TRICYCLIC NEUROLEPTICS: SYNTHESIS OF METABOLITES OF ISOFLOXYTHEPIN AND SOME RELATED COMPOUNDS

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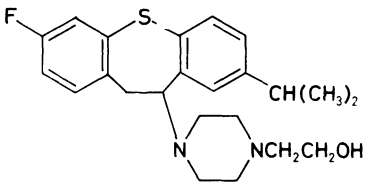
Received December 27, 1989
Accepted February 19, 1990

The isofloxythepin(*I*) metabolite *IV* was synthesized via the acids *IX* and *XI* and the esters *X* and *XII*. The enamine *VIII* was prepared from 3-fluoro-8-(2-propyl)dibenzo[*b,f*]thiepin-10(11*H*)--one by two methods and was reduced to *I*. Cloflumide (*II*) was obtained by reaction of 2,10--dichloro-7-fluoro-10,11-dihydrodibenzo[*b,f*]thiepin with 3-(1-piperazinyl)propionamide and was oxidized to the sulfoxide *XVI*. The unsaturated analogue *XVII* of clopithepin (*III*) was prepared from 2-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one by reaction with 2-bromoethanol in the presence of 4-toluenesulfonic acid in boiling benzene and by the following substitution reaction with 2-(1-piperazinyl)ethanol. An improved synthesis of 6-methyldibenzo[*b,f*]thiepin-10(11*H*)-one (*XIX*) was elaborated. The acid *XXVII* was synthesized and cyclized with polyphosphate ester. A mixture of compounds was formed from which the ketone *XXXVI* was isolated and processed by reaction with formamide and formic acid at 200°C. One of the products was characterized as the formamide *XXXIII* and was reduced with lithium aluminium hydride to a basic product supposed to be *XXXIV*. A series of by-products was isolated and characterized. The enamine *VIII* (VÚFB-17156) was found to be a strong neuroleptic agent, similar to isofloxythepin (*I*). The enol ether *XVII* (VÚFB-17733) was characterized as a mild, practically noncataleptic neuroleptic agent.

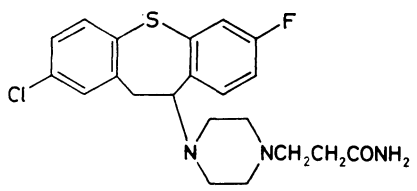
Results of the last stages of our systematic investigations in the series of tricyclic neuroleptics derived from dibenzo[*b,f*]thiepin[1,2] were the following three experimental neuroleptic agents: isofloxythepin (*I*, methanesulfonate VÚFB-14031, refs[3,4]), cloflumide (*II*, methanesulfonate VÚFB-15496, refs[5,6]), and clopithepin (*III*, succinate VÚFB-17076, ref.[7]). The present paper brings some additional data pertaining to the chemistry of *I*–*III* and in general to the chemistry of the series.

Isofloxythepin (*I*) is a clinically successful and very potent oral neuroleptic with long duration of action and relatively few extrapyramidal side effects which was approved for practical use in the therapy of schizophrenia in Czechoslovakia[8–10]; its commercialization, however, was not yet started due to economical considerations (a relatively pretentious manufacturing process[3]). The American[11] and Japanese teams[12–19] contributed importantly to the knowledge of basal pharmacology of *I*.

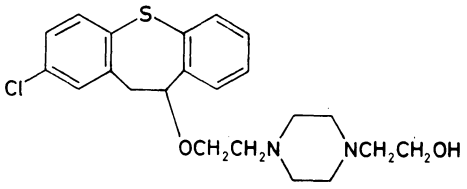
The pharmacokinetics[20-24] and metabolism[20,25] of *I* in experimental animals was investigated in this Institute. The synthesis of isofloxythepin (*I*) S-oxide, N-oxide, N,S-dioxide and N-des(hydroxyethyl) S-oxide as potential metabolites has been described[3]. Out of these only the N,S-dioxide was characterized as a biotransformation product of *I* in a preliminary metabolic study[20] working with [10-^{14}C]isofloxythepin. A more recent study[25] of biotransformation of *I* in rats which used unlabelled *I*, dealt with urine and stools of the animals and was aided by mass spectrometry led to characterization of several metabolites as Ar-hydroxylated derivatives of *I* (position of hydroxyl unknown), Ar- and side chain isopropyl-dihydroxylated derivatives of *I*, Ar-hydroxylated S-oxides, and Ar-hydroxylated and hydroxyethyl--O-ethylated compound, and to identification of *IV*, *V*, and *VIII* as metabolites.



I



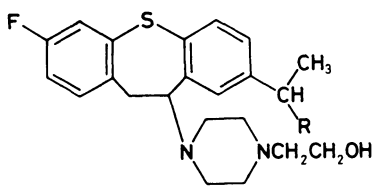
II



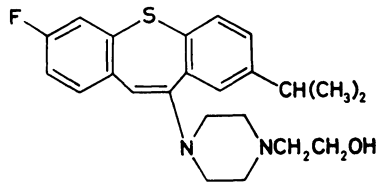
III

The appearance of the Ar- and isopropyl-hydroxylated compounds (including *IV*) and of the corresponding S-oxides could be expected. On the other hand, the appearance of the aliphatic O-ethylated product and of the enamine *VIII* are new phenomena – at least in the present series. Some time ago we followed the idea that the extremely potent enamines of the 10-piperazinodibenzo[*b*,*f*]thiepin series[26-28] (like *VIII*) could be the metabolically originating active products formed from the corresponding 10,11-dihydro compounds which would have explained the originally reported lack of stereoselectivity of action within this series[28]; the whole idea, however, proved erroneous because the stereoselectivity of action of the dihydro compounds was definitely proven[29-32] and the enamines were previously never found as metabolites of the dihydro compounds. The metabolic formation of the ethyl compound *V* may be explained by further metabolic oxidation of *IV* to the acid

VI and by its decarboxylation. Compound *V* has not yet been prepared by synthesis; on the other hand its N-methyl analogue was synthesized[33] and in this way the synthesis of *V* was carried out until the immediate precursor, i.e. 11-chloro-2-ethyl--7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin[33]. The first part of this paper deals with the synthesis of *IV* and *VIII*.



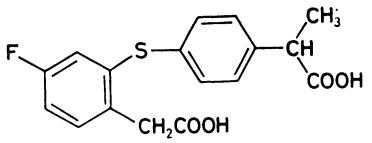
IV, R = CH_2OH
V, R = H
VI, R = COOH
VII, R = $COOC_2H_5$



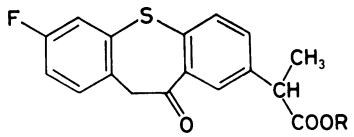
VIII

(4-Fluoro-2-iodophenyl)acetic acid[34] was reacted with 2-(4-mercaptophenyl)propionic acid[35] in a refluxing solution of potassium hydroxide in water in the presence of copper and the oily acid product obtained was chromatographed on silica gel giving 62% of crystalline *IX* which was characterized by mass, IR, and ^{1}H NMR spectra. The product was cyclized with polyphosphate ester[36] (from phosphorus pentoxide and ethanol) in boiling benzene. The very inhomogeneous product was chromatographed on silica gel. The benzene eluates contained small amounts of high-melting contaminants. Chloroform eluted then a homogeneous oily substance which was identified by the ^{1}H NMR spectrum as the keto-ester *X*. It was followed by the crystalline keto-acid *XI*, which was eluted with ethyl acetate and whose structure was confirmed by spectra. The acid *XI* was esterified with ethanol in the presence of chlorotrimethylsilane (for the method, cf. ref.[37]); chromatography of the crude product gave oily *X* in a good yield and the identity with *X*, mentioned above, was confirmed by comparison by thin-layer chromatography. Reduction of *X* with sodium borohydride in aqueous ethanol at room temperature gave a mixture which was separated by chromatography on silica gel. Chloroform eluted the oily hydroxy ester *XII* whose ^{1}H NMR spectrum corroborated the structure. A mixture of chloroform and ethanol eluted then the crystalline diol *XIII* which was also characterized by spectra. The hydroxy ester *XII* was transformed by treatment with hydrogen chloride in benzene to the chloro compound *XIV*, which was reacted in crude state without characterization) with 2-(1-piperazinyl) ethanol in boiling chloroform and gave the oily *VII*. This product was transformed to the crystalline bis(hydrogen maleate) whose analysis and mass spectrum confirmed for the base the expected elemental composition $C_{25}H_{31}FN_2O_3S$. The base *VII*, released from this maleate,

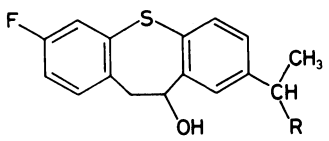
was reduced with an excess of sodium borohydride in aqueous ethanol and afforded the desired *IV* which also was isolated and characterized in the form of the crystalline bis(hydrogen maleate) (analysis and mass spectrum). The enamine *VIII* was prepared from 3-fluoro-8-(2-propyl)dibenzo[*b*,*f*]thiepin-10(11*H*)-one[33] by two methods: (i) by heating with 2-(1-piperazinyl)ethanol mono-4-toluenesulfonate in vacuo to 180 to 190°C (for the method, cf. ref.[28]) and (ii) by reaction with 2-(1-piperazinyl)ethanol in boiling benzene in the presence of titanium tetrachloride (method, cf. refs[27,38,39]). The crystalline *VIII* was obtained in both cases by chromatography of the crude products. was characterized by spectra, and transformed to the crystalline maleate. The enamine *VIII* was reduced with zinc in acetic acid (method, cf. ref.[39]) to *I* which represents a new way of preparation of this compound (the yield, however, is rather moderate).



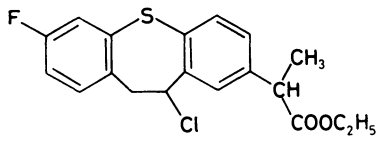
IX



X, R = C_2H_5
XI, R = H



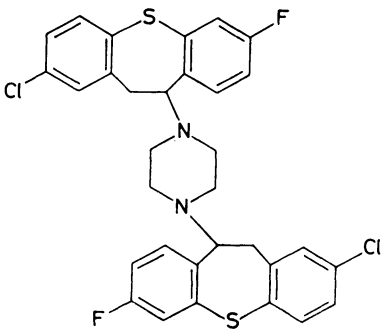
XII, R = $COOC_2H_5$
XIII, R = CH_2OH



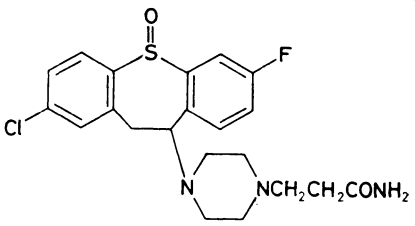
XIV

The preparation of cloflumide (*II*) has been described until now only by addition of 1-(2-chloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl) piperazine to acrylamide[6]. We are describing now its synthesis by substitution reaction of 2,10-dichloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin[40] with 3-(1-piperazinyl)propionamide[6] in boiling chloroform. The strongly basic *II* was transferred from the benzene extract of the crude product into an aqueous solution of methanesulfonic acid and finally obtained in 52% yield as the crystalline base. From the benzene solution a small amount of a highly melting (290–292°C) solid $C_{32}H_{26}Cl_2F_2N_2S_2$ (analysis and mass spectrum) crystallized, to which the structure *XV* was ascribed. The starting 3-(1-piperazinyl)propionamide[6] was evidently slighly contaminated with piperazine which explains the formation of *XV*. It is surprising that this compound crystallized

from the benzene solution directly as the base and was thus not neutralized with methanesulfonic acid used for the isolation of the basic components. The base *II* was transformed to two new crystalline salts – di(methanesulfonate) and (−)-O,O'--dibenzoyl-L-tartrate – both of them solvated with water. Oxidation of *II* methanesulfonate with hydrogen peroxide in water at room temperature gave the crystalline sulfoxide *XVI* which was transformed to the crystalline di(methanesulfonate)monohydrate. The base and the salt were characterized by spectra and the presence of sulfoxide group was verified also by polarographic reduction.

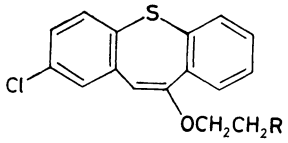


XV



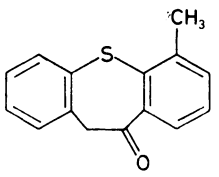
XVI

As a contribution to the series of clopithepin (*III*) (cf. ref.[7]), the corresponding enol ether *XVII* has been prepared. Reaction of 2-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)--one[41] with 2-bromoethanol in boiling benzene in the presence of 4-toluenesulfonic acid and under continuous removal of the formed water by distilling off the benzene–-water azeotrope (method, cf. ref.[42]) gave the enol ether *XVIII* which was oily, was purified by chromatography and fully characterized by spectra. Its substitution reaction with 2-(1-piperazinyl)ethanol was carried out in dimethylformamide at 95 – 100°C in the presence of potassium carbonate. The crude base *XVII* was obtained as a glassy substance and was transformed to the crystalline bis(hydrogen maleate). Its structure was fully corroborated by spectra.

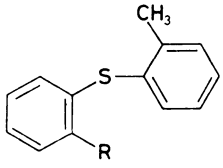


XVII, R = N⟨⟩NCH$_2$CH$_2$OH
XVIII, R = Br

In connection with the necessity to prepare a new batch of 4-methyl-11-(4-methyl-1-piperazinyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin[43] for testing anthelmintic activity, the synthesis of the intermediate *XIX* was importantly improved and partly a new synthetic way was used. Reaction of 2-iodobenzoic acid with 2-methylthiophenol[44] in a boiling potassium hydroxide solution in water in the presence of copper gave *XX* (its synthesis by a different route was described[45]). Reduction of *XX* with lithium aluminium hydride in ether afforded the crystalline *XXI* which was characterized by the IR and ^{1}H NMR spectra. The following treatment of *XXI* with thionyl chloride in boiling benzene gave *XXII* which was processed in crude state by reaction with sodium cyanide in dimethylformamide at 40°C. The oily *XXIII* obtained was processed without purification and characterization by hydrolysis with potassium hydroxide in boiling aqueous ethanol. The acid *XXIV* was obtained, which was prepared formerly by our team[43] by a different route. According to our report[43], the cyclization of *XXIV* with polyphosphoric acid at 130–140°C led mainly to an undesired product and only carrying out the reaction in the presence of boiling toluene gave the ketone *XIX* in a moderate yield. It has been found now that cyclization of *XXIV* with polyphosphoric acid at 100–110°C affords the crystalline and very pure *XIX* in an almost theoretical yield (97%).



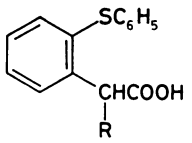
XIX



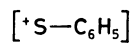
XX, R = COOH
XXI, R = CH_2OH
XXII, R = CH_2Cl
XXIII, R = CH_2CN
XXIV, R = CH_2COOH

The last part of this communication deals with attempts at preparing 10-functionalized 11-phenyl-10,11-dihydrodibenzo[*b*,*f*]thiepins with the final goal to prepare the corresponding 10-amino-11-phenyl compounds. These attempts started with reactions of 2-(phenylthio)benzaldehyde[46] with chloroform and 50% solution of sodium hydroxide in the presence of benzyltriethylammonium chloride (for the method, cf. refs[47–50]) which gave mixtures from which chromatography on silica gel separated crystalline *XXV* and *XXVI*. Reactions of the individual acids *XXV* and *XXVI* or mixture of both with aluminium chloride in benzene at room temperature led to complex mixtures from which the desired *XXVII* was isolated by chromatography and characterized by spectra. There were three more or less important by-products: the least polar one was an oil distilling without decomposition at 114°C/0·13 kPa,

evidently diphenyl sulfide[51]. The more polar components were identified as 2-(phenylthio)benzoic acid[52] and diphenylacetic acid[53]. The last named acid is evidently a product of cleavage of *XXVII* with aluminium chloride. The other cleavage product could be a species equivalent to the phenylsulfenium ion (*XXVIII*) which could react with benzene and afford diphenyl sulfide (cf. ref.[54]). 2-(Phenylthio)benzoic acid is probably a product of oxidation of the starting 2-(phenylthio)benzaldehyde.



XXV, R = Cl
XXVI, R = OH
XXVII, R = C_6H_5

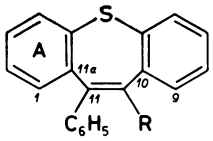


XXVIII

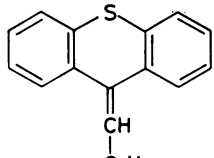
Our attempts at cyclizing *XXVII* had much in common with our earlier trials to cyclize 2-(2-(phenylthio)phenyl)propionic acid[55]. Cyclization of *XXVII* with polyphosphoric acid at 120°C gave a mixture from which chromatography on silica gel separated less than 10% of a crystalline compound $C_{20}H_{14}S$ (analysis and mass spectrum) melting at 117–119·5°C. It is thus an oxygen-free product differing from the starting *XXVII* by the deficit of H_2O_2. The structure *XXIX* was suggested (cf. analogy in ref.[55]) but this compound is known[56] and melts at 150°C. On the other hand, for the isomeric thioxanthene derivative *XXXV* the melting point of 121 to 122°C was reported[56] which is rather close to our value. The very simple ^{1}H NMR spectrum (unresolved aromatic multiplet at δ 6·90–7·80) is in agreement with both formulations. There is one point in favour of *XXXV*: in 70% sulfuric acid it gives an intensive red coloration which is typical for compounds containing the 9-thioxanthenylidene fragment (addition of proton under the formation of the red thioxanthylium cation). Compound *XXXV* could have been formed from the primarily originating *XXIX* by cleavage of the C-11, C-11a bond, by migration of the phenyl ring to C-10 and by the shift of a proton.

On the basis of the just described result, the conditions used in the first cyclization experiment were considered too severe and, therefore, in the following experiments the acid *XXVII* was cyclized with polyphosphoric ester[36] (from phosphorus pentoxide and ethanol) in boiling benzene. Complex mixtures were obtained which were separated by chromatography on silica gel. The following products were isolated and more or less characterized (approximate yield in % given): (i) Thioxanthone[57,58] (20%) partly crystallized from the benzene extract before chromatography, partly was obtained as one fraction of the benzene eluates. It could be formed by oxidation

of compound *XXXV* by air oxygen (compounds of this type are very sensitive to air oxygen and afford easily thioxanthones[59]). (ii) A homogeneous oily product $C_{20}H_{14}OS$ (mass spectrum) was obtained in the yield of about 30% from the first benzene–cyclohexane eluates. It was identified by the IR and ^{1}H NMR spectra as



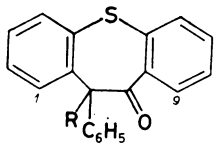
XXIX, R = H
XXX, R = $OCOCH(C_6H_5)_2$
XXXI, R = $NHCH_2CH_2N(CH_3)_2$
XXXII, R = NH_2
XXXIII, R = NHCHO
XXXIV, R = $NHCH_3$



XXXV

the desired ketone *XXXVI*. (iii) A small amount (about 1%) of a crystalline compound $C_{34}H_{24}O_2S$ (analysis and mass spectrum) was obatined by crystallizztion from the crude *XXXVI* from ether and it is considered to be the enol ester *XXX* (spectra are in agreement). (iv) Compounds *XXXVI* and *XXX* were followed in the further benzene eluate by about 17% of the ethyl ester of the starting *XXVII* ($C_{22}H_{20}O_2S$), identified only by the mass spectrum. (v) At the end of elution with benzene some 5% of a crystalline compound $C_{20}H_{14}O_2S$ (analysis and mass spectrum) were obtained which was assigned on the basis of spectra to be the hydroxy ketone *XXXVII*. Such a compound could have been formed by hydrolysis of some ionic intermediate of the complex reaction. (vi) Chloroform eluted some 5% of diphenylacetic acid[53], mentioned already as a product of cleavage of *XXVII*. In the critical cases of the dibenzo[*b*,*f*]thiepin derivatives *XXX*, *XXXVI*, and *XXXVII*, the possibility of their formulation as the corresponding thioxanthene derivatives was seriously considered. For structures *XXXVI* and *XXXVII* there is a rather convincing ^{1}H NMR evidence: shift of the signals of H-9 or H-1 and H-9 which are shielded by the oxygen functions at C-10 or C-10 and C-11. Compound *XXX* did not give the red coloration with 70% sulfuric acid and thus hardly does contain in the molecule the 9-thioxanthenylidene fragment. The reactions of *XXXVI* are mostly anomalous: It did not react with 1-methylpiperazine in boiling benzene in the presence of titanium tetrachloride (cf. ref.[38]) and was recovered unchanged. Reaction of *XXXVI* with sodium hydride in benzene, followed by 2-dimethylaminoethyl chloride (the enol ether or the C-alkylated product was expected) gave almost quantitatively thioxanthone[57,58]. Only reaction of *XXXVI* with 2-dimethylaminoethylamine in boiling benzene in the presence of titanium tetrachloride afforded a basic product which gave a crystalline maleate. Its mass spectrum detected the presence

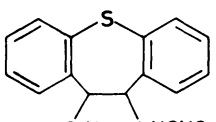
of the desired *XXXI* but the salt was a mixture containing the maleate of 2-dimethylaminoethylamine, which also was detected by the GC-MS spectrometer.



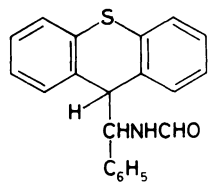
XXXVI, R = H
XXXVII, R = OH

Compound *XXXVI* was subjected to the Leuckart–Wallach reaction[60], i.e. to heating with formic acid and formamide to 200°C. The mixture formed was chromatographed on silica gel. Benzene eluted about 20% of crystalline $C_{20}H_{15}NS$ (analysis and mass spectrum) which was assigned to be *XXXII*. The IR spectrum showed the presence of the conjugated C=C fragment (1 611 cm^{-1}) and of C=C—NH_2 (bands at 1 660 and 3 410 cm^{-1}). This compound was followed by some 15% of a different solid $C_{21}H_{15}NOS$ (analysia nd mass spectrum) which is formulated as *XXXIII*. The IR spectrum indicates clearly the fragment RNHCHO (bands at 1 550 and 1 685 cm^{-1}); on the other hand, the band at 1 611 cm^{-1} is missing. The close relation between *XXXII* and *XXXIII* was confirmed by transformation of *XXXII* to *XXXIII* by formylation with acetic-formic anhydride[61]. The last product of the Leuckart–Wallach reaction, which was eluted with chloroform, was a further solid (some 10%) which crystallized from benzene as a benzene solvate and corresponded to $C_{21}H_{17}NOS + C_6H_6$ (analysis and mass spectrum). On the basis of spectra, the structure *XXXVIII* was assigned to it (probably mixture of stereoisomers). In a further experiment, the crude *XXXVI* was used and the reaction time was prolonged. A different saturated formamido derivative $C_{21}H_{17}NOS$ was obtained which crystallized from benzene as a nonsolvated substance. Its mass spectrum differs greatly from that of *XXXVIII*. Whereas the base peak in the spectrum of *XXXVIII* has m/z 286, the base peak in the spectrum of the isomer has m/z 197 which corresponds to the thioxanthylium cation. This substance is, therefore, formulated as *XXXIX*. Reduction of the crude *XXXIII* with lithium aluminium hydride in tetrahydrofuran led also to a mixture, from which neutralization with maleic acid separated directly one component as the crystalline maleate $C_{21}H_{19}NOS + C_4H_4O_4$ (analysis and mass spectrum). The elemental composition of the base contains evidently one unexpected atom of oxygen which does not belong to a sulfoxide group (the test with polarographic reduction was negative). We have to assume that the precursor of this product was the hydroxy ketone *XXXVII* which contaminated the starting *XXXVI*; this assumption leads to formula *XL* for the compound under discussion. The base, released from the mother liquors after the crystalline

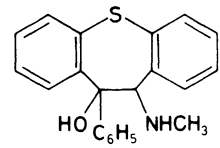
maleate, was chromatographed on silica gel, which led to some 15% of a homogeneous base, characterized by the mass spectrum as the expected base $C_{21}H_{17}NS$. The ^1H NMR spectrum is in agreement with structure *XXXIV* and the compound was transformed to a crystalline hydrochloride which appears to be a 2 : 3 solvate with water. We have to conclude that for preparing 10-amino-11-phenyl-10,11--dihydrodibenzo[*b*,*f*]thiepin derivatives, the approach we used is not suitable and is complicated by many side reactions and formation of complex mixtures.



XXXVIII



XXXIX



XL

It was proven that the isofloxythepin metabolite *IV* (bis(hydrogen maleate) VÚFB-17652) retains some antidopaminergic activity. In the concentration of 1 000 nmol l^{-1} it inhibited the binding of 0·5 nM [^{3}H]spiperone in the rat brain striatum in vitro by more than 50%. The enamine *VIII* was tested as the maleate (VÚFB-17156); cf. ref.[62]; it was administered orally. Acute toxicity in mice, LD_{50} = = 394 mg/kg. Ataxic activity in the rotarod test in mice, ED_{50} = 7·3 mg/kg. Inhibition of spontaneous locomotor activity in mice in the photo-cell method, in 1 h after the administration D_{50} = 1·95 mg/kg, in 24 h D_{50} = 3·1 mg/kg (the central depressant effect is protracted). Cataleptic activity in rats, ED_{50} = 4·4 mg/kg. Inhibition of the apomorphine-induced climbing behaviour in rats, PD_{50} = 2·3 mg/ /kg. Inhibition of apomorphine-induced stereotypies in rats, D_{50} = 4·5 mg/kg. Antagonization of the adrenaline-induced lethality in mice, PD_{50} = 0·32 mg/kg. In conclusion: the enamine *VIII* has similar pharmacological properties like isofloxythepin (*I*) including the protraction of effects.

It is necessary to supplement the data on the pharmacology of cloflumide (*II*, refs[5,6,63,64]) and clopithepin (*III*, refs[7,64]). The finding of a rather important cataleptic activity of *II* after intraperitoneal administration led to reinvestigation of its cataleptic activity after oral administration in rats. It was found that the previously published data were not correct; the ED_{50} value is in fact 46 mg/kg. After a very promising result of comparison of *III* with clozapine[7,64], *III* was also pharmacologically compared with chlorpromazine[65] and the result was less favourable (*III* is less cataleptic than chlorpromazine but also less active in the desirable lines of activity of a neuroleptic agent). These new findings led to discontinuation of development of *II* and *III*.

The enol ether *XVII* (bis(hydrogen maleate) VÚFB-17733) was also pharmacologically tested (oral administration). Acute toxicity in mice, LD_{50} = 892 mg/kg (108 mg/kg i.v.). Ataxic activity in mice, ED_{50} = 112 mg/kg. Inhibition of locomotor activity in mice, D_{50} = 32·7 mg/kg. Intensive inhibition of amphetamine toxicity in aggregated mice, PD_{50} = 32·6 mg/kg (administered 60 min before amphetamine). Inhibition of the apomorphine-induced climbing behaviour in mice, PD_{50} = 21 mg/kg. The compound lacks in doses of 100 and 200 mg/kg any protective action from the adrenaline toxicity in mice and in doses of 50 and 100 mg/kg from the noradrenaline toxicity in rats. Cataleptic activity in rats, the dose of 100 mg/kg brings about catalepsy in 20% of animals. Affinity to dopamine D-2 receptors in rat brain striatum in vitro: in the concentration of 1 000 nmol l^{-1} *XVII* inhibited the binding of 0·5 nM-[^{3}H]spiperone by more than 50%.

Compound *XL* was tested in the form of the hydrogen maleate as a potential antidepresant and showed some activity in this line. It inhibited the re-uptake of 10 nM-[^{3}H]noradrenaline in the rat brain cortex, IC_{50} = 27·2 nmol l^{-1}. It showed some affinity to serotonergic S-2 receptors in the rat brain cortex by inhibition of binding of 1 nM-[^{3}H]ketanserine, IC_{50} = 161 nmol l^{-1}. In oral doses of 100 mg/kg it potentiated the yohimbine toxicity in 40% of mice and did not antagonize the reserpine-induced ptosis in mice.

EXPERIMENTAL

The melting points were determined in the Mettler FP-5 melting point recorder or in a Kofler block; the samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (mostly in NUJOL, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, NMR spectra (in $CDCl_3$ unless stated otherwise, δ in ppm, J in Hz) with the FT-NMR spectrometer TESLA BS 567A (^{1}H at 100 MHz, ^{13}C at 25·14 MHz), and the mass spectra (m/z, %) with a Varian MAT 44S (GC-MS) spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

(2-(4-(1-Carboxyethyl)phenylthio)-4-fluorophenyl)acetic Acid (*IX*)

A mixture of 17·4 g 2-(4-mercaptophenyl)propionic acid[35], 25·3 g (4-fluoro-2-iodophenyl)acetic acid[34], 1·0 g Cu, 18·6 g KOH, and 33 ml water was stirred and refluxed under nitrogen for 5·5 h. After partial cooling the mixture was diluted with 150 ml water, filtered, and the filtrate was acidified with dilute hydrochloric acid (1 : 1). The product was extracted with chloroform. The crude product, obtained by processing of the extract, was chromatographed on 300 g silica gel. The first chloroform eluates were discarded. Further chloroform and ethyl acetate eluates gave 18·9 g (62%) of *IX*, m.p. 159–160·5°C (benzene–hexane). IR spectrum: 800, 859 (2 adjacent and solitary Ar–H); 929, 1 237, 1 692, 2 540, 2 630, 2 720, infl. 3 050 (COOH); 1 482, 1 579, 1 593 (Ar). ^{1}H NMR spectrum (CD_3SOCD_3): 1·37 d, 3 H (CH_3, J = 7·0); 3·70 q, 1 H (ArCHCO, J = 7·0); 3·76 s, 2 H ($ArCH_2CO$); 7·30 s, 4 H (4 ArH of 1,4-substituted benzene); 6·80–7·60 m,

3 H (H-3, H-5, and H-6). For $C_{17}H_{15}FO_4S$ (334·4) calculated: 61·07% C, 4·52% H, 9·59% S; found: 61·06% C, 4·62% H, 9·55% S.

2-(7-Fluoro-11-oxo-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)propionic Acid (*XI*)

A mixture of 130 ml benzene, 30 g P_2O_5, and 15 ml ethanol was refluxed for 3 h and treated with a suspension of 10·6 g *IX* in 250 ml benzene. The mixture was stirred and refluxed for 20 h, the benzene solution was decanted, dried, evaporated, and chromatographed on 200 g silica gel. Benzene eluted some high-melting contaminants and chloroform eluted 0·65 g of homogeneous oily ethyl 2-(7-fluoro-11-oxo-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)propionate (*X*). ^{1}H NMR spectrum: 1·20 t, 3 H (CH_3 of ethyl, J = 7·0); 1·50 d, 3 H (CH_3 of the propionyl residue, J = = 7·0); 3·76 q, 1 H (ArCHCO, J = 7·0); 4·14 q, 2 H (OCH_2, J = 7·0); 4·34 s, 2 H ($ArCH_2CO$ in the ring); 6·90—7·50 m, 4 H (H-3, H-6, H-8, H-9); 7·60 d, 1 H (H-4, J = 9·0); 8·16 d, 1H, (H-1, J = 3·0).

Continued elution with ethyl acetate gave 3·83 g (38%) of homogeneous *XI*, m.p. 152—154°C (benzene). UV spectrum: 241 (4·32), infl. 258 (4·07), 327 (3·56). IR spectrum: 829, 878 (2 adjacent and solitary Ar–H); 925, 1 698, 2 700, infl. 3 160 (COOH); 1 226 (Ar–F and COOH); 1 484, 1 593, 3 020, 3 095 (Ar); 1 671 (ArCOR). ^{1}H NMR spectrum: 1·50 d, 3 H (CH_3, J = 7·0); 3·76 q, 1 H (ArCHCO, J = 7·0); 4·35 s, 2 H ($ArCH_2CO$ in the ring); 7·10 dt, 1 H (H-8, J = 8·5; 1·5); 7·20—7·60 m, 4 H (H-3, H-4, H-6, and H-9); 8·18 d, 1 H (H-1, J = 2·0). For $C_{17}H_{13}FO_3S$ (316·3) calculated: 64·55% C, 4·14% H, 6·01% F, 10·13% S; found: 64·67% C, 4·31% H, 5·98% F, 10·27% S.

Ethyl 2-(7-Fluoro-11-oxo-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)propionate (*X*)

A solution of 3·5 g *XI* in 75 ml ethanol was treated with 4 ml chlorotrimethylsilane and the mixture was allowed to stand for 7 days at room temperature. Evaporation of ethanol and chromatography of the residue on 60 g silica gel gave by elution with benzene 3·08 g (81%) of oily *X*, which was found identical (TLC) with the compound described and characterized above.

Ethyl 2-(7-Fluoro-11-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl) Propionate (*XII*)

A solution of 2·9 g *X* in 30 ml ethanol was stirred and treated with a solution of 0·25 g $NaBH_4$ in 1·5 ml water containing 1 drop of 20% NaOH. The mixture was stirred for 4 h, evaporated, the residue was distributed between water and benzene, the benzene layer was processed, and the residue was chromatographed on 50 g silica gel. Benzene eluted some contaminants and chloroform eluted 0·60 g (21%) of homogeneous oily *XII* which was characterized by the ^{1}H NMR spectrum: 1·18 t, 3 H (CH_3 of ethyl, J = 7·0); 1·42 d, 3 H (CH_3 of the propionyl residue, J = 7·0); 2·08 bd, 1 H (OH); 3·20—3·80 m, 3 H ($ArCH_2$ in the ring and ArCHCO); 4·10 q, 2 H (OCH_2, J = 7·0); 5·30 bm, 1 H (H-11); 6·80—7·60 m, 6 H (ArH).

The elution with a mixture of chloroform and ethanol afforded 0·56 g (22%) of 2-(7-fluoro-11--hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-2-yl)propanol (*XIII*), m.p. 124—127°C (benzene). IR spectrum: 810, 861, 898 (2 adjacent and solitary Ar–H); 1 023, 1 052 (CH_2OH and CHOH in the ring); 1 490, 1 600 (Ar); 3 300 (OH). ^{1}H NMR spectrum: 1·22 d, 3 H (CH_3, J = 7·0); 2·50 bs, 2 H (2 × OH); 2·87 m, 1 H (ArCH); 3·51 d, 2 H (CH_2O, J = 7·0); 3·30 dd and 3·70 dd, 1 and 1 H (2 × H-10, J = 13·0; 8·0 and 13·0; 3·0); 5·30 dd, 1 H (H-11, J = 8·0; 3·0); 6·90 to 7·50 m, 6 H (ArH). For $C_{17}H_{17}FO_2S$ (304·4) calculated: 67·08% C, 5·63% H, 6·24% F, 10·53% S; found: 66·80% C, 5·58% H, 6·21% F, 10·46% S.

Ethyl 2-(7-Fluoro-11-(4-(2-hydroxyethyl)-1-piperazinyl)-10,11-dihydrodibenzo[*b,f*]thiepin-2-yl)propionate (*VII*)

A mixture of 1·6 g *XII*, 0·8 g powdered $CaCl_2$, and 30 ml benzene was saturated during 2 h with HCl under external cooling (ice and water). Afer standing overnight, the mixture was filtered and the filtrate was evaporated. The residue (crude *XIV*) was treated with a solution of 2·8 g 2-(1-piperazinyl)ethanol in 4 ml chloroform and the mixture was refluxed for 8 h. It was diluted with benzene, washed with water and from the benzene layer the base was extracted into dilute aqueous methanesulfonic acid. The aqueous layer was made alkaline with NH_4OH, the product was extracted with benzene, and the benzene extract was processed. The residue was neutralized with 0·45 g maleic acid in ether giving 2·0 g (63%) of *VII* bis(hydrogen maleate), m.p. 63–65°C (ethyl acetate–ether). Mass spectrum: 458 (M^+, $C_{25}H_{31}FN_2O_3S$, 4), 440 (3), 427 (4), 413 (2), 385 (3), 357 (4), 329 (40), 255 (30), 228 (15), 129 (40), 100 (100). For $C_{33}H_{39}FN_2O_{11}S$ (690·8) calculated: 57·38% C, 5·69% H, 2·75% F, 4·06% N, 4·64% S; found: 57·06% C, 5·88% H, 2·86% F, 4·10% N, 4·79% S.

2-(7-Fluoro-11-(4-(2-hydroxyethyl)-1-piperazinyl)-10,11-dihydrodibenzo[*b,f*]thiepin-2-yl)propanol (*IV*)

A solution of 1·35 g *VII* (released from 1·9 g of the maleate) in 30 ml ethanol was treated with a solution of 1·0 g $NaBH_4$ in 2 ml water, the mixture was stirred for 2·5 h, allowed to stand overnight, evaporated, the residue was diluted with water, and extracted with ether. Processing of the extract and neutralization of the residue with 0·7 g maleic acid in a mixture of ether and acetone gave 1·33 g (70%) of bis(hydrogen maleate) of *IV*, m.p. 78–80°C (acetone–ether). Mass spectrum: 416 (M^+, $C_{23}H_{29}FN_2O_2S$, 5). For $C_{31}H_{37}FN_2O_{10}S$ (648·7) calculated: 57·40% C, 5·75% H, 2·93% F, 4·32% N, 4·94% S; found: 57·23% C, 5·86% H, 2·98% F, 4·38% N, 5·20% S.

2-(4-(7-Fluoro-2-(2-propyl)dibenzo[*b,f*]thiepin-11-yl)-1-piperazinyl)ethanol (*VIII*)

(*A*) A mixture of 8·4 g 3-fluoro-8-(2-propyl)dibenzo[*b,f*]thiepin-10(11*H*)-one[33], 11·5 g 2-[1-piperazinyl)ethanol, and 16·7 g 4-toluenesulfonic acid monohydrate was heated for 2 h to 180 to 190°C at normal pressure and for 3 h to the same temperature (bath temperature) under reduced pressure (water pump). After cooling the melt was distributed between 220 ml benzene and 220 ml dilute NH_4OH (1 : 1). The benzene layer was washed with water, dried, and evaporated. The residue was chromatographed on 300 g neutral Al_2O_3 (activity II). Elution with benzene removed some contaminants and elution with a mixture of benzene with 8% ethanol gave 5·8 g (50%) of homogeneous *VIII* which crystallized from cyclohexane, m.p. 77–79°C. UV spectrum: infl. 260 (4·35), 299 (4·15). IR spectrum: 821, 840, 869 (2 adjacent and solitary Ar–H); 1 061, 3 180 (CH_2OH); 1 481, 1 575, 1 590 (Ar); 1 612 (C=C in conjugation). ^1H NMR spectrum: 1·25 d, 6 H (2 × CH_3 of 2-propyl, J = 7·0); 2·50–3·20 m, 12 H (5 × CH_2N, ArCH, and OH); 3·48 bt, 2 H (CH_2O, J = 7·0); 6·28 s, 1 H (H-10); 6·80–7·60 m, 6 H (ArH). For $C_{23}H_{27}FN_2OS$ (398·5) calculated: 69·31% C, 6·83% H, 7·03% N, 8·04% S; found: 69·33% C, 7·16% H, 7·09% N, 7·91% S.

Maleate, m.p. 160–161°C (ethanol–ether). For $C_{27}H_{31}FN_2O_5S$ (514·6) calculated: 63·02% C, 6·07% H, 3·69% F, 5·44% N, 6·23% S; found: 63·34% C, 6·11% H, 3·79% F, 5·63% N, 6·41% S.

(*B*) A solution of 8·6 g 3-fluoro-8-(2-propyl)dibenzo[*b,f*]thiepin-10(11*H*)-one[33] and 29·3 g 2-(1-piperazinyl)ethanol in 60 ml benzene was treated under stirring over 5 min with 7·6 g $TiCl_4$ in 30 ml benzene, added dropwise. The mixture was refluxed for 50 h, after cooling decomposed with 200 ml water, the precipitated solid was filtered off and washed with benzene, the filtrate

was separated, the benzene layer was dried, and evaporated. The residue was chromatographed on 300 g neutral Al_2O_3 (activity II). Benzene with 8% ethanol eluted 3·3 g (28%) of homogeneous *VIII*, m.p. 75—79°C (light petroleum), which was found identical with the product obtained under (*A*).

2-(4-(7-Fluoro-2-(2-propyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-
-11-yl)-1-piperazinyl)ethanol (*I*)

A stirred suspension of 5·5 g Zn in 50 ml acetic acid was treated at 100°C with 3·0 g *VIII*. The mixture was refluxed for 2 h, cooled, filtered, and the filtrate was evaporated in vacuo. The residue was refluxed for 1 h with a solution of 6 ml 35% NaOH in 45 ml ethanol, the mixture was evaporated in vacuo, and the residue was distributed between 100 ml water and 100 ml benzene. From the benzene layer the product was extracted into a solution of 3·5 g methanesulfonic acid in 50 ml water. The acid solution was made alkaline with NH_4OH and the base was extracted with benzene. Processing of the extract and crystallization of the residue from 5 ml light petroleum gave 0·9 g (30%) of *I*, m.p. 92—95°C, identical with the product prepared previously[3]. Ref.[3], m.p. 93—95°C.

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

A solution of 75 g 2,10-dichloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin[40] in 225 ml chloroform was stirred and treated at 50°C with 78 g 3-(1-piperazinyl)propionamide[6]. The mixture was stirred and refluxed for 8 h and chloroform was completely evaporated (at the end under reduced pressure). The residue was stirred for 20 min with a solution of 60 g methanesulfonic acid in 700 ml water and the solution was washed with 500 ml benzene. It was fitered with active carbon, the filtrate was made alkaline with NH_4OH, and the product was isolated by extraction with chloroform. Processing of the extract and crystallization of the residue from benzene gave 55·1 g (52%) of *II*, m.p. 174—178°C. Crystallization from a mixture of ethanol and light petroleum gave pure *II*, m.p. 183—184°C. Ref.[6], m.p. 183—184°C.

Di(methanesulfonate) monohydrate, m.p. 159—160°C with decomposition (ethanol). For $C_{23}H_{31}ClFN_3O_7S_3 + H_2O$ (630·2) calculated: 43·83% C, 5·28% H, 5·63% Cl, 3·02% F, 6·66% N, 15·27% S; found: 44·16% C, 5·54% H, 5·68% Cl, 3·19% F, 6·46% N, 15·00% S.

(—)-O,O'-*Dibenzoyl*-L-*tartrate*, m.p. 118—121°C (ethyl acetate). For $C_{39}H_{37}ClFN_3O_9S$ (778·2) calculated: 60·19% C, 4·79% H, 4·56% Cl, 2·44% F, 5·40% N, 4·12% S; found: 59·97% C, 5·02% H, 4·71% Cl, 2·33% F, 5·17% N, 4·12% S.

The benzene washings (after the isolation of *II* methanesulfonate) were partly evaporated and from the residue there crystallized on standing 2·7 g of 1,4-bis(2-chloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)piperazine (*XV*), m.p. 290—292°C (pyridine). Mass spectrum: 610 (M^+, $C_{32}H_{26}Cl_2F_2N_2S_2$). IR spectrum: 819, 875 (2 adjacent and solitary Ar–H); 1 212 (Ar–F); 1 481, 1 580, 1 600, 3 060 (Ar). For $C_{32}H_{26}Cl_2F_2N_2S_2$ (611·6) calculated: 62·84% C, 4·29% H, 11·60% Cl, 6·21% F, 4·58% N, 10·48% S; found: 62·78% C, 4·11% H, 11·56% Cl, 6·42% F, 4·71% N, 10·56% S.

3-(4-(2-Chloro-7-fluoro-10,11-dihydrodibenzo[*b*,*f*]thiepin-
10-yl)-1-piperazinyl)propionamide S-Oxide (*XVI*)

A solution of 7·65 g *II* methanesulfonate[6] in 75 ml water was acidified with 0·2 g methanesulfonic acid and was treated with 55 ml 30% H_2O_2 and the mixture was allowed to stand for 45 h at

room temperature. It was then filtered, the filtrate was made alkaline with NH_4OH, and the product was extracted with chloroform. Processing gave 3·8 g of the crude product which was crystallized from a mixture of 3 ml acetone and 5 ml light petroleum; 3·6 g (56%) of *XVI*, m.p. 185–186°C (ethanol–light petroleum), UV spectrum: infl. 270 (3·98), infl. 300 (3·76). IR spectrum: 829, 851, 877 (2 adjacent and solitary Ar–H); 1 088 (S–O); 1 484, 1 553, 3 060 (Ar); 1 681 ($CONH_2$); 3 155, 3 373 (NH_2). ^{1}H NMR spectrum: 2·20–2·80 bm, 12 H (5 × CH_2N and CH_2CO); 3·04 m and 3·60 m, 1 and 1 H (2 × H-11); 4·22 dd, 1 H (H-10); 5·60 bs, 2 H (NH_2); 7·00–7·90 m, 6 H (ArH). For $C_{21}H_{23}ClFN_3O_2S$ (435·9) calculated: 57·86% C, 5·32% H, 8·13% Cl, 4·36% F, 9·64% N, 7·35% S; found: 57·85% C, 5·45% H, 8·17% Cl, 4·58% F, 9·53% N, 7·39% S.

Dimethanesulfonate monohydrate, m.p. 138–143°C (ethanol–acetone). Mass spectrum, NDCI: 435 (M^+, $C_{21}H_{23}ClFN_3O_2S$); EI: 364 (1), 349 (14), 347 (37), 262 (16), 249 (11), 232 (27), 230 (80), 196 (14), 194 (17), 174 (10), 96 (30), 85 (57), 79 (38), 56 (100), 44 (66). IR spectrum: 774, 889 (2 adjacent and solitary Ar–H); 1 040 (Ar–S–O); 1 221 (RSO_3^-); 1 540, 1 600, 3 010, 3 050 (Ar); 1 675 ($RCONH_2$); 2 460, 2 580, 2 680 (NH^+); 3 200, 3 400, infl. 3 500 (NH_2, OH, H_2O). Polarographic reduction in 0·25M-H_2SO_4 versus a saturated calomel electrode, $E_{1/2} = -0{\cdot}62$ V (reduction of S–O). For $C_{23}H_{31}ClFN_3O_8S_3 + H_2O$ (646·1) calculated: 42·75% C, 5·15% H, 5·49% Cl, 2·94% F, 6·50% N, 14·88% S; found: 42·67% C, 5·28% H, 5·28% Cl, 3·08% F. 6·18% N, 14·55% S.

10-(2-Bromoethoxy)-2-chlorodibenzo[*b,f*]thiepin (*XVIII*)

A solution of 13·0 g 2-chlorodibenzo[*b,f*]thiepin-10(11*H*)-one[41] in 350 ml benzene was treated with 18·7 g 2-bromoethanol and 1·35 g 4-toluenesulfonic acid monohydrate and the mixture was slowly distilled through a column and the wet distillate was substituted by dry benzene. After 14 h of distillation and after cooling the mixture was washed with 300 ml 5% NaOH and 300 ml water, was dried, and evaporated; The residue (14·9 g) was dissolved in 35 ml benzene and the solution was chromatographed on 300 g silica gel. Benzene eluted in the first fractions 6·0 g (33%) of homogeneous *XVIII*. Mass spectrum: 366 (M^+, $C_{16}H_{12}BrClOS$), 261, 259, 109, 107. UV spectrum: infl. 216 (4·44), 262 (4·22), infl. 320 (3·47). IR spectrum: 760, 715, 880 (4 and 2 adjacent and solitary Ar–H); 1 096, 1 125, 1 229 (=C–O–R); 1 477, 1 560, 1 576, 3 055, 3 080 (Ar); 1 669 (C=C). ^{1}H NMR spectrum: 3·72 t, 2 H (CH_2Br); 4·34 t, 2 H (CH_2O); 6·28 s, 1 H (Ar–CH=C); 7·00–7·80 m and 8·20 m, $\sum$ 7 H (ArH). For $C_{16}H_{12}BrClOS$ (367·7) calculated: 52·26% C, 3·29% H, 21·74% Br, 9·64% Cl, 8·72% S; found: 52·56% C, 3·42% H, 21·74% Br, 9·65% Cl, 8·78% S.

2-(4-(2-(2-Chlorodibenzo[*b,f*]thiepin-10-yloxy)ethyl)-1-piperazinyl)ethanol (*XVII*)

A solution of 5·40 g *XVIII* and 2·6 g 2-(1-piperazinyl)ethanol in 25 ml dimethylformamide was treated with 2·8 g K_2CO_3, stirred for 1 h at room temperature, and heated for 6 h to 100°C. After standing overnight it was diluted with benzene, washed with water, filtered with active carbon, and evaporated. The glassy residue (6·1 g) was neutralized with 1·7 g maleic acid in a mixture of 2 ml ethanol and 35 ml ether; there crystallized 5·4 g (57%) of the bis(hydrogen maleate), m.p. 177–178°C (ethanol). Mass spectrum: 416 (M^+, $C_{22}H_{25}ClN_2O_2S$, 2), 398, 385, 285, 231 (3), 157 (70), 143 (100). UV spectrum: 264 (4·32), infl. 287 (4·18). ^{1}H NMR spectrum (CD_3SOCD_3): 2·80–3·40 m, 12 H (6 × CH_2N); 3·78 t, 2 H (CH_2O of alcohol, $J = 6{\cdot}0$); 4·26 t, 2 H (OCH_2 of ether, $J = 5{\cdot}0$); 6·12 s, 2 H (CH=CH of maleic acid); 6·58 s, 1 H (ArCH=C); 7·00–7·80 m, 7 H (ArH). For $C_{30}H_{33}ClN_2O_{10}S$ (649·1) calculated: 55·51% C, 5·12% H, 5·46% Cl, 4·32% N, 4·94% S; found: 55·21% C, 5·21% H, 5·32% Cl, 4·24% N, 5·11% S.

2-(2-Methylphenylthio)benzoic Acid (*XX*)

2-Methylthiophenol[44] (24·7 g), 47·1 g 2-iodobenzoic acid, and 1·25 g Cu were added to a solution of 36 g KOH in 380 ml water and the mixture was stirred and refluxed for 7 h. The mixture was filtered and the cooled filtrate was acidified with 5M-HCl. The precipitated product was filtered after standing overnight, washed with water, and dried in vacuo; 46·1 g (99%) of *XX*, m.p. 170 to 174°C. Crystallization from toluene gave the product melting at 175–176·5°C. UV spectrum: 224 (4·41), 253 (3·95), infl. 270 (3·69), 314 (3·64). IR spectrum: 749 (4 adjacent Ar–H); 919, 1 258, 1 670, 2 555, 2 640 (ArCOOH); 1 555, 1 584, 3 055 (Ar). ^{1}H NMR spectrum (CD_3SOCD_3): 2·39 s, 3 H ($ArCH_3$); 6·56 bd, 1 H (H-3); 7·00–7·60 m, 6 H (4 × ArH of tolylthio, H-4, and H-5); 7·94 bd, 1 H (H-6). ^{13}C NMR spectrum (CD_3SOCD_3): 20·02 q (CH_3); 124·44 d, 127·51 d, 127·51 s, 130·05 d, 131·09 d, 132·43 d (6 × aromatic —C=); 131·09 d (C-6); 131·09 s (C-2′); 136·54 d (C-4); 141·17 s (C-1′); 142·30 s (C-2); 167·39 s (COOH). Ref.[45], m.p. 175–176°C.

2-(2-Methylphenylthio)benzyl Alcohol (*XXI*)

A solution of 7·3 g *XX* in 50 ml ether was slowly added to a stirred solution of 2·3 g $LiAlH_4$ in 35 ml ether and the mixture was stirred and refluxed for 6 h. After cooling it was decomposed by slow addition under stirring of 2·3 ml water, 2·3 ml 20% NaOH, and 5 ml water. After the addition of 2·3 g K_2CO_3 and standing for 30 min the solid was filtered off, washed with ether, and the filtrate was evaporated giving 6·9 g (theoretical) of *XXI*, m.p. 39–42°C. Recrystallization from a mixture of toluene and hexane gave the product melting at 42–43°C. IR spectrum: 743, 753 (4 adjacent Ar–H); 1 030, 3 240 (CH_2OH); 1 569, 1 589, 3 055 (Ar). ^{1}H NMR spectrum: 2·10 bt, 1 H (OH); 2·38 s, 3 H ($ArCH_3$); 4·78 bd, 2 H ($ArCH_2O$); 7·00–7·60 bm, 8 H (ArH). For $C_{14}H_{14}OS$ (230·3) calculated: 73·00% C, 6·13% H, 13·92% S; found: 72·75% C, 6·08% H, 13·63% S.

(2-(2-Methylphenylthio)phenyl)acetic Acid (*XXIV*)

A solution of 26·4 g *XXI* in 80 ml benzene was treated under stirring with a solution of 25·3 g $SOCl_2$ in 15 ml benzene, added dropwise at 40°C over 20 min. The mixture was stirred for 1 h at 50°C and refluxed for 1·5 h. Complete evaporation of the volatile components in vacuo gave 26·3 g of oily *XXII*. It was dissolved in 25 ml dimethylformamide, the solution was treated with 7·75 g NaCN, stirred for 1 h at 40°C, diluted with water, and extracted with benzene. Processing gave 25·4 g of oily *XXIII*. It was dissolved in 80 ml ethanol, treated with a solution of 23·8 g KOH in 50 ml water and the mixture was refluxed for 3 h. Ethanol was evaporated, the aqueous residue was washed with benzene and acidified with 70 ml 5M-HCl. The precipitated product was crystallized from aqueous ethanol; 22·0 g (80%) of *XXIV*, m.p. 83–86°C. Ref.[43], m.p. 87–89°C.

6-Methyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIX*)

Polyphosphoric acid was prepared from 71 g 85% H_3PO_4 and 33 g P_2O_5 (heating to 120°C for 45 min). At 100°C, 22·0 g *XXIV* were added under stirring, the mixture was stirred for 15 min at 100–110°C, cooled, diluted with 200 ml ice-cold water and extracted with benzene. The extract was washed with 10% NaOH and water, filtered with active carbon, dried, and evaporated; 19·8 g (97%) of crystalline *XIX*, m.p. 100–103°C. Ref.[43], m.p. 103–106°C.

2-Hydroxy-2-(2-(phenylthio)phenyl)acetic Acid (*XXVI*)

A stirred mixture of 42·8 g 2-(phenylthio)benzaldehyde[46], 200 ml chloroform, and 2·5 g benzyl-

triethylammonium chloride was treated at 50°C (occasional cooling was necessary) with 160 g 50% NaOH over 2·5 h. The stirring was continued for 1·5 h, after cooling the mixture was diluted with ether and washed twice with water. The aqueous solution was separated, acidified with hydrochloric acid, and the products were extracted with ether. The extract was processed and the residue was chromatographed on 1 kg silica gel. Elution with chloroform gave 16·8 g (30%) of 2-chloro-2-(2-(phenylthio)phenyl)acetic acid (*XXV*), m.p. 133–134·5°C (benzene–light petroleum). For $C_{14}H_{11}ClO_2S$ (278·8) calculated: 60·32% C, 3·98% H, 11·50% S; found: 60·32% C, 4·03% H, 11·49% S.

The chromatography was continued by elution with chloroform to which first ethyl acetate and then ethanol was added. This led to 26·75 g (51%) of *XXVI*, m.p. 113·5–115°C (benzene–light petroleum). UV spectrum: 249 (3·99), infl. 271 (3·67). IR spectrum: 703, 740, 759 (5 and 4 adjacent Ar–H); 910, 1 300, 1 710, 2 640 (RCOOH); 1 480, 1 582, 3 055 (Ar); 1 100, 3 270 (CHOH). For $C_{14}H_{12}O_3S$ (260·3) calculated: 64·60% C, 4·65% H, 12·32% S; found: 64·30% C, 4·68% H, 12·32% S.

2-Phenyl-2-(2-(phenylthio)phenyl)acetic Acid (*XXVII*)

(*A*) A stirred solution of 13·8 g *XXVI* in 300 ml benzene was treated at 50°C with 60 g $AlCl_3$ and the mixture was stirred at 50°C for 7 h. It was poured to a mixture of 1·5 l water and 375 ml hydrochloric acid, the aqueous layer was extracted with benzene and the benzene layers were combined. The processing of the extract gave a semi-solid residue which was dissolved in 25 ml benzene and chromatographed on 150 g silica gel. The benzene eluates were discarded and chloroform eluted 5·19 g (31%) of homogeneous *XXVII*, m.p. 127–132°C. Analytical sample, m.p. 130–132°C (benzene). UV spectrum: 249 (4·27), infl. 268 (4·07), infl. 306 (3·68). IR spectrum: 700, 750 (5 and 4 adjacent Ar–H); 930, 1 219, 1 700, 2 520, 2 600, 2 700, infl. 3 100 (COOH); 1 494, 1 586, 1 600, 3 020, 3 050 (Ar). ^{1}H NMR spectrum: 5·77 s, 1 H (Ar_2CHCO); 7·30 m, 14 H (ArH). For $C_{20}H_{16}O_2S$ (320·4) calculated: 74·97% C, 5·03% H, 10·01% S; found: 75·01% C, 5·03% H, 10·30% S.

(*B*) A solution of 15·5 g *XXV* in 300 ml benzene was treated with 62 g $AlCl_3$ and the mixture was stirred for 14 h at 30°C. It was then poured into a mixture of ice and hydrochloric acid, the aqueous layer was extracted with chloroform, the organic solutions were combined and evaporated. The residue (18·1 g) was chromatographed on 200 g silica gel. Benzene eluted first 1·97 g of an oil distilling at 114°C/0·13 kPa, considered to be diphenyl sulfide. Its ^{1}H NMR spectrum consists only of an unresolved multiplet at δ 7·32 (ArH). The analysis showed only the presence of C, H, and S and agreed approximately for $C_{12}H_{10}S$. Ref.[51], b.p. 148·5–149·5°C/1·6 kPa.

Further elution with benzene gave 0·10 g of a crystalline solid $C_{13}H_{10}O_2S$ (analysis) melting at 167–168·5°C (benzene). It was identified as 2-(phenylthio)benzoic acid; ref.[52], m.p. 165 to 166°C.

Chloroform eluted 10·27 g (58%) of *XXVII*, m.p. 128·5–131·5°C, identical with the product obtained under (*A*). Last chloroform eluates contained 1·57 g of diphenylacetic acid, m.p. 143 to 145°C (benzene–light petroleum). The analysis confirmed the composition $C_{14}H_{12}O_2$. Ref.[53], m.p. 144–145°C.

9-Benzylidenethioxanthene (*XXXV*)

A mixture of 50 g polyphosphoric acid and 4·4 g *XXVII* ws stirred for 5 h and heated to 120°C. It was then poured on ice, extracted with benzene and the extract was processed. The residue (4·0 g) was dissolved in cyclohexane and was chromatographed on 60 g silica gel. Benzene eluted 1·85 g of a seemingly homogeneous fraction which was rechromatographed on 40 g silica gel.

Cyclohexane eluted 0·33 g of a crystalline solid melting at 117—119·5°C. In 70% sulfuric acid it gave an intensive red coloration which is typical for 9-thioxanthenylidene derivatives. Mass spectrum: 286 (M^+, $C_{20}H_{14}S$, 100), 285 (72), 284 (33). UV spectrum: 211 (4·54), 271 (4·21), 287 (4·21), 338 (3·90). IR spectrum: 695, 745, 755, 767 (5 and 4 adjacent Ar–H); 862, 870 (trisubstituted C=C); 1 490, 1 589, 3 050 (Ar). ^{1}H NMR spectrum: 6·90—7·80 m (ArH). For $C_{20}H_{14}S$ (286·4) calculated: 83·88% C, 4·93% H, 11·20% S; found: 84·10% C, 4·99% H, 10·91% S. Ref.[56], m.p. 121—122°C; cf. also ref.[66], m.p. 114—115°C.

11-Phenyldibenzo[*b,f*]thiepin-10(11*H*)-one (*XXXVI*)

Polyphosphate ester was prepared from 25 g P_2O_5, 100 ml benzene, and 12·5 ml ethanol by refluxing for 30 min. Acid *XXVII* (10·3 g) was added in 70 ml benzene and the mixture was stirred and refluxed for 12 h. After cooling it was decomposed with water and the benzene layer was evaporated. There crystallized 0·40 g of thioxanthone, m.p. 213—214°C (benzene–cyclohexane). The analysis was in agreement with $C_{13}H_8OS$. Ref[57,58], m.p. 211 and 212—214°C, respectively. The remaining oily material was chromatographed on 160 g silica gel. A mixture of cyclohexane and benzene eluted 3·24 g of an almost homogeneous oil from which 0·10 g of a contaminant was separated by crystallization induced by ether. The remaining oily 3·14 g substance was characterized as the desired *XXXVI*. Mass spectrum: 302 (M^+, $C_{20}H_{14}OS$, 90), 301 (100), 273 (50), and 167 (40). IR spectrum film: 701, 755 (5 and 4 adjacent Ar–H); 1 492, 1 585, 3 020, 3 050 (Ar); 1 672 (ArCO). ^{1}H NMR spectrum: 6·12 s, 1 H (H-11); 7·00—7·80 m, 12 H (all Ar–H with the exception of H-9); 8·18 m, 1 H (H-9).

The mentioned crystalline contaminant of *XXXVI* melted at 192—194·5°C. It was assigned to be 10-(diphenylacetoxy)-11-phenyldibenzo[*b,f*]thiepin (*XXX*). Mass spectrum: 496 (M^+, $C_{34}H_{24}O_2S$, 0·4), 302 (89), 301 (100), 273, 271, 197, 167, 165, 152. UV spectrum: 225 (4·62), 273 (4·25), 328 (3·87). IR spectrum: 697, 741, 764 (5 and 4 adjacent Ar–H); 1 117, 1 746 (RCOO—C=C); 1 491, 1 581, 1 596, 3 020, 3 055 (Ar). ^{1}H NMR spectrum: 5·05 s, 1 H (Ar_2CHCO); 6·80—7·20 m (ArH). For $C_{34}H_{24}O_2S$ (496·6) calculated: 82·23% C, 4·87% H, 6·46% S; found: 81·92% C, 5·04% H, 6·55% S.

The last described pair of products was followed by 1·7 g of a homogeneous oil which was shown to be the ethyl ester of *XXVII*. Mass spectrum: 348 (M^+, $C_{22}H_{20}O_2S$), 302, 197, 165, 152, 105. Benzene eluted then a further quantity of thioxanthone (1·5 g), m.p. 213—214°C (benzene–cyclohexane), cf. above.

The last component of the mixture, which was eluted with benzene, was the crystalline 11-hydroxy-11-phenyldibenzo[*b,f*]thiepin-10(11*H*)-one (*XXXVII*) melting at 168—172·5°C (cyclohexane or ethanol). Mass spectrum: 318 (M^+, $C_{20}H_{14}O_2S$, 1), 301, 290, 289, 273, 271, 261, 239, 213 (100), 184, 152, 139, 120, 105, 92, 77. UV spectrum: 256 (4·50), infl. 286 (3·87), 350 (3·75). IR spectrum: 700, 750, 770 (5 and 4 adjacent Ar–H); 1 087, 3 360 (C-OH in the ring); 1 492, 1 554, 1 586, 3 035, 3 060 (Ar); 1 643 (ArCO). ^{1}H NMR spectrum: 5·82 s (disappears after D_2O), 1 H (OH); 8·28 bd and 8·42 bd, 1 and 1 H (H-1 and H-9); 6·80—7·70 m, (11 H remaining ArH). ^{13}C NMR spectrum: 84·85 s (C-11); 126·01 d, 127·13 d (2 C), 128·10 d, 128·33 d (4 C), 129·15 d, 129·75 d, 131·84 d, 133·03 d (2 C), $\sum$ 13 C (13 × =CH—); 130·12 s, 132·58 s, 138·86 s, 140·58 s, 141·92 s, $\sum$ 5 C (C-4a, C-5a, C-9a, C-11a, and C-1′ of phenyl); 194·58 s (CO). For $C_{20}H_{14}O_2S$ (318·4) calculated: 75·45% C, 4·43% H, 10·07% S; found: 75·09% C, 4·38% H, 10·26% S.

Chloroform eluted 0·42 g of diphenylacetic acid, m.p. 143—145°C (cf. above). Mass spectrum: 212 (M^+, $C_{14}H_{12}O_2$, 5), 167 (100), 165 (9), 152 (6).

10-(2-Dimethylaminoethylamino)-11-phenyldibenzo[*b,f*]thiepin (*XXXI*)

A stirred solution of 2·50 g *XXXVI* and 5·7 g 2-dimethylaminoethylamine in 40 ml benzene was treated with a solution of 2·0 g $TiCl_4$ in 30 ml benzene, the mixture was stirred for 1 h at room temperature and was refluxed for 5 h. After standing overnight it was decomposed with water, filtered, and the benzene layer of the filtrate was processed. The residue (2·25 g) was neutralized with maleic acid in ether and gave 0·30 g of an inhomogeneous crystalline maleate melting at 161–165·5°C (ethanol). Its mass spectrum proved the presence of *XXXI*: 372 (M^+, $C_{24}H_{24}N_2S$, 5), 314 (5), 197 (20), 71 (20), 58 (100).

N-(11-Phenyldibenzo[*b,f*]thiepin-10-yl)formamide (*XXXIII*)

A) A mixture of 1·85 g crude *XXXVI*, 15 ml formamide, and 3 ml formic acid was heated for 6·5 h to 200°C. After partial cooling the mixture was diluted with water and the precipitated solid was filtered; 2·0 g of a mixture melting at 60–70°C. It was dissolved in benzene and the solution was chromatographed on 60 g silica gel. Benzene eluted 0·38 g of 10-amino-11-phenyldibenzo[*b,f*]thiepin(*XXXII*) crystallizing from cyclohexane and melting at 172·5–174·5°C (cyclohexane or ether). Mass spectrum: 301 (M^+, $C_{20}H_{15}NS$, 100), 300 (10), 269 (34), 268 (25), 267 (21), 224 (13), 197 (7), 180 (9), 165 (12), 142 (15), 134 (19). UV spectrum: 265 (4·04), 307 (3·95). IR spectrum: 711, 760 (5 and 4 adjacent Ar–H); 1 483, 1 549, 1 577, 1 592, 3 040, 3 070 (Ar); 1 611 (C=C in conjugation); 1 660 (C=C–NH_2); 3 303, 3 410 (NH_2). For $C_{20}H_{15}NS$ (301·4) calculated: 79·70% C, 5·02% H, 4·65% N, 10·64% S; found: 79·53% C, 5·12% H, 4·69% N, 10·84% S.

Elution with chloroform gave 0·26 g of crystalline *XXXIII* melting at 193–195°C (benzene–cyclohexane). Mass spectrum: 329 (M^+, $C_{21}H_{15}NOS$, 20), 301 ($C_{20}H_{15}NS$, 15), 296 ($C_{21}H_{14}NO$, 10), 284 (10), 252 (5), 220 (20), 78 (100). UV spectrum: 259 (4·18), infl. 285 (3·97). IR spectrum: 700, 759 (5 and 4 adjacent Ar–H); 1 490, 1 576, 3 040 (Ar); 1 550, 1 685 (NHCHO); 3 368 (NH). ^{1}H NMR spectrum: 7·00–8·00 m (ArH and NHCHO). For $C_{21}H_{15}NOS$ (329·4) calculated: 76·57% C, 4·59% H, 4·25% N, 9·73% S; found: 76·39% C, 4·85% H, 4·02% N, 9·85% S.

The last compound which was eluted with chloroform was 0·69 g of an oil which crystallized from benzene and melted at 230–235°C. It was assigned to be N-(11-phenyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)formamide (*XXXVIII*), identified by analysis and mass spectrum as a 1 : 1 solvate with benzene. Mass spectrum: 331 (M^+, $C_{21}H_{17}NOS$), 286. IR spectrum: 703, 759 (5 and 4 adjacent Ar–H); 1 542, 1 643 (RNHCHO); 3 028, 3 048 (Ar); 3 200, 3 230 (NH). ^{1}H NMR spectrum (CD_3SOCD_3): 4·80 bs, 1 H (Ar_2CH); 6·50–7·70 m, 14 H (13 × ArH and ArCHN); 8·23 s, 1 H (CHO); 8·47 bd, 1 H (NH, J = 8·0). For $C_{21}H_{17}NOS + C_6H_6$ (409·6) calculated: 79·18% C, 5·66% H, 3·42% N, 7·83% S; found: 79·30% C, 5·65% H, 3·38% N, 8·08% S.

B) A mixture of 6·0 g acetic anhydride and 3·0 g formic acid was allowed to stand for 72 h at room temperature. Compound *XXXII* (0·84 g) was added and the mixture was stirred until a clear solution was formed. After standing for 24 h at room temperature, the solid was filtered and crystallized from a mixture of benzene and cyclohexane; 0·70 g of *XXXIII*, m.p. 192–194·5°C. The product was identical with that obtained under *A*).

N-(α-(9-Thioxanthenyl)benzyl)formamide (*XXXIX*)

A mixture of 7·4 g crude *XXXVI*, 30 ml formamide, and 10 ml formic acid was heated for 14 h to 200°C. After cooling the mixture was distributed between water and chloroform, the chloroform layer was evaporated and the residue was dissolved in 25 ml benzene. The solution deposited on standing 0·25 g of solid *XXXIX* which crystallized from a mixture of chloroform

and benzene and melted at 281–282°C. Mass spectrum: 331 (M^+, $C_{21}H_{17}NOS$, 0·1), 277 (0·2), 276 (0·2), 275 (0·2), 274 (0·2), 197 (100), 165 (14), 152 (5). UV spectrum: infl. 254 (3·85), 264·5 (4·00). IR spectrum: 703, 749, 755 (5 and 4 adjacent Ar–H); 1 495, 1 583, 1 592, 1 599, 3 030, 3 055 (Ar); 1 510, 1 663 (NHCHO); 3 370 (NH). For $C_{21}H_{17}NOS$ (331·4) calculated: 4·23% N, 9·67% S; found: 4·27% N, 9·52% S.

Chromatography of the mother liquor gave successively the following products which were compared by TLC and by the melting points with the products described above: 2·31 g of *XXXII*, 0·41 g of *XXXVII*, 1·8 g of *XXXIII*, and 1·58 g of *XXXVIII*.

10-Methylamino-11-phenyldibenzo[*b,f*]thiepin (*XXXIV*)

Crude *XXXIII* (2·3 g) in 10 ml tetrahydrofuran was added to a stirred solution of 1·0 g $LiAlH_4$ in 40 ml tetrahydrofuran and the mixture was refluxed for 6 h. After cooling it was decomposed with dilute NaOH, diluted with benzene, and the solid was filtered off. The filtrate was dried over K_2CO_3 and evaporated. The residue was dissolved in ether and the solution was neutralized with 0·8 g maleic acid. There crystallized 0·65 g of 11-methylamino-10-phenyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XL*) hydrogen maleate melting at 205–206°C (ethanol–ether). Mass spectrum: 333 (M^+, $C_{21}H_{19}NOS$, 2), 315 (2·5), 303 (2), 273 (2), 197 (12), 120 (100), 105 (13), 77 (12), 42 (22). UV spectrum: 252 (3·66). For $C_{25}H_{23}NO_5S$ (449·5) calculated: 66·80% C, 5·16% H, 3·12% N, 7·13% S; found: 66·91% C, 5·29% H, 3·29% N, 7·28% S.

The mother liquors were evaporated, the residue was made alkaline with NH_4OH and extracted with ether. Processing of the extract gave 1·3 g oily residue which was chromatographed on 70 g silica gel. A mixture of benzene and light petroleum eluted 0·34 g of homogeneous oily *XXXIV*. Mass spectrum: 315 (M^+, $C_{21}H_{17}NS$), 300, 267, 239, 226, 197. ^1H NMR spectrum: 2·40 s, 3 H (NCH_3); 6·90–7·70 m, 14 H (13 × ArH and NH). Neutralization with HCl in ether gave a crystalline hydrochloride which appeared to be a 2 : 3 solvate with water. For $C_{21}H_{18}ClNS + 1·5\ H_2O$ (378·9) calculated: 66·56% C, 5·58% H, 9·36% Cl, 3·70% N, 8·46% S; found: 66·21% C 5·32% H, 9·06% Cl, 3·51% N, 8·48% S.

The authors wish to thank the following colleagues at the Research Institute for Pharmacy and Biochemistry in Prague for their contributions to the present study: Drs I. Koruna, O. Matoušová, and J. Schlanger (a part of the mass spectra), Mrs A. Hrádková and Mrs Z. Janová (recording of the UV *and* IR *spectra); Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech, and Mrs A. Svatošová (elemental analyses); Drs J. Metyš, M. Valchář, N. Dlohožková, Mrs M. Jandová, Mrs L. Horáková, Mrs E. Šulcová, Mrs K. Zabloudilová, Mrs J. Ezrová, and Mrs S. Schubertová (pharmacology and biochemical pharmacology).*

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Translated by the author (M.P.).