NONCATALEPTIC NEUROLEPTIC AGENTS: 4-SUBSTITUTED 1-(2-CHLORO-7-FLUORO-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN-10-YL)-PIPERAZINES AND RELATED COMPOUNDS

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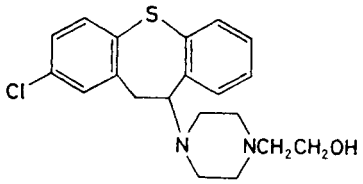
1-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine (*VI*) was used to prepare a new group of potential noncataleptic neuroleptic agents. Addition of acrylonitrile and acrylamide gave the nitrile *VII* and the amide *X*. Further transformations of the nitrile *VII* led to the phenone *VIII* and the amidoxime *IX*. Alkylations of compound *VI* with 2-(2-chloroethyl)-1,3-dioxolane and 2-(2-chloroethyl)-1,3-dioxane resulted in the cyclic acetals *XII* and *XIII*. Several improvements of the synthesis of compound *VI* are reported. Out of the compounds prepared, the amide *X* (methanesulfonate VÚFB-15 496) proved most interesting: it has low acute toxicity, is noncataleptic and has significantly higher antidopaminergic activity than clozapine.

Experimental work, carried out previously[1], showed that in the series of neuroleptic 10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepins the shift of the neuroleptic substituent from position 8 to the quasi-symmetric position 2 leads to compounds which are free or almost free of the cataleptic action in rats, and have, therefore, the chance of being free of the unwanted extrapyramidal side effects in psychotic patients. An indication of a practical result was represented by 2-(4-(2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine-1-yl)ethanol (*I*) (refs[1-4]), called "docloxythepin", which was dropped after several years of preclinical research because of some hepatotoxicity in dogs[5] and of much unwanted side effects (mainly of neurovegetative type) found in the first clinical trial on healthy volunteers[6,7]. Simultaneously with compound *I*, 2-chloro-7-fluoro-10-piperazino derivatives *II*–*IV* were synthesized[1] which attracted our attention by their low acute toxicity in mice (3–7 times less toxic than compound *I*) and by the high discoordinating activity in the rotarod test in mice after oral administration. As far as cataleptic effect in rats was concerned, the oral doses of 50 mg/kg of compounds *II*–*IV* elicited catalepsy in 30–40% of the animals. These compounds were thus not completely noncataleptic and, therefore, did not enter the closer selection of potential noncataleptic neuroleptic agents.

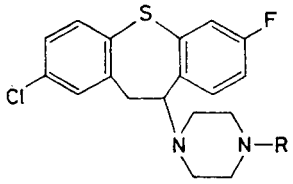
After the failure of docloxythepin (*I*) we returned to the interesting type of the 2-chloro-7-fluoro compounds and attempted to find suitable substituents on the piperazine nitrogen atom which would maintain antidopaminergic activity and pos-

sibly suppress the cataleptogenic character. In addition to the lowest alkyl groups and hydroxyalkyls, we were aware of such properties in series of clorothepin and methiothepin analogues connected with the 2-aminocarbonylethyl group[8], further

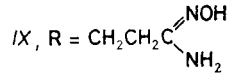


I

3-amino-3-hydroximinopropyl group[8], and finally with groups containing a cyclic acetal fragment, *i.e.* 2-(1,3-dioxolan-2-yl)ethyl and 2-(1,3-dioxan-2-yl)ethyl[9,10]. Using the previously synthesized compounds *V – VII* (ref.[1]) as intermediates, we have now prepared compounds *VIII – XIII*, and a preliminary pharmacological and biochemical screening revealed that at least four of them (*IX*, *X*, *XII*, *XIII*) are practically noncataleptic and have significant antidopaminergic effects. The amide *X* (methanesulfonate), designated by the code number VÚFB-15 496, was selected as the most interesting one for preclinical studies. These investigations, together with some chemically related synthetic experiments, form the object of the present communication.

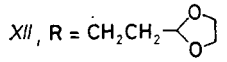


II, R = CH_3
III, R = CH_2CH_2OH
IV, R = $CH_2CH_2CH_2OH$
V, R = $COOC_2H_5$
VI, R = H
VII, R = CH_2CH_2CN
VIII, R = $CH_2CH_2COC_6H_5$

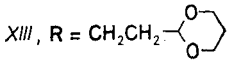


IX, R = $CH_2CH_2C(=NOH)NH_2$

X, R = $CH_2CH_2CONH_2$
XI, R = CH_2CH_2COOH



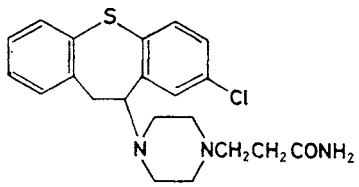
XII, R = CH_2CH_2-(1,3-dioxolan-2-yl)



XIII, R = CH_2CH_2-(1,3-dioxan-2-yl)

The secondary amine *VI* was prepared by hydrolysis of the carbamate *V* (ref.[1]) with ethanolic potassium hydroxide in a yield of 93% (methanesulfonate was prepared for pharmacological testing). The addition of the amine *VI* to acrylonitrile was repeated according to our previous work[1], the base *VII* has now been obtained

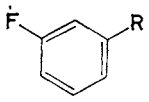
in crystalline form and was characterized by spectra and as dihydrochloride. Reaction of the nitrile *VII* with phenylmagnesium bromide, and the following heating of the formed ketimine with dilute sulfuric acid (method[11]) gave the ketone *VIII* in a fair yield; the spectra confirmed the identity and the dihydrochloride was prepared for pharmacological testing. Treatment of the nitrile *VII* with free hydroxylamine in boiling methanol afforded the amidoxime *IX* which was isolated as the dimaleate (hemihydrate). The amide *X* was prepared by addition of the secondary amine *VI* to acrylamide in tert-butyl alcohol in the presence of benzyltriethylammonium hydroxide and sulfur (*cf.*[12]). The crude base *X* was purified by chromatography and crystallization from ethanol. In most experiments, the higher melting and more stable modification A was obtained; sometimes the crystallization afforded the lower melting and less stable modification B. Both crystal forms have identical ^{1}H NMR spectra (in C^2HCl_3), whereas their IR spectra (in Nujol) showed some minor differences. Both forms afforded the same methanesulfonate and maleate. Hydrolysis of the amide *X* with potassium hydroxide in boiling aqueous ethanol and neutralization of the solution with acetic acid gave the amino acid *XI* crystallizing from aqueous ethanol as the hemihydrate. Treatment with maleic acid resulted in the hemimaleate. Alkylation reactions of the amine *VI* with 2-(2-chloroethyl)-1,3-dioxolane[13] or 2-(2-chloroethyl)-1,3-dioxane[13] in boiling toluene in the presence of triethylamine afforded the bases *XII* and *XIII* which were transformed to water-soluble methanesulfonates and the rather insoluble maleates. As a model experiment which should prove the possibility of preparing the amide *X* by a different route, we carried out the substitution reaction of 2,11-dichloro-10,11-dihydrodibenzo-[*b*,*f*]thiepin[14] with 3-(1-piperazinyl)propionamide[15] in boiling chloroform; the previously prepared amide *XIV* (ref.[8], different synthesis) was obtained in a yield of 79%. The starting 3-(1-piperazinyl)propionamide was obtained by addition of piperazine to acrylamide in warm ethanol; the procedure described in a patent[15] was modified. 1,4-Bis(2-aminocarbonylethyl)piperazine[16,17] was obtained as an important by-product. The wanted 3-(1-piperazinyl)propionamide was characterized as the hemihydrate.



XIV

In comparison with our previous work[1], the synthesis of the starting carbamate *V* was modified importantly in the initial stages. In the first line this was the case of

3-fluorothiophenol (*XVIII*), prepared previously[18] by reaction of 3-flurophenylmagnesium bromide with sulfur. Now we started its preparation from 4-fluoro-2-nitroaniline being accessible in five steps either from fluorobenzene or 4-chloronitrobenzene *via* 4-fluoroaniline (*cf.*[19]). 4-Fluoro-2-nitroaniline was diazotized in nitrosylsulfuric acid (*cf.*[19]) and the obtained solution of 4-fluro-2-nitrobenzenediazonium sulfate was reduced with hypophosphorous acid (method [20,21]), released from sodium hypophosphite monohydrate in the strongly acid reaction medium. This is a new method for preparing 3-fluoronitrobenzene (*XV*) (yield of 74%) whose synthesis was described by heating 3-nitrobenzenediazonium salts with hydrofluoric acid[22,23], from 3-nitraniline by the Schiemann method[24–27], or by fluorodenitration of 1,3-dinitrobenzene[28]. An attempt to reduce 4-fluoro-2-nitrobenzenediazonium sulfate with ethanol (method[20]) (diazotization carried out in the presence of ethanol) was not successful: the diazotization was followed by substitution of the fluorine atome with ethoxyl and the final reduction resulted in 3-ethoxynitrobenzene (ref.[29]). 3-Fluoronitrobenzene (*XV*) was transformed to 3-fluoroaniline (*XVI*) by reduction with hydrazine hydrate in boiling ethanol in the presence of active carbon and a small amount of ferric chloride, which is also new for the case (method[30]); this transformation was carried out previously by many other methods (*cf.*[31]) out of which the most closely related to our procedure is the reduction of 3-fluoronitrobenzene with hydrazine in the presence of Raney nickel in boiling methanol[32]. Attempted catalytic hydrogenation of 3-fluoronitrobenzene on Raney nickel in ethanol at normal conditions (temperature, pressure) (*cf.*[33]) led only to a very low yield on the amine *XVI*; the main product was identified as 3,3'-difluorohydrazobenzene (*XVII*) (ref.[34]). The transformation of compound *XVI* to 3-fluorothiophenol (*XVIII*) was carried out by making use of the Leuckart method (refs[35,36]), *i.e. via* 3-fluorobenzenediazonium xanthate and 3-fluorophenyl xanthate.

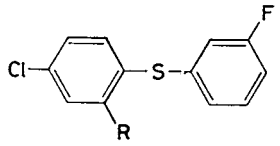


XV, R = NO_2 *XVII*, R = NH—NH—(F)

XVI, R = NH_2 *XVIII*, R = SH

In further steps of the synthesis we used Kindler's modification of the Willgerodt reaction[37]. To this end we needed 5-chloro-2-(3-fluorophenylthio)acetophenone (*XIX*) as the starting material; it was obtained by reaction of 2,5-dichloroacetophenone[38] with 3-fluorothiophenol in the presence of potassium carbonate and copper at 140–150°C in dimethyl formamide or without any solvent. Its reaction

with sulfur and excessive boling morpholine gave i na good yield the thiomorpholide *XX* which was hydrolyzed either with a boling ethanolic potassium hydroxide solution or with a refluxing mixture of dilute sulfuric acid and acetic acid to give (5-chloro-2-(3-fluorophenylthio)phenyl)acetic acid (*XXI*), prepared previously[1] *via* the nitrile. The following intermediates of the synthesis of compound *V*, *i.e.* 2-chloro-7-fluorodibenzo[*b*,*f*]thiepin-10(11*H*)one, 2-chloro-7-fluoro-10,11-dihydrodibenzo-[*b*,*f*]thiepin-10-ol and 2,10-dichloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin, were prepared precisely like described in our previous communication[1].

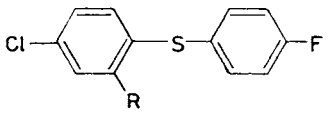


XIX, R = $COCH_3$ *XX*, R = CH_2CSN  O

XXI, R = CH_2COOH

Some new experimental material is devoted to intermediates of the isomeric 2-chloro-8-fluoro series[1]. In the synthesis of the starting (5-chloro-2-(4-fluorophenylthio)phenyl)acetic acid (*XXVII*), the alcohol *XXII* has now been prepared by reduction of the mixed anhydride of 5-chloro-2-(4-fluorophenylthio)benzoic acid[39] with monoethyl carbonate, prepared *in situ* by treatment of the acid with ethyl chloroformate in boiling dioxane, with sodium borohydride. The alcohol *XXII* was transformed by the published procedure[1] *via* the chloride to the nitrile *XXIII* .The Willgerodt–Kindler approach[37] in this series did not lead to the desired result. Reaction of 2,5-dichloroacetophenone[38] with 4-fluorothiophenol[39] at 125–130°C in the presence of potassium carbonate and copper gave the ketone *XXIV* which was subjected to treatment with sulfur and excessive boiling morpholine. An oily mixture was obtained from which in the first experiment crystallization from a mixture of benzene and light petroleum afforded in a low yield a compound melting at 174 to 177°C which was identified by analysis and spectra as the oxothiomorpholide *XXVI* (for analogy, *cf.*[40–44]). In a different experiment, the oily product was crystallized from methanol and gave first 38% of the lower melting (m.p. 77–79°C) crystal form A of the desired thiomorpholide *XXV*. In another case, crystallization from methanol and then from a mixture of benzene and light petroleum gave 42% of the higher melting (m.p. 92–94°C) crystal form B of the thiomorpholide *XXV*. The crystal forms A and B had identical UV and ^1H NMR spectra but differed slightly in the IR spectra in nujol. The hydrolysis of form B of the thiomorpholide *XXV* by refluxing with a concentrated solution of potassium hydroxide in ethanol gave an oily mixture of acids whose composition was elucidated only on the basis of products of further synthetic steps. It consisted of a minor part of the fluoro acid

XXVII and of the major part of the ethoxy acid *XXVIII*, formed by substitution of the fluorine atom (activated by the *para*-standing sulfur atom) with ethoxyl during the hydrolysis with ethanolic potassium hydroxide (for analogy, *cf.*[45]). Cyclization of the mixture of acids by heating with polyphosphoric acid to 120° to 130°C led to a crystalline mixture of ketones, *XXIX* and *XXX*, which did succeed to separate neither by crystallization, nor by chromatography on alumina (only TLC on silica gel differentiated both compounds). Without further characterization the mixture of ketones was subjected to treatment with piperazine 4-toluenesulfonate at 190°C *in vacuo* (method[41]). The crude product was transformed to the maleate, its crystallization from ethanol eliminated completely the fluorine-containing component, and the product was identified by analysis, mass spectrum and ^{1}H NMR spectrum of the released base as 1-(2-chloro-8-ethoxydibenzo[*b*,*f*]thiepin-10-yl)-piperazine (*XXXI*). The reduction of this enamine with zinc in acetic acid (analogy[41]) gave the 10,11-dihydro compound *XXXII*.

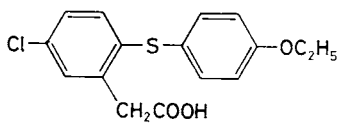


XXII, R = CH_2OH
XXIII, R = CH_2CN
XXIV, R = $COCH_3$

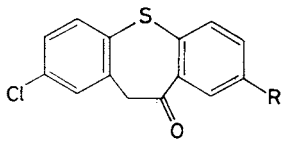
XXV, R = CH_2CSN O
XXVI, R = $COCSN$ O
XXVII, R = CH_2COOH

Compounds *VI*, *VIII*–*X*, *XII*, and *XIII* were pharmacologically tested as potential noncataleptic neuroleptic agents; they were administered orally in the form of salts (preferably methanesulfonates) and the doses given were calculated per bases. The most interesting proved to be the amide *X*, tested first as the maleate (VÚFB-14 080) and then as the methanesulfonate (VÚFB-15 496). Acute toxicity in mice evaluated in 48 h after the administration, LD_{50}: 336 mg/kg (male mice) and 316 mg/kg (female mice). When evaluated in an interval longer than 48 h, the LD_{50} values were lower due to a deep central depression of the animals perishing on the basis of insufficient food and water intake. For comparison, LD_{50} of clozapine[46], 199 mg/kg. Acute toxicity in rats, LD_{50}: 654 mg/kg (male rats), 384 mg/kg (female rats). Inhibition of the spontaneous locomotor activity in mice, evaluated by the photo-cell method of Dews, D_{50} = 1·05 mg/kg; for comparison the D_{50} values of haloperidol (0·4), chlorpromazine (4·8), clozapine (4·0), sulpiride (318). Incoordinating effect in the rotarod test, ED_{50}: 2·0 mg/kg in mice, 19·5 mg/kg in rats. In the test of catalepsy in rats the dose of 50 mg/kg was completely inactive (the same with clozapine). In the test of antiapomorphine action in rats, the doses of 20 and 50 mg/kg in 2 h after the administration inhibited significantly the agitation whereas the stereo-

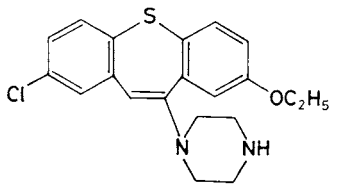
typies were not influenced (clozapine in the same doses did affect neither agitation nor stereotypies). In the test of inhibition of apomorphine emesis in dogs, the threshold dose was 2 mg/kg in the interval of 4 h after the administration (the effect disappeared within 24 h). In the test of apomorphine-induced climbing in mice[47], PD_{50} = 2·9 mg/kg (for haloperidol 0·11, chlorpromazine 4·6, clozapine 13·1, sulpiride 340). In 3 h after the administration the compound increased intensively the homovanillic acid (HVA) (the main dopamine metabolite) level in corpus striatum and tuberculum olfactorium of the rat brain[48]. The threshold doses, which increased significantly the HVA concentrations were 5 mg/kg for corpus striatum and 2 mg/kg for tuberculum olfactorium. This test is the most decisive indicator of the antidopaminergic activity. Clozapine had approximately 10% of activity of VÚFB-15 496 in both brain structures mentioned. In the dose of 20 mg/kg, VÚFB-15 496 did not influence significantly the dopamine (DA) level in the same brain structures (clozapine decreased slightly the DA level). For checking the affinity of compound VÚFB-15 496 (*X*) to DA D_2 receptors in the same brain structures, the inhibition of 0·5 nmol. $.l^{-1}$ [^{3}H]spiperone binding was determined[49], IC_{50} = 49·7 nmol l^{-1} in corpus striatum (for haloperidol 10·8, chlorpromazine 81·4, clozapine 288·5, sulpiride 1 686), and 30·6 nmol l^{-1} in tuberculum olfactorium (for haloperidol 8·15, chlorpromazine 37·2, clozapine 112·8, sulpiride 4 875). The serum prolactin secretion in rats (determined by the RIA method) was significantly increased by the dose of 10 mg/kg (threshold dose) of VÚFB-15 496. The anticholinergic activity of VÚFB-15 496 was significantly weaker than that of clozapine. It antagonized the oxotremorine effects in mice in doses 10 times higher than clozapine. The inhibition of [^{3}H]quinuclidinyl benzilate binding in the rat brain was weak (IC_{50} = 7 628 nmol. $.l^{-1}$), clozapine was much more effective (IC_{50} = 72·1 nmol l^{-1}). In conclusion,



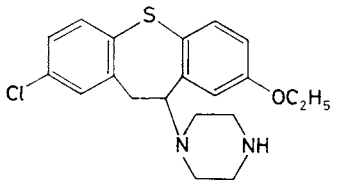
XXVIII



XXIX, R = F
XXX, R = OC_2H_5



XXXI



XXXII

compound VÚFB-15 496 (*X*) is little toxic, noncataleptic and has 5–10 times higher antidopaminergic activity than clozapine. It is considered to warrant preclinical and eventually clinical investigation.

Properties of the other compounds: Acute toxicity in mice, LD_{50} in mg/kg: *VI*, 125; *VIII*, >400 (this dose was lethal for only 10% of the animals); *IX*, 320; *XII* 200, *XIII*, >500 (77·6 *i.v.*). Rotarod test in mice, ED_{50} in mg/kg: *VIII*, 3·5; *XII*, 3·5; *XIII*, 2·86. Influence on motility of mice in the test of Ther, ED_{50} in mg/kg: *IX*, 50. Test of catalepsy in rats: *VI*, *VIII*, *XII*, and *XIII* were noncataleptic in doses of 50 mg/kg; *XII* and *XIII* in doses of 10 and 50 mg/kg mildly potentiated the cataleptic effect elicited by perphenazine (1·5 mg/kg *i.p.*). Influence on the apomorphine effect in rats: *VI* and *XIII* inactive in doses of 50 mg/kg; *XII*, a slight effect in the same dose. Influence on the levels of HVA and DA in *corpus striatum* of the rat brain: *VIII*, in the dose of 80 mg/kg no effect; *IX*, the dose of 80 mg/kg increased the HVA level by more than 300%, the dose of 20 mg/kg had still a significant effect; *XII*, the dose of 80 mg/kg (in 3 h) increased the level of HVA by 504% and decreased the DA level by 25%, the dose of 10 mg/kg did influence the levels neither of HVA, nor of DA; *XIII*, the dose of 80 mg/kg increased the HVA level (3 h) by 150–200%, the levels of DA and 5-hydroxyindoleacetic acid were not influenced, the dose of 20 mg/kg had still a significant effect on the HVA level, the dose of 10 mg/kg was inactive. Inhibition of [^{3}H]spiperone binding in rat brain striatum: *VI*, inactive in the concentration of 200 nmol l^{-1}; *XIII*, IC_{50} = 1 227 nmol l^{-1}. Compound *VI* in the dose of 10 mg/kg potentiated significantly the reserpine hypothermia in mice; the same dose had hypothermic effect in mice (in 1·5–3 h after the administration); the dose of 50 mg/kg significantly antagonized the formation of reserpine gastric ulcers in rats.

Antimicrobial activity *in vitro* (the microorganisms and the minimum inhibitory concentrations in μg/ml — unless they exceed 100 μg/ml — are given): *Streptococcus β-haemolyticus*, *X* 6·25, *XII* 12·5, *XIII* 12·5; *Streptococcus faecalis*, *X* 25; *Staphylococcus pyogenes aureus*, *X* 6·25, *XII* 50, *XIII* 50; *Pseudomonas aeruginosa*, *X* 100; *Escherichia coli*, *X* 25, *XII* 100, *XIII* 100; *Proteus vulgaris*, *X* 100; *Mycobacterium tuberculosis* H37Rv, *X* 6·25, *XII* 12·5; *Saccharomyces pasterianus*, *XII* 50; *Trichophyton mentagrophytes*, *XII* 12·5, *XIII* 25.

EXPERIMENTAL

The melting points of analytical preparations were determined mostly in the Mettler FP-5 melting point recorder, partly in Kofler's block (these 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 recorded with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in nujol) with a Unicam SP 200 G or a Perkin–Elmer 298 spectrophotometers, ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487 C (80 MHz) spectrometer, ^{19}F NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument, and the mass spectra with MCH 1 320 and Varian MAT 44 S spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromato-

graphy on silica gel (Silufol). The extracts were dried with $MgSO_4$, Na_2SO_4 or K_2CO_3, and evaporated under reduced pressure on a rotating evaporator.

3-Fluoronitrobenzene (*XV*)

$NaNO_2$ (50 g) was slowly added to 570 g stirred 98–99% H_2SO_4 at 5–10°C over 1 h and the mixture was heated during 30–60 min to 70°C. The obtained nitrosylsulfuric acid solution was cooled to 10°C and treated under stirring over 1 h with a solution of 90 g 4-fluoro-2-nitroaniline[19] in 590 g acetic acid with maintaining the temperature at 15–20°C. Stirring the mixture at this temperature for 3 h gave the solution of 4-fluoro-2-nitrobenzenediazonium sulfate. This solution was added over 25 min to a stirred solution of 320 g $NaH_2PO_2.H_2O$ in 600 ml water and 150 g 94% H_2SO_4, cooled to 10°C by a bath with ice and water. The mixture was stirred and cooled for further 2 h (strong formation of N_2, temperature rise to 35°C) and allowed to stand overnight at room temperature. The other day the mixture was distilled with steam. The distillate (3·5 l), which contained a separated oily layer, was cooled to 5°C and was made alkaline by addition of a solution of 420 g NaOH in 420 ml water. The product was extracted with chloroform, the extract was filtered and evaporated. The residue (65 g) was *XV* of 92·5% purity; it could be used for further work. Its distillation gave 60 g (74%) pure *XV*, b.p. 76–78°C/1·6 kPa, or 198 to 200°C/100 kPa. The analysis confirmed the composition $C_6H_4FNO_2$. Ref.[24], b.p. 86°C/2·5 kPa.

3-Ethoxynitrobenzene

A mixture of 90 g 4-fluoro-2-nitroaniline[19] and 360 ml 96% ethanol was treated with 145 g H_2SO_4, the solution obtained was cooled to 7–9°C and treated over 1 h under stirring with a solution of 48·5 g $NaNO_2$ in 70 ml water, added dropwise. The stirring was continued for 1 h without cooling. Over 1 h the mixture was heated to 25–50°C; this was accompanied by a copious development of gases. In the next 1 h the temperature was raised to 50–60°C and in the third hour the mixture was refluxed at a bath temperature of 80–90°C. After standing overnight, ethanol was distilled off (320 ml during 2·5 h) and the residue was distilled with steam. The distillate (2 l) was extracted with ether, and the extract was distilled. The first fraction (6·65 g, b.p. 78–81°C/1·6 kPa) corresponded to the desired *XV*. The main fraction (26·5 g, 28%), however, was identified as 3-ethoxynitrobenzene. Redistillation gave a product boiling at 124°C/1·6 kPa. Cooling led to crystallization, m.p. 31–32°C (light petroleum). The analysis confirmed the composition $C_8H_9NO_3$. Ref.[29], m.p. 34°C.

3-Fluroaniline (*XVI*)

To a solution of 30 g 92·5% *XV* in 500 ml ethanol there were added 93 g 98% $N_2H_4.H_2O$, 15 g active carbon and a solution of 4·0 g $FeCl_3.6\,H_2O$ in 50 ml ethanol, and the stirred mixture was heated over 1 h to 70°C. At this temperature the reaction started and was mildly exothermic which led to a refluxing under formation of N_2. The heating was discontinued and further 85 g 92·5% *XV*, dissolved in 50 ml ethanol, were added with such a rate that the mixture was maintained in refluxing. The stirring without heating was continued for 30 min and the mixture was then refluxed for 8 h. After cooling, the solid was filtered off, washed with 50 ml ethanol, and the filtrate was evaporated in a bath of 100°C, at the end under reduced pressure of about 25 to 30 kPa. The residue was dissolved in 300 ml chloroform, the solution was stirred with 20 g $MgSO_4$ for 20 min, it was filtered, the filtrate was evaporated and the residue was distilled; 77 g (93%) *XVI*, b.p. 72–74°C/1·6 kPa. The analysis confirmed the composition C_6H_6FN. Ref.[31], b.p. 82°C/2·4 kPa.

3,3'-Difluorohydrazobenzene (*XVII*)

A mixture of 50 g *XV*, 500 ml ethanol, and 25 g Raney Ni (aqueous suspension) was shaken in H_2 atmosphere at normal temperature for 48 h. The reaction was exothermic but the calculated consumption of H_2 did not take place. It was filtered, the filtrate was evaporated, the residue was dissolved in 250 ml benzene and the evaporation was repeated *in vacuo*. The residue was distilled. First a fraction (8·0 g, 20%) boiling at 72—75°C/1·6 kPa was obtained corresponding to the desired *XVI*. The main product (17·7 g, 45%), identified as *XVII*, distilled at 126°C/40 Pa, and melted at 54°C (ether–light petroleum). IR spectrum: 685, 760, 776 (3 adjacent Ar—H), 1 484, 1 519, 1 610 (Ar), 3 335 cm^{-1} (NH). ^1H NMR spectrum: δ 7·10 (m, 2 H, 5,5'-H_2), 6·50 (m, 6 H, remaining ArH), 5·60 (bs, 2 H, ArNHNHAr). The analysis corresponded to $C_{12}H_{10}F_2N_2$. Ref.[34], m.p. 57°C.

3-Fluorothiophenol (*XVIII*)

XVI (111 g) was added under stirring to a warm mixture of 200 ml hydrochloric acid and 200 ml water and the solution formed was cooled to 0°C. The resulting suspension of *XVI* hydrochloride was stirred and diazotized with a solution of 71 g $NaNO_2$ in 160 ml water, added in such a rate that the temperature could be maintained by cooling at 0—5°C. The mixture was stirred at 0°C for another 30 min giving a clear solution of 3-fluorobenzenediazonium chloride. This was then added over 1·5—2 h to a stirred solution of 224 g potassium ethyl xanthate in 250 ml water, heated to 70—75°C. After the addition was complete, the heating was discontinued, the mixture was stirred for 2 h, allowed to stand overnight at room temperaure, the separated oily 3-fluorophenyl ethyl xanthate was extracted with chloroform, the extract was filtered, and evaporated. The residue (240 g) was dissolved in 650 ml ethanol, the solution was heated under nitrogen to reflux, the heating was discontinued and under stirring there was added over 1 h a solution of 240 g KOH in 150 ml water. Afterwards, the mixture was refluxed for 10 h. Ethanol was distilled off at normal pressure, the rest under reduced pressure (25—35 kPa). The residue was dissolved under stirring in 700 ml water, the solution was washed with toluene, 20 g Zn were added, and the mixture was acidified at 10°C over 30—40 min with hydrochloric acid (under nitrogen). The oily product was extracted twice with chloroform, the extract was dried and chloroform was distilled off through a short column. The residue was distilled under protection with nitrogen; 83 g (65%) *XVIII*, b.p. 130—135°C/30 kPa. The analysis corresponded to C_6H_5FS. Ref.[18], b.p. 156°C/10 MPa.

5-Chloro-2-(4-fluorophenylthio)benzyl Alcohol (*XXII*)

A mixture of 28·3 g 5-chloro-2-(4-fluorophenylthio)benzoic acid[39] and 60 ml dioxane was stirred and treated over 15 min with 12·0 g ethyl chloroformate. The mixture was refluxed for 3 h and then treated over 6 h with 8·5 g $NaBH_4$ at 60—70°C. It was stirred for 3 h at this temperature, allowed to stand overnight and decomposed under cooling by addition of 60 ml water. The solid was filtered off and the filtrate was extracted with chloroform. Processing of the extract gave 23·4 g (87%) *XXII*, b.p. 178°C/0·2 kPa. Redistillation gave the product boiling at 160°C/0·2 kPa. Analysis corresponded to $C_{13}H_{10}ClFOS$. Ref.[1], b.p. 148°C/1·3 Pa.

(5-Chloro-2-(4-fluorophenylthio)phenyl)acetonitrile (*XXIII*)

A boiling solution of 54·4 g *XXII* in 150 ml benzene was stirred, treated with 36·0 g $SOCl_2$, refluxed for 1·5 h, allowed to stand overnight, and evaporated *in vacuo*. The residue was diluted with 150 ml benzene and the evaporation was repeated. After cooling, the residue was dissolved

in 85 ml dimethylformamide, 5 ml water and 15·7 NaCN were added, and the mixture was stirred at room temperature for 2·5 h. After cooling it was diluted with 100 ml water and extracted with benzene. Processing of the extract gave 50·8 g (84%) crude *XXIII*. A sample (5·0 g) was chromatographed on a column of 150 g silica gel. The product was eluted with benzene (3·2 g), b.p. 130°C/0·1 kPa. ^{1}H NMR spectrum: δ 7·55 (bs, 1 H, 6-H), 6·80—7·40 (m, 6 H, remaining ArH), 3·81 (s, 2 H, $ArCH_2CN$). For $C_{14}H_9ClFNS$ (277·7) calculated: 60·54% C, 3·27% H, 12·76% Cl, 6·84% F, 5·04% N, 11·54% S; found: 60·69% C, 3·49% H, 12·38% Cl, 7·05% F, 4·84% N, 11·83% S.

5-Chloro-2-(3-fluorophenylthio)acetophenone (*XIX*)

A) A mixture of 51 g *XVIII*, 380 ml dimethylformamide, 75·2 g 2,5-dichloroacetophenone[38], 180 g K_2CO_3, and 5·0 g Cu was stirred for 5 h under nitrogen in a bath of 140—150°C. After cooling to 100°C, 10 g active carbon were added, the mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue (125 g) was dissolved in benzene and chromatographed on a column of 420 g silica gel. Elution with benzene gave 80·9 g homogeneous oily *XIX* which was distilled; 54·7 g (50%), b.p. 160—164°C/0·1 kPa, m.p. 53—55°C (ethanol). UV spectrum: λ_{max} 231 nm (log ε 4·30), 234·5 nm (4·30), 265 nm (3·89), 340 nm (3·63), and inflex at 285 nm (3·77). IR spectrum: 696, 786, 822, 874, 883 (3 and 2 adjacent and solitary Ar—H), 1 582, 1 590, 1 600, 3 028, 3 046 (Ar), 1 670 cm^{-1} (ArCO). ^{1}H NMR spectrum: δ 7·73 (d, J = 2·5 Hz, 1 H, 6-H), 7·00—7·40 (m, 5 H, 4-H and 4 ArH of fluorophenyl), 6·84 (d, J = 8·5 Hz, 1 H, 3-H), 2·60 (s, 3 H, $COCH_3$). For $C_{14}H_{10}ClFOS$ (280·7) calculated: 59·89% C, 3·59% H, 12·63% Cl, 6·77% F, 11·42% S; found: 60·49% C, 3·62% H, 12·95% Cl, 6·97% F, 11·74% S.

B) A stirred mixture of 106 g *XVIII*, 145·6 g 2,5-dichloroacetophenone[38] and 4·0 g Cu was treated under nitrogen with 190 g K_2CO_3. The temperature rose spontaneously to 80°C. The mixture was then heated for 6·5 h to 128—135°C (bath of 150—155°C). After cooling to 50°C it was diluted with 300 ml benzene, the mixture was stirred for 15 min, the solid was filtered off and washed with benzene. The filtrate was evaporated *in vacuo*, the residue was dissolved in 1 l ethanol, the solution was filtered with 20 g charcoal, and the filtrate was evaporated under reduced pressure. The residue (216 g) was dissolved in 240 ml boiling ethanol, the cooled solution was seeded with some crystals of *XIX* and allowed to crystallize overnight in a refrigeraor. Filtration, washing with a little of ethanol and drying *in vacuo* gave 114 g product, m.p. 51—53°C. The mother liquor was processed by distillation; 46 g, b.p. 160—162°C/73 Pa. The distillate crystallized to give the product melting at 49—52°C. The total yield was thus 160 g (69%); the product was identical with that obtained under *A*.

5-Chloro-2-(4-fluorophenylthio)acetophenone (*XXIV*)

A mixture of 105 g 4-fluorothiophenol[39], 138 g 2,5-dichloroacetophenone[38], 185 g K_2CO_3, and 3·0 g Cu was stirred and heated for 2 h to 125—130°C. After partial cooling the mixture was distributed between benzene and water, the organic layer was dried, filtered with charcoal, and evaporated. The residue was crystallized from 250 ml methanol; 155 g (76%), m.p. 82—84°C. Analytical sample, m.p. 83—84°C (methanol). UV spectrum: λ_{max} 233·7 nm (log ε 4·35), 271 nm (3·94), 348 nm (3·65). IR spectrum: 829, 836, 841, 886 (2 adjacent and solitary Ar—H), 1 494, 1 596, 3 035, 3 080 (Ar), 1 678 cm^{-1} (ArCOR). ^{1}H NMR spectrum: δ 7·75 (d, J = 2·5 Hz, 1 H, 6-H), 7·56 (dd, J_{H-H} = 8·5 Hz; J_{H-F} = 5·5 Hz, 2 H, 2′,6′-H_2), 7·15 (q, J = 8·5; 2·5 Hz, 1 H, 4-H), 7·08 (t, $J_{H-H} = J_{H-F}$ = 8·5 Hz, 2 H, 3′,5′-H_2), 7·60 (d, J = 8·5 Hz, 1 H, 3-H), 2·60 (s, 3 H, $COCH_3$). For $C_{14}H_{10}ClFOS$ (280·7) calculated: 59·89% C, 3·59% H, 12·63% Cl, 6·77% F, 11·42% S; found: 59·82% C, 3·70% H, 12·67% Cl, 6·61% F, 11·43% S.

(5-Chloro-2-(3-fluorophenylthio)phenyl)acetic Acid Thiomorpholide (*XX*)

A mixture of 175 g *XIX*, 40·2 g S, and 185 g morpholine was stirred and heated for 1 h in a bath of 120°C and for 10 h under reflux in a bath of 150–155°C. After partial cooling, the mixture was diluted with 1·5 l chloroform, the solution was washed with water, 1·5M HCl and again with water, dried with K_2CO_3, and after the addition of 15 g charcoal filtered through a layer of 135 g silica gel. The filtrate was evaporated under reduced pressure and the residue was crystallized from 275 ml ethanol; 177 g (74%) *XX*, m.p. 100–105°C. Analytical sample, m.p. 111 to 112°C (ethanol). IR spectrum: 686 (C—Cl), 750, 779, 826, 889 (3 and 2 adjacent and solitary Ar—H), 1 122, 1 209, 1 235, 1 282 (R—O—R), 1 478, 1 487 (C(=S)—N), 1 580, 1 591, 1 604, 3 045 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·60–7·60 (m, 7 H, ArH), 4·29 (s, 2 H, $ArCH_2CS$), 4·29 (t), 3·72 (t) and 3·45 (s) (2 + 2 + 4 H, 4 CH_2 of morpholine). ^{19}F NMR spectrum: δ −111·8 (m). For $C_{18}H_{17}ClFNOS_2$ (381·9) calculated: 56·60% C, 4·49% H, 9·28% Cl, 4·97% F, 3·67% N, 16·79% S; found: 56·96% C, 4·60% H, 9·29% Cl, 4·94% F, 3·79% N, 16·73% S.

(5-Chloro-2-(4-fluorophenylthio)phenyl)acetic Acid Thiomorpholide (*XXV*)

A) A mixture of 2·3 g *XXIV*, 0·6 g S, and 1·5 g morpholine was stirred and heated under reflux for 8 h to 140–150°C. Morpholine (1·0 g) was added and the heating was continued for 2 h. After cooling the mixture was diluted with ether, the solution was washed with water, 1M HCl and water, dried and evaporated. The residue was dissolved in boiling methanol, the solution was filtered with charcoal, and the filtrate was allowed to stand for several days in a refrigerator; 1·2 g (38%) modification A of *XXV*, m.p. 64–74°C. Analytical sample, m.p. 77–79°C (methanol). UV spectrum: λ_{max} 280 nm (log ε 4·32). IR spectrum: 830, 875, 890 (2 adjacent and solitary Ar—H), 1 030, 1 120, 1 239, 1 280 (R—O—R), 1 490 (C(=S)—N), 1 588 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·75–7·40 (m, 7 H, ArH), 4·21 (s, 2 H, $ArCH_2CS$), 4·28 (t), 3·68 (t) and 3·40 (s) (2 + 2 + 4 H, 4 CH_2 of morpholine). For $C_{18}H_{17}ClFNOS_2$ (381·9) calculated: 56·60% C, 4·49% H, 9·28% Cl, 4·97% F, 3·67% N, 16·79% S; found: 57·01% C, 4·48% H, 9·54% Cl, 5·29% F, 3·65% N, 16·59% S.

B) A mixture of 153 g *XXIV*, 35 g S, and 96 g morpholine was stirred and heated under reflux for 10 h to 140–150°C. Similar processing like under *A* gave 87·8 g (42%) crude product which crystallized from methanol and melted at 88–92°C. Crystallization to the constant melting point proceeded from a mixture of benzene and light petroleum, and afforded crystal modification B, m.p. 92–94°C. UV and ^1H NMR spectra in solutions were identical with those of the modification A. IR spectrum: 810, 844, 879, 895 (2 adjacent and solitary Ar—H), 1 032, 1 100, 1 120, 1 157 (R—O—R), 1 494 (C(=S)—N), 1 590 cm^{-1} (Ar). For $C_{18}H_{17}ClFNOS_2$ (381·9) calculated: 56·60% C, 4·49% H, 9·28% Cl, 4·97% F, 3·67% N, 16·79% S; found: 57·01% C, 4·50% H, 9·10% Cl, 5·14% F, 3·56% N, 16·56% S.

5-Chloro-2-(4-fluorophenylthio)phenylglyoxylic Acid Thiomorpholide (*XXVI*)

A mixture of 10·0 g *XXIV*, 1·8 g S, and 6·2 g morpholine was stirred and heated under reflux for 4·5 h to 140–150°C. After cooling it was diluted with 30 ml chloroform, the mixture was filtered with charcoal, the filtrate was washed with 1M HCl and water, dried and evaporated. The residue (14·0 g) was dissolved in a mixture of benzene and light petroleum. On standing there crystallized 1·6 g (11%) crude *XXVI*, m.p. 142–169°C. Repeated crystallization from methanol gave the analytical sample, m.p. 174–177°C. UV spectrum: λ_{max} 237·5 nm (log ε 4·35), 272·5 nm (4·32), 356 nm (3·78). IR spectrum: 756, 767 (C—Cl), 820, 842, 870 (2 adjacent and solitary Ar—H), 1 117, 1 211, 1 221, 1 231 (R—O—R), 1 491, 1 502 (C(=S)—N), 1 542,

1 589, 3 045, 3 070 (Ar), 1 658 cm^{-1} (ArCOCSN). ^1H NMR spectrum: δ 7·74 (d, J = 2·5 Hz, 1 H, 6-H), 7·43 (dd, J_{H-H} = 8·0 Hz; J_{H-F} = 5·5 Hz, 2 H, 2′,6′-H_2), 7·19 (q, J = 8·0; 2·5 Hz, 1 H, 4-H), 7·08 (t, $J_{H-H} = J_{H-F}$ = 8·0 Hz, 2 H, 3′,5′-H_2), 6·75 (d, J = 8·0 Hz, 1 H, 3-H), 4·25 (t), 3·82 (t), and 3·68 (s) (2 + 2 + 4 H, 4 CH_2 of morpholine). For $C_{18}H_{15}ClFNO_2S_2$ (395·9) calculated: 54·61% C, 3·82% H, 8·95% Cl, 4·80% F, 3·54% N, 16·20% S; found: 54·79% C, 3·74% H, 9·28% Cl, 4·76% F, 3·49% N, 16·41% S.

(5-Chloro-2-(3-fluorophenylthio)phenyl)acetic Acid (*XXI*)

A) A mixture of 100 g *XX*, 240 ml ethanol, and 73 g KOH was stirred and refluxed for 2·5 h (bath of 120°C). Ethanol was evaporated *in vacuo*, the residue was dissolved in 1·1 l water, the aqueous solution of the potassium salt was washed with benzene, filtered with charcoal, and the filtrate was acidified under stirring and cooling with 280 ml 1 : 1 dilute hydrochloric acid. The separated product was extracted with benzene, the extract was washed with water, dried and evaporated under reduced pressure. The warm residue was treated with 100 ml hexane which induced crystallization. After 12 h standing the product was filtered, washed with hexane and dried *in vacuo*; 67·6 g (87%) *XXI*, m.p. 115–121°C. Crystallization of a sample from cyclohexane gave the completely pure product, m.p. 127–128°C. The analysis agreed with the composition $C_{14}H_{10}ClFO_2S$. Ref.[1], m.p. 127–128°C.

B) A mixture of 32·4 g *XX*, 100 ml acetic acid, 50 ml water, and 50 ml H_2SO_4 was stirred and refluxed for 17 h. After cooling it was poured into 700 ml water and after 3 h standing and cooling the precipitated crude *XXI* (28 g) was filtered. It was crystallized from 300 ml ethanol; 20·0 g (80%), m.p. 121–127°C. Recrystallization from cyclohexane afforded the pure acid, m.p. 127–128°C, identical with the substance obtained under *A*.

3-(1-Piperazinyl)propionamide

A stirred solution of 8·6 g anhydrous piperazine in 25 ml ethanol was treated over 15 min with a solution of 7·1 g acrylamide in 25 ml ethanol, added dropwise. The reaction was mildly exothermic. The stirring without heating was continued for 15 min and the mixture was then heated under reflux for 15 h to 75–80°C. It was allowed to stand overnight at room temperature and the separated 1,4-bis(2-aminocarbonylethyl)piperazine was filtered off, washed with ethanol and dried; 4·7 g (21%), m.p. 230–232°C. Crystallization from aqueous ethanol gave the pure compound, m.p. 232–233°C. The analysis agreed with $C_{10}H_{20}N_4O_2$. Refs[16,17], m.p. 236 to 237°C.

The filtrate was evaporated on the water bath *in vacuo* and from the residue, piperazine was removed by sublimation at 90°C under reduced pressure (2 kPa). The residue (8·8 g, 56%) was the desired 3-(1-piperazinyl)propionamide, m.p. 120–123°C. Crystallization from chloroform, as well as sublimation (115–120°C/7 Pa) gave a product melting at 125°C whose analysis characterized it as the hemihydrate (the primary product was probably anhydrous but mechanical handling on air led to taking up 0·5 H_2O). Mass spectrum, m/z (composition, %): 157 (M^+ corresponding to $C_7H_{15}N_3O$, 2·5%), 127 ($C_6H_{11}N_2O$, 8), 115 ($C_5H_{10}N_2O$, 90), 101 ($C_4H_9N_2O$, 9), 99 ($C_5H_{11}N_2$, 35), 86 ($C_3H_6N_2O$, 38), 72 (C_3H_6NO, 50), 56 (100), 44 (97). IR spectrum: 1 670 ($RCONH_2$), 2 638, 2 666, 2 770 (C—H in CH_2N), 3 070, 3 268 cm^{-1} (NH_2, NH, H_2O). ^1H NMR spectrum: δ 7·98 (bs) and 6·35 (bs) (1 + 1 H, $CONH_2$), 2·85 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·41 (t and m, 8 H, $CH_2N^1CH_2$ of piperazine and NCH_2CH_2CO), 1·85 (s, 1 H, NH). For $C_7H_{15}N_3O$ + 0·5 H_2O (166·2) calculated: 50·57% C, 9·70% H, 25·27% N; found: 50·41% C, 9·43% H, 24·97% N. Ref.[15] did not mention the presence of water and gave the m.p. 125°C.

1-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine (*VI*)

Hydrolysis of 262 g *V* (ref.[1]) with a boiling solution of 132 g KOH in 260 ml ethanol, carried out similarly like previously described[1], afforded 202 g (93%) base *VI*, m.p. 155–159°C (benzene–light petroleum) (ref.[1], m.p. 155–157°C). Neutralization of 3·5 g base with 0·96 g methanesulfonic acid was carried out in 20 ml ethanol, the solution was evaporated *in vacuo* and the methanesulfonate crystallized from ethyl acetate; 4·0 g, m.p. 118–123°C. Analytical sample, m.p. 134–136°C (ethanol–ether). For $C_{19}H_{22}ClFN_2O_3S_2$ (445·0) calculated: 51·28% C, 4·98% H, 7·97% Cl, 4·27% F, 6·30% N, 14·41% S; found: 50·84% C, 5·20% H, 8·10% Cl, 4·26% F, 6·43% N, 14·40% S.

3-(4-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)-piperazine-1-yl)propionitrile (*VII*)

The addition of 10·1 g *VI* to 4·6 g acrylonitrile in 80 ml tert-butyl alcohol in the presence of 1·5 ml 50% benzyltriethylammonium hydroxide in methanol was carried out like described in the previous paper[1]. The oily base obtained was induced to crystallize from a mixture of ethanol and hexane and then from ethanol alone; m.p. 97–99°C. IR spectrum: 815, 836, 870, 877 (2 adjacent and solitary Ar—H), 1 485, 1 561, 1 581, 1 600, 3 043 (Ar), 2 240 cm^{-1} (R—CN). ^1H NMR spectrum: δ 6·70–7·70 (m, 6 H, ArH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·20–3·90 (m, 12 H, 6 CH_2). For $C_{21}H_{21}ClFN_3S$ (401·9) calculated: 62·75% C, 5·27% H, 8·82% Cl, 4·73% F, 10·45% N, 7·98% S; found: 62·88% C, 5·24% H, 8·70% Cl, 4·73% F, 10·02% N, 8·15% S.

Dihydrochloride was obtained by neutralization of the base *VII* with HCl in a mixture of ethanol and ether. Crystallization from aqueous ethanol led to the hemihydrate, m.p. 216–219°C. For $C_{21}H_{23}Cl_3FN_3S + 0·5\ H_2O$ (483·9) calculated: 52·12% C, 5·00% H, 21·98% Cl, 3·93% F, 8·68% N, 6·63% S; found: 52·58% C, 5·09% H, 21·78% Cl, 3·82% F, 8·44% N, 6·41% S.

3-(4-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine-1-yl)-1-phenylpropanone (*VIII*)

Grignard reagent was prepared by treatment of 0·36 g Mg with 2·35 g bromobenzene in 20 ml ether. *VII* (4·02 g), dissolved in a mixture of 25 ml benzene and 15 ml ether was slowly added to the stirred solution of the reagent, the mixture was slowly heated and finally it was refluxed for 1·5 h. After cooling, it was decomposed by addition of 15 ml water, a solution of 3·5 ml H_2SO_4 in 7 ml water was added and the mixture was refluxed for 45 min. After cooling, the organic layer was separated, the aqueous acid layer was made alkaline with NH_4OH and the product was extracted with benzene. Processing of the extract gave 3·4 g (71%) crude base *VIII* which crystallized from ethanol and melted in the pure state at 99–102°C. UV spectrum: λ_{max} 241 nm (log ε 4·30), infl. 270 nm (3·94). IR spectrum (KBr): 695, 749, 820, 880 (5 and 2 adjacent and solitary Ar—H), 1 216 (Ar—F), 1 489, 1 563, 1 585, 1 600, 3 005, 3 045 (Ar), 1 681 cm^{-1} (ArCO). For $C_{27}H_{26}ClFN_2OS$ (481·0) calculated: 67·41% C, 5·45% H, 7·37% Cl, 3·95% F, 5·82% N, 6·67% S; found: 67·14% C, 5·68% H, 7·60% Cl, 3·80% F, 6·26% N, 6·76% S.

Dihydrochloride, m.p. 161–163°C (ethanol–benzene). For $C_{27}H_{28}Cl_3FN_2OS$ (554·0) calculated: 58·54% C, 5·09% H, 19·20% Cl, 3·43% F, 5·06% N, 5·79% S; found: 58·11% C, 5·41% H, 18·82% Cl, 3·37% F, 4·99% N, 6·02% S.

3-(4-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine-1-yl)propionamidoxime (*IX*)

$NH_2OH.HCl$ (0·74 g) was added to a stirred solution of sodium methoxide in methanol, pre-

pared by dissolving 0·25 g Na in 6 ml methanol. *VII* (3·54 g) was added and the mixture was refluxed for 7·5 h. After cooling it was filtered and the filtrate was evaporated *in vacuo*. The residue (4·0 g, almost theoretical yield) represented the crude oily base *IX*. Neutralization of 3·1 g of this base with 2·5 g maleic acid in 30 ml ethanol gave 2·5 g dimaleate which was crystallized from a mixture of 96% ethanol and ether; hemihydrate, m.p. 161–163°C. For $C_{29}H_{32}ClFN_4O_9S + 0{\cdot}5\ H_2O$ (676·1) calculated: 51·51% C, 4·92% H, 5·24% Cl, 2·81% F, 8·29% N, 4·74% S; found: 51·48% C, 5·05% H, 5·21% Cl, 2·60% F, 7·74% N, 4·87% S.

A sample of the base *IX*, released from the maleate, was used for recording of the IR spectrum (CS_2): 813, 876, 892 (2 adjacent and solitary Ar—H), 1 660 (C=N—OH), 3 270, 3 365, 3 455 cm^{-1} (NH_2, OH).

3-(4-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)piperazine-1-yl)propionamide (*X*)

A mixture of 400 ml tert-butyl alcohol, 40·0 g *VI*, 0·45 g S, 4 ml 40% solution of benzyltriethylammonium hydroxide in methanol and 36·5 g acrylamide was stirred for 15 h at 50–55°C. The solution obtained was allowed to stand overnight at room temperature and the first part of the crystallized product (35·4 g, m.p. 172–178°C) was filtered, washed with tert-butyl alcohol, toluene and hexane, and dried. The mother liquor was evaporated *in vacuo*, the residue was distributed at 30–35°C by shaking between 350 ml toluene and 400 ml water, the toluene layer was washed three times with 250 ml lukewarm water, it was filtered, and the product was extracted from the toluene solution into a solution of 10 g methanesulfonic acid in 100 ml water by shaking. The toluene layer was washed with 60 ml water, the combined aqueous solutions were filtered with charcoal, the filtrate was made alkaline with NH_4OH, and the product was extracted with chloroform. The extract was washed with water, dried, filtered and evaporated. The residue was crystallized from 22 ml toluene; 10·1 g (second part of the product), m.p. 174 to 175°C. The total yield was 45·5 g (95%). For preparing the pure product, the crude substance was chromatographed on a column of neutral Al_2O_3 (activity II). Elution with benzene removed some less polar impurities and the homogeneous base was eluted by a mixture of benzene with 5% ethanol. Crystallization from a 1 : 1 mixture of ethanol and light petroleum and then from ethanol only gave the more stable crystal form A of the base *X*, m.p. 183–184°C. IR spectrum: 826, 834, 856, 877, 892 (2 adjacent and solitary Ar—H), 1 482, 1 560, 1 580, 1 596, 3 075 (Ar), 1 668 ($CONH_2$), 3 345 cm^{-1} (NH_2). ^1H NMR spectrum: δ 7·98 (bs) and 6·05 (bs) (1 + 1 H, $CONH_2$), 6·60–7·60 (m, 6 H, ArH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), c. 2·50 (bm, 12 H, remaining 6 CH_2). For $C_{21}H_{23}ClFN_3OS$ (419·9) calculated: 60·06% C, 5·52% H, 8·44% Cl, 4·42% F, 10·01% N, 7·64% S; found: 60·24% C, 5·59% H, 8·48% Cl, 4·69% F, 10·10% N, 7·61% S.

In some cases the crystallization of the crude base from ethanol afforded the less stable crystal form B of the base *X*, m.p. 154–155°C. Mass spectrum, *m/z* (%): 419·1232 (M^+ corresponding to $C_{21}H_{23}ClFN_3OS$, calculated: 419·1235, 3%), 263 (35), 228 (32), 156 (40), 142 (33), 127 (100). UV spectrum: inflexes at 242 nm (log ε 3·64), 267 nm (3·58). IR spectrum in nujol: 815, 844, 865, 894 (2 adjacent and solitary Ar—H), 1 480, 1 560, 1 580, 1 591, 3 050 (Ar), 1 679 ($CONH_2$), 3 140, 3 310 cm^{-1} (NH_2); in KBr: 820, 870, 895 (2 adjacent and solitary Ar—H), 1 665 ($CONH_2$), 3 200, infl. 3 300 cm^{-1} (NH_2). ^1H NMR spectrum is identical with that of the crystal form A. ^{19}F NMR spectrum: δ −115·9 (dt, $J_{F(o-H)} = 7{\cdot}5$ Hz; $J_{F(m-H)} = 6{\cdot}0$ Hz). For $C_{21}H_{23}ClFN_3OS$ (419·9) calculated: 60·06% C, 5·52% H, 8·44% Cl, 4·52% F, 10·01% N, 7·64% S; found: 59·97% C, 5·69% H, 8·65% Cl, 4·64% F, 9·90% N, 7·84% S.

Methanesulfonate, m.p. 172–173°C (ethanol–ether). For $C_{22}H_{27}ClFN_3O_4S_2$ (516·0) calculated: 51·20% C, 5·28% H, 5·87% Cl, 3·68% F, 8·14% N, 12·43% S; found: 51·17% C, 5·34% H, 6·92% Cl, 3·84% F, 8·24% N, 12·49% S.

Maleate, m.p. 124–127°C (99% ethanol). For $C_{25}H_{27}ClFN_3O_5S$ (536·0) calculated: 56·02% C, 5·08% H, 6·61% Cl, 3·54% F, 7·84% N, 5·98% S; found: 55·99% C, 5·38% H, 6·51% Cl, 3·74% F, 7·61% N, 6·00% S.

3-(4-(2-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-11-yl)-piperazine-1-yl)propionamide (*XIV*)

A mixture of 2·8 g 2,11-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[14], 3·2 g 3-(1-piperazinyl)-propionamide hemihydrate and 10 ml chloroform was stirred and refluxed for 8 h. Chloroform was evaporated *in vacuo* and the residue was distributed between 30 ml benzene and a solution of 4 ml methanesulfonic acid in 50 ml water. The separated organic layer was evaporated and the residue (0·90 g) gave by crystallization from cyclohexane the unreacted 2,11-dichloro compound, m.p. 99–102°C (*cf.*[14]). The aqueous layer was made alkaline with 10 ml NH_4OH, the precipitated base was dissolved by addition of 100 ml ethanol and by heating to the boiling point of the mixture. Crystallization was induced by cooling for 6 h; 2·13 g (79% per conversion), m.p. 205–209°C. Analytical sample, m.p. 210–211°C (ethanol). The analysis corresponded to $C_{21}H_{24}ClN_3OS$. Ref.[8], m.p. 210–211°C.

3-(4-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin--10-yl)piperazine-1-yl)propionic Acid (*XI*)

A stirred mixture of 2·0 g *X*, 4 ml ethanol, 0·5 ml water, and 2·0 g KOH was refluxed for 5 h and evaporated *in vacuo*. The residue was dissolved in 70 ml water and the solution was treated under stirring with 2 ml acetic acid. The separated oil crystallized. the solid was filtered, washed with water and dried; 1·90 g (93%) *XI* hemihydrate, m.p. 106–109°C. Crystallization from aqueous ethanol did not change the melting point. Mass spectrum, *m/z* (%): 420 (M^+ corresponding to $C_{21}H_{22}ClFN_2O_2S$, 0·2%), 348 (8), 263 (21), 228 (22), 196 (15), 183 (17), 85 (55), 71 (35), 56 (100). IR spectrum: 810, 876 (2 adjacent and solitary Ar—H), 1 210 (Ar—F), 1 482, 1 580, 3 065 (Ar), 1 596, 1 663 (COO^-), 3 350 cm^{-1} (OH, H_2O). ^1H NMR spectrum: δ 9·00 (bs, 1 H, COOH), 6·70–7·60 (m, 6 H, ArH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), c. 2·80 (m, 12 H, remaining 6 CH_2). For $C_{21}H_{22}ClFN_2O_2S + 0·5\ H_2O$ (429·9) calculated: 58·66% C, 5·39% H, 8·24% Cl, 4·41% F, 6·51% N, 7·45% S; found: 58·93% C, 5·23% H, 8·45% Cl, 4·47% F, 6·49% N, 7·70% S.

Hemimaleate, m.p. 144–148°C (ethanol–ether). For $C_{21}H_{22}ClFN_2O_2S + 0·5\ C_4H_4O_4$ (479·0) calculated: 57·67% C, 5·05% H, 7·40% Cl, 5·85% N, 6·69% S; found: 57·82% C, 4·97% H, 7·20% Cl, 5·81% N, 6·28% S.

2-(2-(4-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin--10-yl)piperazine-1-yl)ethyl)-1,3-dioxolane (*XII*)

A mixture of 10·9 g *VI*, 70 ml toluene, 10·9 g triethylamine, and 16·5 g 2-(2-chloroethyl)-1,3--dioxolane[13] was stirred and refluxed for 24 h. After cooling the separated solid was filtered off, the filtrate was washed with water, dried with K_2CO_3, filtered with charcoal, and evaporated under reduced pressure. The inhomogeneous residue (17·6 g) was dissolved in benzene and chromatographed on a column of 400 g neutral Al_2O_3 (activity II). Benzene eluted first 5·9 g noncrystallizing components and in the following fractions 7·6 g (54%) base *XII*, m.p. 110–114°C. Analytical sample, m.p. 112–114°C (benzene). ^1H NMR spectrum: δ 6·70–7·80 (m, 6 H, ArH), 4·91 (t, J = 5·0 Hz, 1 H, O—CH—O), c. 3·90 (m, 4 H, OCH_2CH_2O), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·40 (m, 6 H, 3 CH_2N^1), 1·85 (m,

2 H, remaining CH_2 adjacent to the dioxolane). ^{19}F NMR spectrum: δ −116·2 (dt, $J_{F(o-H)}$ = = 7·5 Hz; $J_{F(m-H)}$ = 6·0 Hz). For $C_{23}H_{26}ClFN_2O_2S$ (449·0) calculated: 61·53% C, 5·84% H, 7·90% Cl, 4·23% F, 6·24% N, 7·14% S; found: 62·30% C, 6·14% H, 7·91% Cl, 3·96% F, 6·09% N, 7·06% S.

Maleate, m.p. 166—168°C (ethanol). For $C_{27}H_{30}ClFN_2O_6S$ (565·1) calculated: 57·39% C, 5·35% H, 6·27% Cl, 3·36% F, 4·96% N, 5·67% S; found: 57·49% C, 5·42% H, 6·49% Cl, 3·32% F, 4·82% N, 5·89% S.

Methanesulfonate, m.p. 158—159°C (ethanol–ether). For $C_{24}H_{30}ClFN_2O_5S_2$ (545·1) calculated: 52·78% C, 5·55% H, 6·50% Cl, 3·49% F, 5·14% N, 11·76% S; found: 53·24% C, 5·54% H, 6·78% Cl, 3·48% F, 5·07% N, 11·68% S.

2-(2-(4-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin--10-yl)piperazine-1-yl)ethyl)-1,3-dioxane (*XIII*)

A mixture of 10·0 g *VI*, 60 ml toluene, 10 g triethylamine, and 15·3 g 2-(2-chloroethyl)-1,3--dioxane[13] was stirred and refluxed for 23 h. After cooling the solid was filtered off and washed with benzene, the filtrate was washed with water, dried with K_2CO_3, filtered with charcoal, and evaporated *in vacuo*. The residue (19·0 g) crystallized on standing. Crystallization from a mixture of 50 ml benzene and 50 ml light petroleum gave 8·5 g (65%) *XIII*, m.p. 150·5—152°C. Further crystallization from the same mixture did not change the melting point. ^1H NMR spectrum: δ 6·70—7·70 (m, 6 H, ArH), 4·55 (t, J = 5·0 Hz, 1 H, O—CH—O), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·50—4·20 (m, 4 H, 2 CH_2O), 2·58 (m. 4 H, $CH_2N^4CH_2$ of piperazine), 2·40 (m, 6 H, 3 CH_2N^1), 1·10—2·00 (m, 4 H, remaining 2 CH_2). For $C_{24}H_{28}ClFN_2O_2S$ (463·0) calculated: 62·26% C, 6·09% H, 7·66% Cl, 4·10% F, 6·05% N, 6·92% S; found: 62·80% C, 6·24% H, 7·69% Cl, 3·65% F, 5·96% N, 7·09% S.

Maleate, m.p. 184—185°C (ethanol). For $C_{28}H_{32}ClFN_2O_6S$ (579·1) calculated: 58·07% C, 5·57% H, 6·12% Cl, 3·28% F, 4·84% N, 5·54% S; found: 58·73% C, 5·63% H, 6·21% Cl, 3·09% F, 4·70% N, 5·78% S.

Methanesulfonate m.p. 201—203°C (ethanol). For $C_{25}H_{32}ClFN_2O_5S_2$ (559·1) calculated: 53·70% C, 5·77% H, 6·34% Cl, 3·40% F, 5·01% N, 11·47% S; found: 53·99% C, 5·80% H, 6·32% Cl, 3·22% F, 4·89% N, 11·19% S.

1-(2-Chloro-8-ethoxydibenzo[*b*,*f*]thiepin-10-yl)piperazine (*XXXI*)

A mixture of 52·4 g *XXV* (crystal form B), 80 ml ethanol, and 40 g KOH was stirred and refluxed for 2 h (bath of 120°C), ethanol was evaporated *in vacuo*, the residue was diluted with 250 ml water, the solution was acidified with hydrochloric acid and the product was extracted with chloroform. Processing of the extract gave 41·6 g oily mixture of the acids *XXVII* and *XXVIII*. This mixture was heated under stirring to 125—130°C with 500 g polyphosphoric acid for 2 h. The cooled mixture was decomposed with ice and water, and the product was extracted with benzene. Processing of the extract gave 31·8 g solid mixture of ketones *XXIX* and *XXX* (m.p. 118—134°C). An attempt at separating the mixture by crystallization from ethanol did not lead to homogeneous substances. For this reason, 5·6 g mixture was heated with 40 g piperazine hexahydrate and 36 g 4-toluenesulfonic acid for 1 h in an open flask in a bath of 160—170°C, and then for 2 h *in vacuo* to 190°C. After partial cooling, the mixture was distributed between benzene and 1 : 3 diluted NH_4OH. The benzene layer was dried and evaporated, the residue was dissolved in 25 ml acetone and the solution was treated with a solution of 1·6 g maleic acid in 15 ml ethanol. There crystallized 7·0 g crude *XXXI* maleate, m.p. 204—207°C. Recrystalliza-

tion from ethanol gave the analytical sample, m.p. 209–210°C. Mass spectrum, *m/z*: 372 (M^+ corresponding to $C_{20}H_{21}ClN_2OS$), 329 ($M - CH_2NHCH_2$), 72, 56. For $C_{24}H_{25}ClN_2O_5S$ (489·0) calculated: 58·95% C, 5·15% H, 7·25% Cl, 5·73% N, 6·56% S; found: 58·74% C, 4·96% H, 7·29% Cl, 5·69% N, 6·62% S.

The released base was used for recording the ^1H NMR spectrum: δ 6·70–7·50 (m, 6 H, ArH), 6·12 (s, 1 H, 11-H), 3·98 (q, 2 H, CH_2O), 2·90 (bs, 8 H, 4 CH_2N of piperazine), 1·82 (s, 1 H, NH), 1·35 (t, 3 H, CH_3).

1-(2-Chloro-8-ethoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)-piperazine (*XXXII*)

A solution of 4·2 g *XXXI* in 40 ml acetic acid was added dropwise over 30 min to a boiling mixture of 8·0 g Zn and 40 ml acetic acid, and the mixture was refluxed for 2 h. After cooling the mixture was filtered, the solid washed with acetic acid and the filtrate was evaporated *in vacuo*. The residue was treated with 20 ml 5% NaOH and extracted with benzene. The extract was washed with water and then shaken with an excess of 1 : 1 dilute hydrochloric acid. The precipitated hydrochloride was combined with the aqueous layer, the suspension was made alkaline with 20% NaOH, and the base was isolated by extraction with benzene; 2·6 g (62%) base *XXXII* which crystallized from a mixture of cyclohexane and hexane, m.p. 114–117°C. Mass spectrum, *m/z*: 374 (M^+ corresponding to $C_{20}H_{23}ClN_2OS$), 289 (base peak). IR spectrum (KBr): 819, 880 (2 adjacent and solitary Ar—H), 1 237, 1 275, 1 300, 1 320 (Ar—O—R), 1 470, 1 597, 3 035 (Ar), 3 400 cm^{-1} (NH). ^1H NMR spectrum: δ 7·40 (d, J = 8·5 Hz, 1 H, 4-H), 7·30 (d, J = 8·5 Hz, 1 H, 6-H), c. 7·20 (m, 2 H, 1,9-H_2), 7·03 (q, J = 8·5; 2·5 Hz, 1 H, 3-H), 6·60 (q, J = 8·5; 2·5 Hz, 1 H, 7-H), 3·98 (q, J = 7·0 Hz, 2 H, CH_2O), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·85 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·60 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 1·72 (bs, 1 H, NH), 1·37 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{20}H_{23}ClN_2OS$ (374·9) calculated: 64·07% C, 6·18% H, 9·46% Cl, 7·47% N, 8·55% S; found: 64·20% C, 5·89% H, 9·35% Cl, 7·47% N, 8·47% S.

Maleate, m.p. 177–178°C (ethanol–ether). For $C_{24}H_{25}ClN_2O_5S$ (489·0) calculated: 58·95% C, 5·15% H, 7·25% Cl, 5·73% N, 6·56% S; found: 58·89% C, 5·60% H, 7·19% Cl, 5·80% N, 6·54% S.

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