processing of the extract gave 8·0 g (68%) base, m.p. 121—123°C (benzene). Analytical sample, m.p. 122—124°C (benzene). ^{1}H-NMR spectrum: δ 7·58 (dd, J = 8·0; 6·0 Hz, 1 H, 1-H), 6·70—7·50 (m, 6 H, remaining Ar—H), 3·00 to 4·00 (m, 3 H, $ArCH_2CHAr$), 2·62 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·38 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3). ^{19}F-NMR: δ —116·6 (dt). For $C_{19}H_{21}FN_2S$ (328·4) calculated: 69·48% C, 6·44% H, 5·78% F, 8·53% N, 9·76% S; found: 69·54% C, 6·54% H, 5·58% F, 8·70% N, 9·86% S.

Methanesulfonate, m.p. 215—216°C (ethanol). For $C_{20}H_{25}FN_2O_3S_2$ (424·5) calculated: 56·58% C, 5·93% H, 4·47% F, 6·60% N, 15·11% S; found: 56·68% C, 6·01% H, 4·34% F, 6·63% N, 15·37% S.

Processing of the benzene layer (after the extraction with dilute H_2SO_4) gave 1·5 g neutral product which was chromatographed on a column of 30 g Al_2O_3 (activity II). Benzene eluted 0·6 g 3-fluorodibenzo[*b,f*]thiepin (*XX*), m.p. 71—72°C (light petroleum). ^{19}F-NMR: δ —114·0 (dt). The compound has already been prepared and the m.p. of 71—72°C has been reported[13].

3-Trifluoromethyl-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*VII*)

A mixture of 7·8 g *XIX*, 10 ml 1-methylpiperazine and 10 ml chloroform was refluxed for 8 h, diluted with benzene and washed with water. The base was then extracted with an excess of 5% hydrochloric acid. The suspension of hydrochloride was filtered, the solid hydrochloride combined with the aqueous layer of the filtrate, the suspension made alkaline with NH_4OH and the base isolated by extraction with benzene; 6·65 g (71%) oil. Neutralization with 4·4 g maleic acid in acetone and addition of ether gave 7·7 g maleate, m.p. 193—195°C (acetone–ether). For $C_{24}H_{25}F_3N_2O_4S$ (494·5) calculated: 58·29% C, 5·10% H, 11·53% F, 5·67% N, 6·48% S; found: 58·09% C, 5·28% H, 11·83% F, 5·90% N, 6·71% S.

Decomposition of a sample of pure maleate with NH_4OH and extraction with ether gave a sample of pure base which was used for recording the ^{1}H-NMR spectrum: δ 7·00—8·00 (m, 7 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·65 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3).

Processing of the benzene layer (after the extraction of the base with hydrochloric acid) gave 2·0 g (29%) 3-trifluoromethyldibenzo[*b,f*]thiepin (*XXI*), m.p. 63—64°C (ethanol). UV spectrum: λ_{max} 223 nm (log ε 4·32), 261 nm (4·33), 298 nm (3·92), infl. 340 nm (2·96). IR spectrum: 745, 752, 796, 850, 909 (4 and 2 adjacent and solitary Ar—H, olefinic CH=CH), 1 124, 1 174, 1 329 ($ArCF_3$), 1 605, 3 060 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·75 (bs. 1 H, 4-H), 7·20—7·60 (m, 6 H, remaining Ar—H), 7·15 and 6·95 (ABq, J = 12·5 Hz, 2 H, CH=CH). ^{19}F-NMR: δ —63·3 (s, 3 F). For $C_{15}H_9F_3S$ (278·3) calculated: 64·74% C, 3·26% H, 20·48% F, 11·52% S; found: 64·72% C, 3·19% H, 20·75% F, 11·76% S.

Dibenzo[*b,f*]thiepin-3-ol (*XXII*)

A) A solution of 7·7 g *XVII* and 10 g triethylamine in 130 ml dichloromethane was stirred and treated at —10 to 0°C over 10 min with 8·0 g methanesulfonyl chloride, added dropwise. The mixture was stirred at the indicated temperature for 1·5 h, washed with ice-cold water, ice-cold 10% hydrochloric acid and 5% $NaHCO_3$, dried with $MgSO_4$ and filtered. The filtrate was treated with 15 ml 1-methylpiperazine, dichloromethane was evaporated and the residue heated for 8 h to 140—150°C. After cooling, it was dissolved in benzene and the solution chromatographed on a column of 500 g Al_2O_3 (activity II). Elution with benzene gave 4·25 g (76%) 1-methyl-4-(methylsulfonyl)piperazine (*XXVI*), m.p. 93—94°C followed by resolidification and a new melting at 97—97·5°C (benzene–light petroleum). ^{1}H-NMR: δ 3·30 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·81 (s, 3 H, SO_2CH_3), 2·55 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·36 (s, 3 H, NCH_3) (cf.[28]). The literature[27] reported for the compound, prepared differently, the m.p. of 98—99°C.

Continuation of the chromatography under elution with a mixture of chloroform and ethanol gave 6·42 g (62%) 1-methylpiperazine salt of *XXII*, m.p. 75—79°C (benzene–cyclohexane). Mass spectrum, *m/e*: 226 (M^+, corresponds to $C_{14}H_{10}OS$, *i.e. XXII*), 100 (M^+, corresponds to $C_5H_{12}N_2$, *i.e.* 1-methylpiperazine). IR spectrum: 754, 790, 831, 856 (4 and 2 adjacent and solitary Ar—H, olefinic CH=CH), 1271, 1320 (ArOH), 1500, 1592, 3020 (Ar), 2480 (NH_2^+, NH^+), 3115 (OH···N), 2780 cm^{-1} (NCH_3). ^{1}H-NMR spectrum: δ 7·00—7·60 (m, 6 H, 1,4,6,7,8,9-H_6), 6·90 (s, 2 H, CH=CH), 6·65 (mcs, J = 8·0; 2·5 Hz, 1 H, 2-H), 6·00 (s, 1 H, OH), 2·92 and 2·45 (2 def. t, 8 H, 4 NCH_2 of piperazine), 2·28 (s, 3 H, NCH_3). For $C_{19}H_{22}N_2OS$ (326·4) calculated: 69·90% C, 6·79% H, 8·58% N, 9·82% S; found: 69·88% C, 7·05% H, 8·32% N, 10·01% S.

Reaction of 0·71 g salt just described with 0·60 g maleic acid in acetone gave (after the addition of ether) 0·70 g 1-methylpiperazine bis(hydrogen maleate), m.p. 169—171°C (ethanol), the identity of which was confirmed by analysis. For the same salt we reported[12] previously the m.p. of 172—173°C.

B) A solution of 0·70 g 1-methylpiperazine salt of *XXII* in 20 ml ethanol was treated with 5 ml NH_4OH, ethanol was evaporated *in vacuo*, the residue diluted with water and extracted with ether. Evaporation of the extract gave 0·47 g (97%) free *XXII*, m.p. 126—127°C. Analytical sample, m.p. 137·5—138°C (benzene–cyclohexane). UV spectrum: λ_{max} 230 nm ($\log \varepsilon$ 4·37), 266·5 nm (4·36), infl. 300 nm (3·76), 335 nm (3·51). IR spectrum: 752, 792, 836, 866 (4 and 2 adjacent and solitary Ar—H, olefinic CH=CH), 1220, 1244 (ArOH), 1493, 1592 (Ar), 3105 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·88 (s, 1 H, OH), 7·20—7·50 (m, 5 H, 4,6,7,8,9-H_5), 7·15 (d, J = 8·0 Hz, 1 H, 1-H), 6·88 (s, 2 H, CH=CH), 6·73 (mcd, J = 8·0; 2·0 Hz, 1 H, 2-H). For $C_{14}H_{10}OS$ (226·3) calculated: 74·31% C, 4·45% H, 14·17% S; found: 74·99% C, 4·83% H, 14·18·% S.

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