DIBENZO[*b,f*]THIEPIN-10-CARBONITRILE, ITS 10,11-DIHYDRO DERIVATE, SOME TRANSFORMATION PRODUCTS AND RELATED COMPOUNDS*

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Reactions of 10-bromodibenzo[*b,f*]thiepin (*IIIa*), its 2-chloroderivative *IIIb* and 2,8-dichloro derivative *IIIc* with cuprous cyanide in boiling dimethylformamide gave the carbonitriles *Iabc* out of which the first two were reduced with sodium borohydride to the 10,11-dihydro derivatives *IVab*; the amides *VIIab* were obtained as by-products. Alkaline hydrolysis of the nitriles *IVab* or their mixtures with the amides *VIIab* afforded the acids *VIIIab*. By the addition of 3-dimethylaminopropylmagnesium chloride to the nitrile *Ia cis* and *trans*-11-(3-dimethylaminopropyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-carbonitriles (*XVIII*) were obtained. Alkylation of the nitrile *IVa* with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride resulted in the 10-(dimethylaminoalkyl) derivatives *XX* and *XXI*. A reaction of the crude cyano alcohol *XXIII* with phosphorus tribromide afforded the 2-bromoethyl derivative *XXIV* as a by-product only. The main product was the hydrobromide of the spirocyclic imidate *XXX* which affords by acid hydrolysis the spirocyclic lactone *XXXI*. An analogous sequence proceeding *via* the ether *XXVI* and the alcohol *XXVII* leads to the 10-(3-bromopropyl) derivative *XXVIII* as the main product. An attempt at preparing the same substance by alkylation of the nitrile *IVa* with 1,3-dibromopropane gave stereoisomeric dinitriles *XXXII*. At high doses the amides *VIIab* reveal an anticonvulsant effect, the acids *VIIIab* antiinflammatory actions, the basic nitrile *cis*-*XVIII* antireserpine activity and the basic nitriles *XX* and *XXI* a central depressant and pseudo-analgesic activity in addition to further peripheral and cardiovascular effects.

The araliphatic nitriles with the cyano group on a primary or secondary benzylic carbon atom are suitable intermediates of synthesis of potential pharmacotherapeutic agents[1,2]. This fact and our search in the series of dibenzo[*b,f*]thiepin derivatives and the corresponding 10,11-dihydro compounds[3] led us to investigate the synthesis and reactions of the dibenzo[*b,f*]thiepin-10-carbonitrile (*Ia*) and its 10,11-dihydro derivative *IVa*. The present communication describes experimental work carried out in this line.

Dibenzo[*b,f*]thiepin (*IIa*) was selected as the starting compound. Various methods of preparation of *IIa* are mentioned in reviews[3,4]. The most favourable one was

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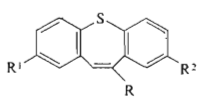
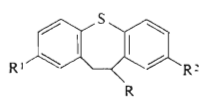
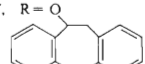
considered the elimination of hydrogen chloride from 10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Va*) (ref.[5,6]) which was observed as an undesirable side reaction of the chloro compound *Va* with secondary amines, *e.g.* with 1-methylpiperazine[3,5,6]



I, R = CN
II, R = H
III, R = Br



IV, R = CN
V, R = Cl
VI, R = O

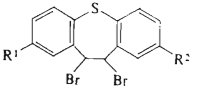


VII, R = $CONH_2$
VIII, R = COOH

In formulae *I*–*IX*: *a*, $R^1 = R^2 = H$; *b*, $R^1 = Cl$, $R^2 = H$; *c*, $R^1 = R^2 = Cl$

This reaction represented in the preparation of the substitution products a serious difficulty[7,8] and its considerable extent was explained by the presence of some 1,4-dimethylpiperazine in 1-methylpiperazine which was used in the first phase of our studies[9]. Its preparative use proved rather uneasy. The reaction of compound *Va* with boiling triethylamine proceeds sluggishly and after 5 h an inhomogeneous product is obtained which still contains a considerable amount of the starting compound. Even the dehydrochlorination of the chloride *Va* with boiling 2,4,6-collidine does not proceed smoothly. The dehydrochlorination with potassium carbonate in boiling dimethylformamide proved the best suitable method; the crude product obtained affords by a single crystallization from ethanol and by processing of the mother liquors some 70% of an almost homogeneous compound *IIa*. From the mother liquors after the mentioned crystallization there was obtained in small amount a further substance identified as bis(10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl) ether (*VIa*). This compound was described as one of the minor products of the reaction of thioxanthylium perchlorate with diazomethane[10]. In our case its formation has to be explained by *1*) the formation of one molecule of water by the reaction of potassium carbonate with hydrogen chloride cleaved, *2*) interaction of this water with the chloro compound *Va* affording some 10,11-dihydrodibenzo[*b*,*f*]-thiepin-10-ol and *3*) Williamson reaction of this alcohol with the chloride *Va* in the presence of potassium carbonate and under the severe reaction conditions used. Dibenzo[*b*,*f*]-thiepin (*IIa*) was treated with bromine in a mixture of ether and chloroform[6] and there was obtained in a satisfactory yield a mixture of stereoisomeric dibromides

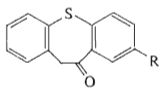
IXa (*cf.*[11]) which was dehydrobrominated by reaction with 1-methylpiperazine in benzene[6] under the formation of 10-bromodibenzo[*b*,*f*]thiepin (*IIIa*). Reaction of this compound with cuprous cyanide in boiling dimethylformamide afforded in a good yield the new dibenzo[*b*,*f*]thiepin-10-carbonitrile (*Ia*) whose identity was confirmed by spectra.



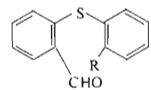
IX

The described synthesis of *Ia* requires 12 steps starting from the commercially available intermediates; the result is a rather low overall yield. We attempted at finding some shorter synthetic procedures. In the first line we were able to apply in our case a method[12] consisting in a reaction of ketones with trimethylsilyl cyanide[13] affording silylated cyanohydrines which are then cleaved and dehydrated by the treatment with phosphoryl chloride. In this way we obtained the nitrile *Ia* from dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*X*) (ref.[5]) in a moderate yield. An attempt at preparing the silylated cyanohydrine by treatment of the ketone *X* with trimethylchlorosilane and potassium cyanide in dimethylformamide (which also has a described analogy[14]) was not successful; the starting ketone *X* was recovered. A further attempt started from 2-(2-hydroxymethylphenylthio)benzaldehyde (*XII*) which was obtained in a yield of 60% by a reaction of 2-mercaptobenzyl alcohol[8,15] with 2-chlorobenzaldehyde in hexamethylphosphortriamide at 100°C in the presence of aqueous sodium hydroxide (compound *XII* was described[16] previously as an oil). Treatment with thionyl chloride in boiling benzene resulted in a non completely homogeneous oily product, apparently the chloride *XIII*, which was directly used for the reaction with potassium cyanide in dimethyl sulfoxide at 100°C. A mixture was obtained which was separated by chromatography on silica gel: the oily more polar main product was characterized by the ^{1}H NMR spectrum as the nitrile-aldehyde *XIV*; the less polar minor product is the nitrile *Ia*, formed by a spontaneous cyclization of *XIV*. A practically homogeneous *XIV* was obtained from the crude chloride *XIII* and potassium cyanide in dimethylformamide at 50°C. Attempts at cyclizing compound *XIV* with sodium ethoxide in boiling ethanol or with potassium fluoride in ethanol led to mixtures whose chromatography on aluminium oxide afforded the nitrile *Ia* in minute yields. In mixtures obtained from attempts at cyclization of compound *XIV* in a system benzene–aqueous potassium hydroxide and in the presence of tetrabutylammonium bromide as the phase-transfer catalyst, as well as with powdered potassium hydroxide in dimethyl sulfoxide, the presence of the nitrile *Ia* could be proven only by means of the thin-layer chromatography. After the rather extensive experimental work carried out,

the synthesis of the nitrile *Ia via* intermediates *Va*, *IIa*, *IXa* and *IIIa* appears most favourable.



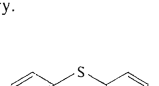
X, R = H
XI, R = Cl



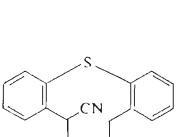
XII, R = CH_2OH
XIII, R = CH_2Cl
XIV, R = CH_2CN

The literature described the reduction of 2,3-diarylacrylonitriles to 2,3-diarylpropionitriles[17] with sodium borohydride and similarly for a case when the diarylacrylonitrile fragment is a part of a tricyclic system with a central seven-membered ring[18]; the reaction was carried out either in dimethylformamide (or its mixture with tetrahydrofuran) or in anhydrous methanol. We found that our nitrile *Ia* is smoothly reduced to the dihydro derivative *IVa* with sodium borohydride in aqueous ethanol. Also in this case we tried to find a shorter synthesis for the nitrile *IVa*. In the first line, the reaction of the chloro derivative *Va* (ref.[5,6]) with potassium cyanide was investigated. It was found that in dimethylformamide at 50°C no reaction takes place and the starting derivative *Va* is recovered. At 120°C the elimination of hydrogen chloride proceeds smoothly giving dibenzo[*b*,*f*]thiepin (*IIa*). A further attempt started from the reaction of 2-iodophenylacetonitrile[19,20] with 2-mercaptobenzyl aclohol[8,15] in boiling dimethylformamide in the presence of potassium carbonate and copper as a catalyst. In a satisfactory yield there was obtained the hydroxy nitrile *XV* which was treated with thionyl chloride in boiling benzene. The resulting oily chloronitrile *XVI* was considered a convenient intermediate which could afford the nitrile *IVa* by intramolecular alkylation. Attempts at this cyclization were carried out under various conditions: In the first line, it was a reaction in a two-phase system of benzene and 50% aqueous sodium hydroxide in the presence of triethylbenzylammonium chloride, further in dimethylformamide with powdered potassium hydroxide in the presence of tetrabutylammonium bromide and finally in dimethylformamide in the presence of sodium hydride. In all the three cases a high-melting solid (m.p. 305–308°C) resulted as the main product; its IR spectrum indicated the presence of the nitrile group (band at 2 238 cm^{-1}) and the mass spectrum and analysis settled the elemental composition $C_{30}H_{22}N_2S_2$, *i.e.* that of a dimer *XVII* of the nitrile *IVa*, formed by a simultaneous alkylation between two molecules of the starting compound *XVI*. Only in the last mentioned case (cyclization with sodium hydride) the presence of nitrile *IVa* in some fractions after chromatography of the mother liquors after compound *XVII* could be proven by thin-layer chromatography. On the other hand in the second case (reaction in dimethylformamide with

potassium hydroxide and tetrabutylammonium bromide) the mother liquor after compound *XVII* contained considerable quantities of dibenzo[*b*,*f*]thiepin-10(11*H*)--one (*X*), identified by thin-layer chromatography. This ketone[5] was found to be the main product of an attempt at the intramolecular alkylation of the chloro nitrile *XVI* with powdered potassium hydroxide in dimethyl sulfoxide. In these last two cases we evidently meet with an oxidative decyanation of nitriles with a CH group in α-position to the CN group which was described as a preparative method[21] for ketones of the type ArCOR by means of aqueous sodium hydroxide and a phase--transfer catalyst (triethylbenzylammonium chloride) with passing oxygen through the mixture. In our case, the formation of ketone *X* is a proof of the primary formation of the nitrile *IVa* by the desired alkylation; this nitrile, however, underwent the oxidative decyanation which, evidently, does not require the presence of a phase--transfer catalyst and as a source of oxygen the access of air to the reaction mixture is satisfactory.



XV, R = CH_2OH
XVI, R = CH_2Cl

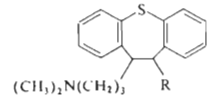


XVII

In one experiment with the reduction of nitrile *Ia* with sodium borohydride in aqueous ethanol, in which the reaction mixture was refluxed for a longer time, there came in a considerable extent to hydration of the nitrile *IVa* and the amide *VIIa* was obtained as the main product. The mixture of the nitrile *IVa* and amide *VIIa*, whose separation was uneasy, was subjected to alkaline hydrolysis in order to prepare the acid *VIIIa*. This hydrolysis was found unsuitable for the purpose mentioned: A reaction with boiling aqueous–ethanolic potassium hydroxide eliminated the nitrile *IVa* from the mixture, the amide *VIIa* was the main product and the acid *VIIIa* resulted only in a low yield. Only the hydrolysis of the amide *VIIa* with a boiling 50% potassium hydroxide in ethanol afforded the acid *VIIIa* in a satisfactory yield.

α-Arylcinnamonitriles and their heterocyclic analogues react with Grignard reagents by a 1,4-addition; the following hydrolysis affords the α,β-diaryl-β-substituted propionitriles[22–25]. A reaction of the nitrile *Ia* with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran and the following decomposition of the mixture with hydrochloric acid gave a mixture of two isomeric bases *XVIII*, from which the by-products were separated by chromatography and the isomers were then separated

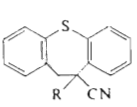
by crystallization of the oxalates. The oily bases, prepared from the oxalates, were investigated by the ^{1}H NMR spectra; the major product was identified as *cis-XVIII* and the minor isomer, whose oxalate was isolated from the mother liquors, as *trans-XVIII*. The *cis*-aminonitrile was hydrolyzed with a boiling mixture of acetic acid and 48% hydrobromic acid and the desired amino acid *XIX* was isolated in the form of hydrochloride in a low yield; its identity was confirmed by means of the mass and IR spectra.



XVIII, R = CN
XIX, R = COOH

The alkylation of the nitrile *IVa* with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride in dimethylformamide at 90°C with sodium hydride as the carbanion-forming reagent gave the basic nitriles *XX* and *XXI*. In a different connection we needed as intermediates 10,11-dihydrodibenzo[*b,f*]thiepin-10-carbonitrile derivatives alkylated in position 10 with halogenoalkyls, *e.g.* the 2-bromoethyl derivative *XXIV* and the 3-bromopropyl derivative *XXVIII*. In the first case we started from the alkylation of the nitrile *IVa* with 2-(tetrahydro-2-pyranyloxy)ethyl chloride[26] in dimethylformamide in the presence of sodium hydride. The molecules of the product *XXII* contain two centres of chirality; in agreement with this fact we obtained a mixture of stereoisomers, from which one homogeneous racemate was isolated in a small quantity and was characterized by spectra. The remaining mixture of stereoisomers was hydrolyzed with a dilute solution of hydrochloric acid in methanol. The oily product, obtained in an almost theoretical yield, was considered the alcohol *XXIII* and was processed without characterization. It was subjected to treatment with phosphorus tribromide in benzene at 70°C and after cooling there was separated by filtration a considerable quantity of a high-melting substance (compound *A*), considered first on the basis of analysis to be the amide $C_{17}H_{16}BrNOS$ corresponding to the bromo nitrile *XXIV*. The filtrate was washed with water and with a solution of sodium carbonate and by chromatography there was obtained the desired 2-bromoethyl derivative *XXIV* in a low yield as the least polar component. It was followed by a small amount of the nitrile *IVa* for whose appearing here a plausible explanation is lacking. Finally, acidification of the alkaline washings afforded a considerable quantity of a further crystalline substance having acid character. Its analysis and spectra indicate that we are dealing here with a dihydrogen phosphite, *i.e.* the immediate precursor of compound *XXIV* (*cf.*[27]), for which we have

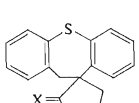
to prefer on the basis of literature data (spectral studies[28,29]) the structure *XXV*, derived from the asymmetric form of phosphorous acid $(HO)_2PH{=}O$. We assumed that a reaction fo compound *XXV* with a solution of hydrogen bromide in acetic acid could afford a further quantity of the desired bromo derive *XXIV*; contrary to this expectation a further amount of compound A was obtained.



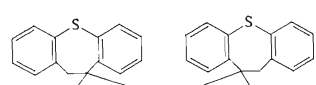
XX, R = $(CH_2)_2N(CH_3)_2$
XXI, R = $(CH_2)_3N(CH_3)_2$
XXII, R = $(CH_2)_2O$– 
XXIII, R = $(CH_2)_2OH$
XXIV, R = $(CH_2)_2Br$

XXV, R = $(CH_2)_2OPH(=O)(OH)$
XXVI, R = $(CH_2)_3$– 
XXVII, R = $(CH_2)_3OH$
XXVIII, R = $(CH_2)_3Br$
XXIX, R = $(CH_2)_3OPH(=O)(OH)$

The IR spectrum of compound A indicated for it the character of an amine salt (band at 2 730 cm^{-1}). It was decomposed with 10% sodium hydroxide and the oily base was isolated by extraction with chloroform. By neutralization with hydrogen chloride in ether it gave the crystalline hydrochloride, corresponding on the basis of analysis to the elemental composition $C_{17}H_{16}ClNOS$; compound A is thus the corresponding hydrobromide. The mass spectrum showed the molecular ion with m/z 281 corresponding to $C_{17}H_{15}NOS$ which is the composition of the base. The structure of hydrobromide of the spirocyclic imidate *XXX* was suggested foı compound *A*; this compound would be a logical product of the interaction of the nitrile group in compound *XXIII* with the alcoholic hydroxyl in the side chain under the action of hydrogen bromide, formed in the reaction with phosphorus tribromide. The resistance of this imidate towards hydrolysis (the possibility of preparing the free base in aqueous alkaline medium) could be explained by the strong steric hindrance of the imidate group. The hydrolysis was achieved by longer boiling with 1 : 1 dilute hydrochloric acid. The product was a nitrogen-free compound $C_{17}H_{14}O_2S$ (mass spectrum; the analysis indicates a 2 : 1 solvate with benzene); the IR spectrum shows a band at 1 750 cm^{-1} corresponding to the carbonyl group of a lactone with a five-membered ring. The product evidently has the structure of the spirocyclic lactone *XXXI*. ^1H NMR spectra of the hydrobromide and hydrochloride of the imidate *XXX* and of the lactone *XXXI* are not at variance with the structures suggested. For the hydrochloride of the imidate *XXX* as well as for the lactone *XXXI* the ^{13}C NMR spectra confirm also the structures.



XXX, X = NH
XXXI, X = O



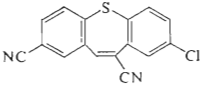
XXXII

Similarly, the alkylation of the nitrile *IVa* with 3-(tetrahydro-2-pyranyloxy)propyl chloride[30] was carried out and the homogeneous oily product *XXVI* was obtained by chromatography of the crude product. Without characterization it was hydrolyzed with dilute methanolic hydrochloric acid and the obtained homogeneous oily alcohol *XXVII* was again processed without characterization. It was subjected to treatment with phosphorus tribromide in benzene. After hydrolysis the product was separated to neutral and acid components. Chromatography of the neutral components on silica gel afforded in this case in a satisfactory yield the desired 3-bromopropyl derivative *XXVIII*. As the product of acid character there was isolated in a considerable quantity a dihydrogen phosphite, formulated as *XXIX* on the basis of reasons already discussed. In this case we did not observe at all the formation of a spirocyclic imidate, *i.e.* of the homologue of *XXX*. In the effort to prepare compound *XXVIII* by an alternative method an attempt was made to alkylate the nitrile *IVa* with excessive 1,3-dibromopropane in dimethylformamide in the presence of sodium hydride. There was obtained an inhomogeneous product which proved bromine-free; the crystallization separated the major and higher melting product and the minor and lower melting component. Mass spectra and analysis showed that the products are isomers $C_{33}H_{26}N_2S_2$, *i.e.* the stereosisomeric dinitriles *XXXII*. The ^{1}H NMR spectrum of the higher melting isomer indicates the symmetry of the molecule and it is considered to be the *meso*-form. With the lower melting isomer the protons of the two $ArCH_2$ groups appear as 4 doublets (each of them corresponding to 1 proton) and this isomer is considered to be the racemic form.

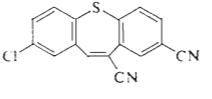
There was further to our disposal as starting material the 10-bromo-2-chlorodibenzo[*b*,*f*]thiepin (*IIIb*) whose synthesis and proof of the structure were described in our previous communication[31]. Its reaction with cuprous cyanide in boiling dimethylformamide afforded the nitrile *Ib* which was reduced with sodium borohydride in aqueous ethanol to the dihydro derivative *IVb*. It was accompanied with some amide *VIIb*, separated on the basis of its low solubility in benzene. A further quantity of this amide was prepared by partial hydrolysis of the nitrile *IVb* with a boiling solution of sodium hydroxide in a mixture of ethanol and water. A complete hydrolysis of the nitrile *IVb* by heating with dilute sulfuric acid afforded the acid *VIIIb*. An attempt was also carried out at transforming 8-chlorodibenzo[*b*,*f*]-

thiepin-10(11*H*)-one (*XI*) (ref.[7]) directly to 8-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-carbonitrile by treatment with tosyl methylisocyanide[32,33] in the presence of potassium tert-butoxide in 1,2-dimethoxyethane (method, *cf.*[34]); the attempt was unsuccessful and the starting ketone *XI* was regenerated.

A similar synthetic work like in the series *a* and *b* was started also in the series of 2,8-dichlorodibenzo[*b*,*f*]thiepin derivatives (series *c*). 2,8,10-Trichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Vc*) (ref.[35]) was dehydrochlorinated to 2,8-dichlorodibenzo[*b*,*f*]thiepin (*IIc*) (*cf.*[36]) with 2,4,6-collidine on the one hand, and by treatment with potassium carbonate in boiling dimethylformamide on the other. The addition of bromine was carried out in a mixture of ether, chloroform and tetrachloromethane and the obtained inhomogeneous dibromo derivative *IXc* (mixture of stereoisomers) was subjected without purification and characterization to dehydrobromination by treatment with 1-methylpiperazine in boiling benzene; 10-bromo-2,8-dichlorodibenzo[*b*,*f*]thiepin (*IIIc*) was obtained. The reaction with cuprous cyanide in boiling dimethylformamide in this case had not a homogeneous course; an inhomogeneous products was obtained which had to be chromatographed on aluminium oxide. The desired nitrile *Ic* was eluted as the main and less polar product in a yield of 66%. It was followed by a smaller amount of a more polar compound for which the mass spectrum and the analysis determined the elemental composition $C_{16}H_7Cl_2NS$; in addition to the substitution of the atom of bromine in position 10, one of the chlorine atoms on the benzene nuclei was also substituted. Using methods, which were at disposal, it was not possible to resolve whether the product has the structure *XXXIII* or *XXXIV*.



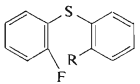
XXXIII



XXXIV

Finally we would like to report about a further attempt at a new synthesis of the dibenzo[*b*,*f*]thiepin system, to which we were encouraged by positive results of cyclization of substituted 2-(2-fluorophenoxy)benzyl alcohols[37] and 2-(2-fluorophenylthio)benzyl alcohols[38–40] with sodium hydride to derivatives of 11*H*-dibenzo[*b*,*e*]-1,4-dioxepin and 6*H*-dibenz[*b*,*e*]-1,4-oxathiepin. In these cases the reactions consisted in nucleophilic substitutions of the fluorine atom with the alkoxide anion. The purpose of the present work was to check the reactivity and usefullness of a carbanion in a similar situation. By a reaction of 2-iodobenzoic acid with 2-fluorothiophenol[41] and potassium hydroxide in a boiling aqueous solution in the presence of copper the acid *XXXV* was obtained which was reduced with diborane (*cf.*[19]), to the alcohol *XXXVI*. A reaction with thionyl chloride in the presence of pyridine

afforded the oily substituted benzyl chloride *XXXVII* which could be distilled without decomposition. It was used for alkylation of diethyl malonate on the one hand, and of ethyl cyanoacetate on the other (method, *cf.*[42]). Compounds *XXXVIII* and *XXXIX* were obtained and were considered suitable sources of the carbanions for the mentioned purpose. The attempts at their cyclization by treatment with sodium hydride in dimethylformamide at 90°C (method, *cf.*[37–40]), however, did not lead to the desired goal: the starting compounds *XXXVIII* and *XXXIX* were recovered. During processing of the reaction mixtures there were observed only hydrolysis and the following decarboxylation; the products were identified as the malonic acid *XL* and the 3-substituted propionic acid *XLI*. In all of these products the fluorine atom remained untouched which proves the insufficient reactivity of carbanions under the conditions used.



XXXV, R = COOH
XXXVI, R = CH_2OH
XXXVII, R = CH_2Cl
XXXVIII, R = $CH_2CH(COOC_2H_5)_2$

XXXIX, R = $CH_2CH(CN)COOC_2H_5$
XL, R = $CH_2CH(COOH)_2$
XLI, R = CH_2CH_2COOH

Compounds *VIIa*, *VIIb*, *VIIIa*, *VIIIb*, *cis-XVIII* (hydrogen oxalate), *XX* (hydrogen oxalate) and *XXI* (hydrogen maleate) were pharmacologically tested mostly with emphasis to the effects which could be expected. The amides *VIIa* and *VIIb* were tested for anticonvulsant activity in mice which was found to be rather weak. Both compounds are very little toxic; their LD_{50} in mice are above 1 g/kg *p.o.* High doses of both compounds brought about signs of excitation in mice. In the test of maximal electroshock seizures in mice *VIIa* showed some activity; PD_{50} = 175 mg/kg *p.o.* Compound *VIIb* in this test is inactive at a dose of 800 mg/kg *p.o.* but it showed some activity against the pentetrazole convulsions in mice, PD_{50} = 640 mg/kg. The acids *VIIIa* and *VIIIb* were tested as potential antiinflammatory agents. Their toxicity in mice (LD_{50}) is lower than 1 g/kg *p.o.*; this dose of *VIIIa* is lethal for 80% animals and with *VIIIb* for 60% animals. The antiinflammatory activity was assessed in the tests of kaolin, adjuvant and carrageenin edema in rats. At doses of 200 mg/kg *p.o.* compound *VIIIa* showed a statistically significant activity only in the adjuvant edema test and compound *VIIIb* in the tests of kaolin and adjuvant edema; they were almost inactive in the test of carraggeenin edema (ibuprofene used as the standard had significant and more intensive activity in all the three tests at a dose of 100 mg/kg *p.o.*).

Compound *cis-XVIII* was tested especially for central effects. Acute toxicity in mice, LD_{50} = 460 mg/kg *p.o.* Analgetic effect in the Haffner test in mice, PD_{50} = = 62 mg/kg *p.o.* Ataxia in mice in the rotarod test, ED_{50} = 47·5 mg/kg. Antireserpine activity: a dose of 100 mg/kg *p.o.* has a significant effect towards the gastric ulcer formation after reserpine in rats; only a very high dose of 250 mg/kg *p.o.* brought about a significant antireserpine effect in the test of ptosis in mice.

Compounds *XX* and *XXI* (in the form of salts mentioned) were tested using a general screening program (water-solubility enabled parenteral administration): LD_{50} (mice), *XX*, 45 mg/kg *i.v.*, 240 mg/kg *p.o.*; *XXI*, 35 mg/kg *i.v.*, 325 mg/kg *p.o.* The basic doses (D) used in the screening: *XX*, 9 mg/kg *i.v.*; *XXI*, 6 mg/kg *i.v.* In doses D both compounds brought about brief and deep drops of blood pressure of normotensive rats. In concentration of 1 – 10 μg/ml both compounds had spasmolytic effect on the isolated rat duodenum towards acetylcholine, as well as barium chloride contractions. Compound *XX* in doses of 2·5 – 5·0 mg/kg *s.c.* had antihistamine effect in the test of histamine detoxication in guinea-pigs. Compound *XXI* in *i.v.* doses of 2·5 – 7 mg/kg had an antiarrhythmic effect in rats towards aconitine. Analgesic activity in mice using chemical stimulation (intraperitoneal administration of acetic acid), *XX*, ED_{50} = 9·3 mg/kg *p.o.*; *XXI*, ED_{50} = 1·3 mg/kg; with mechanical stimulation (pressure), *XX*, ED_{50} = 11·4 mg/kg *p.o.*; *XXI*, ED_{50} = = 3 mg/kg *p.o.* Both compounds, however, showed central depressant action manifested in the rotarod test in mice; doses of 10 – 50 mg/kg *p.o.* brought about ataxia in 10 – 50% animals (there was not a clear dependence of effect on the dose). An oral dose of 10 mg/kg of *XX* inhibited significantly the spontaneous activity of mice in the photo-cell test of Dews. On the basis of these facts, the results obtained in the line of analgesic activity are considered influenced by the central depressant effects and being, therefore, non-specific. Compound *XX* showed an antireserpine effect in the test of ptosis in mice at the dose D, administered intraperitoneally.

EXPERIMENTAL

The melting points of analytical preparations were determined partly in a Mettler FP-5 melting point recorder, partly in Kofler's block and are not corrected. The samples were dried *in vacuo* of 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, the IR spectra (mostly in Nujol) with Unicam SP 200G and Perkin Elmer 298 spectrophotometers, the ^1H NMR spectra (mostly in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with the spectrometers MCH 1320 and/or MAT 44S. The ^{13}C NMR spectra were measured on a Jeol FX-60 NMR spectrometer (15·036 MHz) in FT mode in C^2HCl_3 at 25°C. Chemical shifts are given in the δ-scale referenced to tetramethylsilane (internal standard) with accuracy of ±0·08 ppm. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel (Silufol). The column chromatographic separations were carried out either on neutral Al_2O_3 (activity II) or on silica gel (Silpearl).

Dibenzo[*b*,*f*]thiepin (*IIa*)

A) A mixture of 27 g *Va* (ref.[5,6]) and 50 ml 2,4,6-collidine was refluxed for 2 h, after cooling diluted with water and extracted with benzene. The extract was washed with 10% hydrochloric acid and water, dried with $MgSO_4$ and distilled *in vacuo*; 17·0 g, b.p. 180—190°C/0·4 kPa. The inhomogeneous distillate crystallized on standing and was recrystallized from 25 ml ethanol; 14·1 g (61%), m.p. 79—85°C. Lit.[5,6], m.p. 87—88°C.

B) A solution of 350 g *Va* (ref.[6]) in 700 ml dimethylformamide was treated with 180 g K_2CO_3 and the stirred mixture was refluxed for 12 h. After cooling it was diluted with 3·5 l water and extracted with benzene. The extract was washed with water, dried with $MgSO_4$, evaporated under reduced pressure and the residue was crystallized from 300 ml ethanol; 211 g (71%), m.p. 80—86°C.

One third of the mother liquor was evaporated and the residue (40 g) was dissolved in a mixture of 200 ml light petroleum and 100 ml benzene and the solution was chromatographed on a column of 400 g Al_2O_3. Elution with light petroleum gave further quantity of *IIa* which was crystallized from ethanol; 12·3 g, m.p. 82—86°C. The total yield on *IIa* is thus 248 g (83%). The chromatography was continued by elution with a 1 : 3 mixture of light petroleum and benzene; 6·0 g semi-solid compound which was crystallized from ethanol, m.p. 173—175°C. It was identified as bis(10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl) ether (*VIa*). Mass spectrum, *m*/*z* (%): 438·1138 (M^+ corresponding to $C_{28}H_{22}OS_2$, calculated 438·1113, 4%), 301 (2), 227 (13), 211 (100), 197 (7), 178 (25). IR spectrum: 745, 755 (4 adjacent Ar—H), 1 090 (R—O—R), 1 562, 3 055 cm^{-1} (Ar). ^1H NMR spectrum δ 6·80—7·70 (m, 16 H, ArH), 5·70 (dd, J = 10·0; 4·0 Hz, 2 H, 2 Ar—CH—O), 3·70 and 3·35 (2 dd, J = 16·0; 4·0 and 16·0; 10·0 Hz, 4 H, 2 $ArCH_2$). Lit.[10], m.p. 175—177°C.

C) A mixture of 6·3 g *Va* (ref.[6]), 15 ml dimethylformamide and 5·0 g KCN was stirred and heated for 7 h to 120°C, after cooling diluted with 200 ml water and extracted with benzene. The extract was washed with water, dried with $MgSO_4$ and evaporated; 5·0 g (93%) crude *IIa* (comparison with authentic samples by TLC), which was purified by crystallization from a mixture of benzene and light petroleum, m.p. 85·5—87·5°C.

2,8-Dichlorodibenzo[*b*,*f*]thiepin (*IIc*)

A) A mixture of 15·8 g *Vc* (ref.[35]), 25 ml dimethylformamide and 7·0 g K_2CO_3 was stirred and refluxed for 24 h, after cooling diluted with water and extracted with benzene, 14·0 g (100%) crude product melting at 155—169°C. Crystallization from benzene afforded an almost homogeneous product, m.p. 164—169°C. Lit.[36], m.p. 164—166°C.

B) A stirred mixture of 12·6 g *Vc* (ref.[35]) and 20 ml 2,4,6-collidine was refluxed for 7 h. After cocling it was diluted with water and extracted with benzene. The extract was washed with 10% hydrochloric acid and water, dried with Na_2SO_4 and evaporated. The crude solid product was crystallized from 40 ml benzene; 7·2 g (65%), m.p. 163—167·5°C. The product is identical with that obtained under *A*.

10-Bromo-2,8-dichlorodibenzo[*b*,*f*]thiepin (*IIIc*)

A solution of 8·9 g *IIc* in a mixture of 160 ml ether, 170 ml tetrachloromethane and 90 ml chloroform was stirred and treated at 13°C dropwise with a solution of 5·1 g Br in 20 ml tetrachloromethane. The mixture was allowed to stand for 7 days at room temperature, filtered with charcoal and evaporated *in vacuo*; 12·8 g (92%) crude solid *IXc* which was used for the further step. Repeated crystallization gave products melting at 128—131°C which are still inhomogeneous (mixture of stereoisomers).

A mixture of 9·3 g crude *IXc*, 50 ml benzene and 2·5 ml 1-methylpiperazine was stirred for 7 h at room temperature and then refluxed for 1·5 h. After cooling the mixture was diluted with benzene, washed with 10% hydrochloric acid and water, dried with Na_2SO_4 and evaporated *in vacuo*. Crystallization of the residue from benzene gave 6·4 g (84%) crude *IIIc*, m.p. 102—109°C. Analytical sample, m.p. 119—121°C (benzene). UV spectrum: λ_{max} 295 nm (log ε 3·85), 266 nm (4·31), 226 nm (4·56). IR spectrum: 810, 818, 888 (2 adjacent and solitary Ar—H), 1 540, 1 575 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·70 (d, J = 2·0 Hz, 1 H, 1-H), 7·60 (s, 1 H, 11-H), 7·00—7·50 (m, 5 H, remaining ArH). For $C_{14}H_7BrCl_2S$ (358·1) calculated: 46·95% C, 1·97% H, 22·32% Br, 19·80% Cl, 8·96% S; found: 47·36% C, 2·04% H, 22·16% Br, 19·67% Cl, 9·05% S.

2-(2-Hydroxymethylphenylthio)benzaldehyde (*XII*)

A solution of 68·9 g 2-mercaptobenzyl alcohol[8,15] in 120 ml hexamethylphosphortriamide was treated with a solution of 19 g NaOH in 30 ml water and then with 66 g 2-chlorobenzaldehyde and the mixture was stirred and heated for 7 h to 100°C. After standing overnight the mixture was poured into 1 l water and extracted with benzene. The extract was washed with 5% NaOH and water, dried with $MgSO_4$ and evaporated under reduced pressure. The residue (114 g) was dissolved in benzene and chromatographed on a column of 500 g silica gel. Elution with benzene recovered 16·2 g starting 2-chlorobenzaldehyde. Continued chromatography (elution with a 1 : 1 mixture of benzene and chloroform and finally only with chloroform) afforded 72·5 g (84% per conversion) homogeneous product which crystallized and melted at 66—69°C. Analytical sample, m.p. 67·5—69°C (benzene–cyclohexane). ^1H NMR spectrum: δ 10·24 (s, 1 H, CHO), 7·80 (m, 1 H, ArH adjacent to CHO), 6·50—7·70 (m, 7 H, remaining ArH), 4·73 (d, J = = 6·0 Hz, 2 H, $ArCH_2O$), 2·29 (t, J = 6·0 Hz, 1 H, OH). For $C_{14}H_{12}O_2S$ (244·3) calculated: 68·83% C, 4·95% H, 13·12% S; found: 69·04% C, 4·97% H, 12·90% S.

Dibenzo[*b,f*]thiepin-10 carbonitrile (*Ia*)

A) A mixture of 14·8 g *IIIa* (ref.[6]), 9·0 g CuCN and 75 ml dimethylformamide was stirred and refluxed for 5 h, poured into 300 ml NH_4OH and the product was extracted with dichloromethane. The extract was washed with 2M HCl and water, dried with $MgSO_4$ and evaporated. The residue was crystallized from 25 ml benzene. Filtration and processing of the mother liquor gave 10·0 g (83%) product melting at 133—137°C. Analytical sample, m.p. 136—137°C (benzene). UV spectrum: λ_{max} 211·5 nm (log ε 4·39), 227 nm (4·40), 265 nm (4·27), 303·5 nm (4·03). IR spectrum: 756 (4 adjacent Ar—H), 1 475, 1 560, 1 567, 1 585, 3 030 (Ar), 1 606 (ArC=CAr), 2 205, 2 220 cm^{-1} (CN). ^1H NMR spectrum: δ 7·80 (s, 1 H, 11 H), 7·20—7·70 (m, 8 H, ArH). For $C_{15}H_9NS$ (235·3) calculated: 76·57% C, 3·86% H, 5·95% N, 13·62% S; found: 76·51% C, 3·88% H, 5·98% N, 13·36% S.

B) A solution of 4·52 g *X* (ref.[5]) in 100 ml benzene was treated with 2·6 g trimethylsilyl cyanide[13] and 0·3 g ZnI_2, the mixture was stirred for 8 h at room temperature and allowed to stand for 2 days. Pyridine (300 ml) and 10 g $POCl_3$ were added, the mixture was refluxed for 6 h, decomposed by pouring on ice and the product was extracted with benzene. The extract was dried with K_2CO_3 and evaporated under reduced pressure; 3·8 g (81%) crude *Ia* (m.p. 115—130°C) which was crystallized from ethanol giving 2·34 g *Ia* melting at 130—135°C. Its identity with the product obtained under *A* was established in usual way (TLC, mixed m.p.).

C) A solution of 5·0 g *XII* in 60 ml benzene was treated with 15 ml $SOCl_2$, the mixture was refluxed for 1 h, benzene was evaporated *in vacuo*, another 50 ml benzene were added and the evaporation was repeated. The oily residue (5·3 g, almost theoretical yield) was considered crude 2-(2-chloromethylphenylthio)benzaldehyde (*XIII*). It was dissolved in 20 ml dimethyl sulfoxide,

2·70 g KCN were added and the mixture was stirred and heated for 4 h to 100°C. After cooling it was diluted with water and extracted with benzene. The extract was washed with water, dried with $MgSO_4$ and evaporated. The residue (4·5 g) was chromatographed on 180 g silica gel. In the first fractions benzene eluted 0·37 g homogeneous substance which crystallized from cyclohexane and melted at 136—137°C. It was identified as *Ia*.

Continuing elution with benzene afforded 1·2 g homogeneous oil which was identified by the ^{1}H NMR spectrum as 2-(2-formylphenylthio)phenylacetonitrile (*XIV*): δ 10·30 (s, 1 H, CHO), 7·85 (m, 1 H, ArH adjacent to CHO), 7·10—7·70 (m, 6 H, 4 ArH of phenylacetonitrile and 4,5-H_2 of 2-formylphenylthio), 6·85 (m, 1 H, 6-H of 2-formylphenylthio), 4·75 (s, 2 H, $ArCH_2CN$).

D) A solution of 47·1 g *XII* in 200 ml warm benzene was stirred and treated over 10 min with 50 ml $SOCl_2$, the mixture was stirred for 1 h at room temperature, refluxed for 1 h and evaporated. The evaporation with 100 ml benzene was repeated, the residue was dissolved in 100 ml dimethylformamide and the solution was treated with 26 g KCN. The mixture was stirred for 8 h at 50°C, diluted with water and extracted with benzene. Processing of the extract gave 48·8 g (100%) of the almost homogeneous *XIV*. A solution of 5·3 g of this product in 200 ml ethanol was added dropwise over 6 h to a stirred and refluxing solution prepared from 300 ml ethanol and 0·4 g Na. The mixture was refluxed for 1 h, evaporated under reduced pressure, the residue was diluted with water and extracted with benzene. After drying with K_2CO_3 the extract was evaporated and the residue was chromatographed on 400 g Al_2O_3. A mixture of benzene and light petroleum eluted 1·42 g (29%) *Ia*, m.p. 132—136°C (light petroleum).

2-Chlorodibenzo[*b*,*f*]thiepin-10-carbonitrile (*Ib*)

A mixture of 22·3 g *IIIb* (ref.[31]), 12·5 g CuCN and 100 ml dimethylformamide was refluxed for 4 h, poured into 300 ml NH_4OH and extracted with dichloromethane. The extract was washed with dilute hydrochloric acid and evaporated. Crystallization of the residue from benzene and processing of the mother liquors gave 10·8 g (58%) crude *Ib*, m.p. 156—166°C. Analytical sample, m.p. 161—168°C (ethanol). UV spectrum: λ_{max} 217·5 nm (log ε 4·50), 228 nm (4·50), 267·5 nm (4·32), 304 nm (4·07). IR spectrum: 756, 830, 890, 900 (4 and 2 adjacent and solitary Ar—H), 1 550, 1 580, 3 040 (Ar), 1 602 (ArC=CAr), 2 200, 2 218 cm^{-1} (C=C—CN). ^{1}H NMR spectrum: δ 7·80 (s, 1 H, 11-H), 7·20—7·65 (m, 7 H, ArH). For $C_{15}H_8ClNS$ (269·8) calculated: 66·79% C, 2·99% H, 13·14% Cl, 5·19% N, 11·89% S; found: 67·00% C, 2·92% H, 13·03% Cl, 5·09% N, 11·72% S.

2,8-Dichlorodibenzo[*b*,*f*]thiepin-10-carbonitrile (*Ic*)

A mixture of 1·6 g *IIIc*, 0·8 CuCN and 7 ml dimethylformamide was stirred and refluxed for 7 h, poured into a mixture of 20 ml water and 20 ml NH_4OH, the product was extracted with chloroform, the extract washed with water, 3M-HCl and water, dried with Na_2SO_4 and evaporated. The inhomogeneous residue was chromatographed on 60 g Al_2O_3. Elution with light petroleum yielded 0·90 g (66%) homogeneous compound *Ic* which was crystallized from benzene–light petroleum and benzene, m.p. 184—186°C. UV spectrum: λ_{max} 302 nm (log ε 3·99), 268 nm (4·33), 252 nm (4·31), 230 nm (4·56), infl. at 351 nm (2·72). IR spectrum: 815, 890, 900 (2 adjacent and solitary Ar—H), 1 545, 1 570 (Ar), 2 210 cm^{-1} (C=C—CN). ^{1}H NMR spectrum: δ 7·10 to 7·70 (m, ArH and ArCH=C). For $C_{15}H_7Cl_2NS$ (304·2) calculated: 59·22% C, 2·32% H, 23·31% Cl, 4·61% N, 10·54% S; found: 58·91% C, 2·52% H, 22·56% Cl, 4·29% N, 10·07% S.

Continuation of the chromatography gave 0·3 g of a different homogeneous (according to TLC) compound, m.p. 247—251°C (benzene–light petroleum) which proved to be either 8-chlorodibenzo[*b*,*f*]thiepin-2,10-dicarbonitrile (*XXXIII*) or 2-chlorodibenzo[*b*,*f*]thiepin-8,10-dicarbo-

nitrile (*XXXIV*) or a mixture of both. Mass spectrum, *m/z* (%): 294 (M^+ corresponding to $C_{16}H_7ClN_2S$, 100%), 259 (77), 258 (75), 215 (35). UV spectrum: λ_{max} 232 nm (log ε 4·60), 277 nm (4·34), infl. at 303 nm (3·92). IR spectrum (KBr): 810, 830, 888 (2 adjacent and solitary Ar—H), 1 543, 1 570, 1 600 (Ar), 2 225 cm^{-1} (ArCN). For $C_{16}H_7ClN_2S$ (294·8) calculated: 65·19% C, 2·39% H, 12·03% Cl, 9·51% N, 10·88% S; found: 65·08% C, 2·49% H, 12·23% Cl, 9·09% N, 10·87% S.

10,11-Dihydrodibenzo[*b,f*]thiepin-10-carbonitrile (*IVa*)

A stirred solution of 102 g *Ia* in 2·8 l ethanol was treated dropwise with a solution of 49·1 g $NaBH_4$ in 200 ml water containing 1·2 ml 20% NaOH. The mixture was refluxed for 1 h and ethanol was evaporated under reduced pressure. The residue was diluted with water and extracted with benzene. The extract was washed with 4% NaOH and water, dried with K_2CO_3, evaporated under reduced pressure and the residue was crystallized from ethanol; 86·2 g (84%), m.p. 91·5 to 93°C. Analytical sample, m.p. 95—96°C (ethanol). IR spectrum: 760, 777 (4 adjacent Ar—H), 1 565, 1 587 (Ar), 2 228 cm^{-1} (R—CN). ^1H NMR spectrum: δ 7·00—7·70 (m, 8 H, ArH), 5·08 (dd, J = 10·0; 3·5 Hz, 1 H, Ar—CH—CN), 3·85 and 3·41 (2 dd, J = 16·0; 3·5 and 16·6; 10·0 Hz, 2 H, $ArCH_2$). For $C_{15}H_{11}NS$ (237·3) calculated: 75·91% C, 4·67% H, 5·90% N, 13·51% S; found: 75·75% C, 4·82% H, 5·94% N, 13·38% S.

2-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-carbonitrile (*IVb*)

Ib (9·2 g) in 500 ml ethanol was reduced with a solution of 6·4 g $NaBH_4$ in 30 ml water containing 3 drops 20% NaOH similarly like in the preceding case. The benzene extract deposited on standing 0·7 g crystals, m.p. 222—223°C (benzene-ethanol), identified as the amide *VIIb*, *vide infra*. The filtrate was evaporated and the inhomogeneous residue was crystallized from a mixture of benzene and light petroleum, 5·0 g (54%), m.p. 113·5—115·5°C. Analytical sample, m.p. 114·5—116°C (cyclohexane). IR spectrum: 760, 820, 884 (4 and 2 adjacent and solitary Ar—H), 1 562, 1 580 (Ar), 2 238 cm^{-1} (R—CN). ^1H NMR spectrum: δ 7·00—7·70 (m, 7 H, ArH), 5·02 (dd, J = 9·0; 3·5 Hz, 1 H, Ar—CH—CN), 3·82 and 3·40 (2 dd, J = 16·0; 3·5 and 16·6; 9·0 Hz, 2 H, $ArCH_2$). For $C_{15}H_{10}ClNS$ (271·8) calculated: 66·29% C, 3·71% H, 13·05% Cl, 5·15% N, 11·80% S; found: 66·23% C, 3·78% H, 13·45% Cl, 4·87% N, 12·00% S.

10,11-Dihydrodibenzo[*b,f*]thiepin-10-carboxamide (*VIIa*)

A solution of 9·8 g *Ia* in 300 ml ethanol was treated with a solution of 11·9 g $NaBH_4$ in 50 ml water containing 0·25 ml 20% NaOH and the mixture was refluxed for 11 h. Ethanol was evaporated, the residue diluted with water and extracted with benzene. Processing of the extract gave 10·4 g inhomogeneous residue which was crystallized from 100 ml benzene; 4·41 g (38%) 3 : 1 solvate of *VIIa* with benzene, m.p. 169—171°C. Analytical sample, m.p. 170—171°C (benzene). Mass spectrum, *m/z* (%): 255 (M^+ corresponding to $C_{15}H_{13}NOS$, 47%), 211 (100), 210 (67), 197 (36), 179 (23), 178 (66), 165 (18), 149 (21). IR spectrum: 750 (4 adjacent Ar—H), 1 560, 1 587, 3 040 (Ar), 1 625, 1 655 ($CONH_2$), 3 170, 3 355 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·60 (bs, 2 H, NH_2), 5·90-7·50 (m, ArH), 4·31 (dd, 1 H, Ar—CH—CO), *c.* 3·50 (m, 2 H, $ArCH_2$). For $C_{15}H_{13}NOS + 1/3\ C_6H_6$ (281·4) calculated: 72·57% C, 5·37% H, 4·98% N, 11·40% S; found: 72·48% C, 5·46% H, 4·88% N, 11·11% S.

The mother liquors were evaporated, the residue was extracted with hexane and the extract gave by crystallization 1·22 g (12%) nitrile *IVa*, m.p. 90—92°C. The undissolved material and the combined mother liquors (mixture of *IVa* and *VIIa*) was used for preparing the acid *VIIIa*.

2-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-carboxamide (*VIIb*)

A mixture of 2·0 g *IVb*, 100 ml ethanol and 5 ml 20% NaOH was refluxed for 8 h. Cooling of the mixture led to crystallization of 1·6 g (75%) *VIIb*, m.p. 221–223°C. Analytical sample, m.p. 222–223°C (benzene–ethanol). IR spectrum: 753, 816, 857, 880 (4 and 2 adjacent and solitary Ar—H), 1 552, 1 580, 3 040 (Ar), 1 612, 1 663 ($CONH_2$), 3 180, 3 272, 3 308, 3 390 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·90–7·60 (m, 7 H, ArH), 4·22 (dd, 1 H, Ar—CH—CO), *c.* 3·50 (m, 2 H, $ArCH_2$). For $C_{15}H_{12}ClNOS$ (289·8) calculated: 62·17% C, 4·17% H, 12·24% Cl, 4·83% N, 11·07% S; found: 62·13% C, 4·10% H, 12·45% Cl, 4·73% N, 11·18% S.

10,11-Dihydrodibenzo[*b,f*]thiepin-10-carboxylic Acid (*VIIIa*)

A mixture of *IVa* and *VIIa* (see above) (3·4 g) was refluxed for 5 h with 5 g KOH in 5 ml ethanol (bath temperature 135°C). After cooling it was diluted with 200 ml water, the solution was washed with chloroform and acidified with hydrochloric acid. The separated acid was isolated by extraction with chloroform; 1·73 g, m.p. 126–128°C (benzene). IR spectrum: 736, 760, 769 (4 adjacent Ar—H), 915, 1 207, 1 230, 1 695, infl. 3 160 (RCOOH), 1 565, 1 590, 3 045 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·00–7·60 (m, 8 H, ArH), 4·48 (bd, 1 H, Ar—CH—CO), *c.* 3·62 (m, 2 H, $ArCH_2$). For $C_{15}H_{12}O_2S$ (256·3) calculated: 70·29% C, 4·72% H, 12·51% S; found: 69·85% C, 4·93% H, 12·09% S.

2-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-carboxylic Acid (*VIIIb*)

A mixture of 4·3 g *IVb*, 30 ml water and 20 ml H_2SO_4 was stirred and heated under reflux for 8 h in a bath of 150°C. It was then diluted with water, the separated solid was extracted with warm 5% NaOH, the undissolved part was filtered, washed with water, dried and crystallized from a mixture of benzene and ethanol; 1·2 g *VIIb*, m.p. 220–222°C. The alkaline solution was acidified with hydrochloric acid, the precipitated product was filtered, washed with water, dried and crystallized from benzene; 2·8 g (61%), m.p. 181·5–183·5°C. IR spectrum: 753, 809, 819, 861, 880 (4 and 2 adjacent and solitary Ar—H), 940, 1 204, 1 216, 1 221, 1 691, 2 675, 2 700, 2 790, 3 120 (R—COOH), 1 530, 1 550, 1 580, infl. 3 120 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·00–7·60 (m, 7 H, ArH), 4·45 (bt, 1 H, Ar—CH—CO), 3·58 (m, 2 H, $ArCH_2$). For $C_{15}H_{11}ClO_2S$ (290·8) calculated: 61·96% C, 3·81% H, 12·19% Cl, 11·03% S; found: 61·93% C, 3·95% H, 11·92% Cl, 10·88% S.

2-(2-Hydroxymethylphenylthio)phenylacetonitrile (*XV*)

A mixture of 69·7 g 2-iodophenylacetonitrile[19,20], 42·2 g 2-mercaptobenzyl alcohol[8,15], 40 g K_2CO_3, 4 g Cu and 400 ml dimethylformamide was refluxed for 14 h, dimethylformamide was distilled off, the residue was diluted with water and extracted with benzene. The extract was filtered, dried with K_2CO_3 and distilled; 47·7 g (65%), b.p. 230–240°C/80 Pa. IR spectrum (film): 752 (4 adjacent Ar—H), 1 030 (CH_2OH), 1 565, 1 585, 3 010, 3 050 (Ar), 2 250 (R—CN), (3 430 cm^{-1} (OH). ^1H NMR spectrum: δ 6·90–7·60 (m, 8 H, ArH), 4·70 (s, 2 H, $ArCH_2O$), 3·75 (s, 2 H, $ArCH_2CN$), 2·30 (bs, 1 H, OH). For $C_{15}H_{13}NOS$ (255·3) calculated: 70·56% C, 5·13% H, 5·49% N, 12·56% S; found: 70·90% C, 5·33% H, 5·29% N, 12·60% S.

2-(2-Chloromethylphenylthio)phenylacetonitrile (*XVI*)

A solution of 42·1 g *XV* in 200 ml benzene was treated with 70 ml $SOCl_2$, the mixture was refluxed for 2 h, evaporated and the evaporation *in vacuo* was repeated with 200 ml fresh benzene.

The residue was distilled *in vacuo*; 41·5 (92%), b.p. 217°C/0·1 kPa. ^{1}H NMR spectrum: δ 6·90 to 7·60 (m, 8 H, ArH), 4·71 (s, 2 H, $ArCH_2Cl$), 3·80 (s, 2 H, $ArCH_2CN$). For $C_{15}H_{12}ClNS$ (273·8) calculated: 65·80% C, 4·42% H, 12·95% Cl, 5·12% N, 11·71% S; found: 66·52% C, 4·51% H, 12·33% Cl, 4·81% N, 11·53% S.

Dibenzo[*b,f*]thiepin-10(11*H*)-one (*X*)

A solution of 5·5 g *XVI* in 30 ml dimethyl sulfoxide was dropped over 2 h at 25–30°C into a stirred mixture of 2·8 g powdered KOH and 20 ml dimethyl sulfoxide, the mixture was stirred for 2 h and poured into water. The precipitated solid was filtered, dissolved in benzene, the solution was washed with water, dried with K_2CO_3 and evaporated under reduced pressure. The residue was dissolved in benzene, a small quantity of undissolved solid was filtered off, the filtrate was diluted with light petroleum and chromatographed on 100 g silica gel. Elution with a mixture of benzene and light petroleum and then with benzene gave 1·15 g (25%) almost pure *X*, m.p. 70–72·5°C. In admixture with an authentic sample of *X* (m.p. 72–73°C, ref.[5]) the melting point does not show a depression.

5,6,16,17-Tetrahydrotetrabenzo[*b,f,i,m*]-1,8-dithiacyclotetradecin-5,16-dicarbonitrile (*XVII*)

A) A solution of 5·5 g *XVI* in 100 ml benzene was treated with 0·6 g triethylbenzylammonium chloride and 10 g 50% NaOH, the mixture was stirred for 4 h at 60°C, allowed to stand for 2 days, diluted with water, the solid was filtered and crystallized from dimethylformamide; 3·1 g (65%), m.p. 305–308°C. Mass spectrum, *m/z* (%): 474·1261 (M^+, for $C_{30}H_{22}N_2S_2$ calculated 474·1225, 30%), 236 (100), 198 (88), 197 (78), 211 (26). IR spectrum: 760 (4 adjacent Ar–H), 1 567, 1 586, 3 005, 3 050, 3 070 (Ar), 2 238 cm^{-1} (R–CN). For $C_{30}H_{22}N_2S_2$) 474·5) calculated: 75·93% C, 4·67% H, 5·90% N, 13·49% S; found: 75·17% C, 4·66% H, 6·70% N, 13·29% S.

B) A mixture of 2·8 g powdered KOH, 0·5 g tetrabutylammonium bromide and 100 ml dimethylformamide was stirred and treated dropwise over 8 h with a solution of 5·5 g *XVI* in 100 ml benzene at 25–30°C. It was stirred for 6 h, diluted with water and extracted with benzene. Processing of the extract and crystallization of the semi-solid residue from a mixture of benzene and ethanol gave 0·8 g (33%) *XVII*, m.p. 293–303°C. TLC of the mother liquor indicated the presence of *X* but not of *IVa*.

C) A stirred solution of 6·2 g *XVI* in 100 ml dimethylformamide was treated at room temperature over 30 min with 0·8 g 80% NaH (suspension in oil). The mixture was stirred for 6 h, poured into water, the solid was filtered, suspended in benzene and filtered again; 2·7 g (50%) *XVII*, m.p. over 300°C (compared by TLC with the product obtained under *A*). The mother liquor was chromatographed on 50 g SiO_2. The fractions eluted with benzene (1·43 g) consisted mainly of *IVa* (TLC comparison with the authentic substance).

11-(3-Dimethylaminopropyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-carbonitrile (*cis*- and *trans*-*XVIII*)

The Grignard reagent was prepared from 3·1 g Mg and 15·5 g 3-dimethylaminopropyl chloride in 60 ml tetrahydrofuran (initiation with a grain of iodine and a few drops of 1,2-dibromoethane and refluxing for 1 h) and treated under stirring over 10 min with a solution of 15 g *Ia* in 60 ml tetrahydrofuran. The mixture was refluxed for 5 h, cooled, decomposed with 90 ml 10% hydrochloric acid and 100 ml water and washed with ether. The acid aqueous layer was made alkaline with NH_4OH, the mixture of bases was extracted with ether, the extract was dried with K_2CO_3 and the extract was evaporated. The residue was chromatographed on 500 g Al_2O_3.

The benzene and the first chloroform eluates were evaporated and gave the mixture of stereoisomeric bases *XVIII*; 18·7 g (91%) oil. Neutralization with oxalic acid and crystallization of the oxalate from a mixture of aqueous ethanol and ether gave 16·0 (61%) hydrogen oxalate of *cis*-*XVIII*, m.p. 184–186·5°C. Analytical sample, m.p. 186–189°C (aqueous ethanol–ether). For $C_{22}H_{24}N_2O_4S$ (412·5) calculated: 64·05% C, 5·86% H, 6·79% N, 7·77% S; found: 63·89% C, 5·95% H, 6·62% N, 7·90% S. A sample of the oxalate was decomposed with NH_4OH and the homogeneous oily base was isolated by extraction with ether and used for recording the ^1H NMR spectrum: δ 7·00–7·70 (m, 8 H, ArH), 4·80 (d, J = 2·0 Hz, 1 H, Ar—CH—CN), 4·28 (dt, J = 2·0; 7·0 Hz, 1 H, the remaining ArCH), 1·30–2·50 (m, 6 H, $CH_2CH_2CH_2N$), 2·16 (s, 6 H, CH_3NCH_3).

The mother liquors after the oxalate described were evaporated and the residue was crystallized from a mixture of ethanol and ether. There were obtained 1·4 g (5%) of a different hydrogen oxalate corresponding to *trans*-*XVIII*, m.p. 158–159·5°C. For $C_{22}H_{24}N_2O_4S$ (412·5) calculated: 64·05% C, 5·86% H, 6·79% N, 7·77% S; found: 63·42% C, 5·99% H, 6·83% N, 7·60% S. Decomposition of a sample of this oxalate with NH_4OH and extraction with ether gave the oily base *trans*-*XVIII*. ^1H NMR spectrum: δ 7·00–7·70 (m, 8 H, ArH), 5·18 (d, J = 10·5 Hz, 1 H, Ar—CH—CN), 3·52 (m, 1 H, remaining ArCH), 1·20–2·50 (m, 6 H, $CH_2CH_2CH_2N$). 2·15 (s, 6 H, CH_3NCH_3).

10-(3-Dimethylaminopropyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-carboxylic Acid (*XIX*)

A mixture of 7·3 g *cis*-*XVIII*, 40 ml acetic acid and 40 ml 48% hydrobromic acid was refluxed for 20 h, cooled and neutralized with 20% NaOH and then NH_4OH to pH 7. The amino acid was extracted with chloroform and the extract was washed with a slight excess of 20% NaOH and then with water. The combined alkaline and aqueous washings were neutralized with acetic acid, the product was extracted with chloroform, the extract was evaporated, the residue was dissolved in a mixture of acetone and ether and the solution was acidified with a solution of HCl in ether. There crystallized 1·0 g (12%) hydrochloride of *XIX*, m.p. 200–207°C (acetone–ether). Mass spectrum, m/z (%): 341 (M^+ corresponding to $C_{20}H_{23}NO_2S$, 1·4%), 297·(9), 296 (11), 197 (3), 100 (3), 58 [$CH_2{=}N(CH_3)_2^+$, 100]. IR spectrum: 769 (4 adjacent Ar—H), 1 190, 1 712 (R—COOH), 2 700 cm^{-1} (NH^+). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·00–7·50 (m, 8 H, ArH), 4·30 (d, J = 7·0 Hz, 1 H, Ar—CH—CO), 3·75 (bm, 1 H, remaining ArCH), 2·90 (bm, 2 H, CH_2N), 2·60 (s, 6 H, $CH_3N^+CH_3$), 1·60 (bm, 4 H, remaining 2 CH_2). For $C_{20}H_{24}ClNO_2S$ (377·9) calculated: 63·56% C, 6·40% H, 9·38% Cl, 3·71% N, 8·48% S; found: 63·08% C, 6·47% H, 9·37% Cl, 3·31% N, 8·23% S.

10-(2-Dimethylaminoethyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-carbonitrile (*XX*)

A mixture of 11·35 g *IVa*, 50 ml dimethylformamide and 2·35 g 80% NaH (suspension in oil) was stirred for 10 min at 50°C, it was then treated with 7·70 g 2-dimethylaminoethyl chloride and the mixture was stirred for 20 min at 90°C. After cooling it was poured into 400 ml water, extracted with benzene, the benzene layer was shaken with 450 ml 3M-HCl, the aqueous layer was made alkaline with 20% NaOH and the base was isolated by extraction with benzene. Drying with K_2CO_3 and evaporation under reduced pressure yielded 13·1 g (89%) base *XX*, m.p. 75 to 85°C. Analytical sample, m.p. 88–89°C (benzene–light petroleum). IR spectrum: 755 (4 adjacent Ar—H), 2 230 (R—CN), 2 745, 2 790, 2 795 (CH_3—N—CH_3), 3 010, 3 025 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·00–7·60 (m, 8 H, ArH), 4·21 and 3·30 (ABq, J = 13·5 Hz, 2 H, $ArCH_2$), 2·20 to 2·70 (m, 4 H, CH_2CH_2N), 2·12 (s, 6 H, CH_3NCH_3). For $C_{19}H_{20}N_2S$ (308·4) calculated: 73·99% C, 6·54% H, 9·08% N, 10·39% S; found: 74·14% C, 6·70% H, 8·78% N, 10·60% S.

Hydrogen oxalate, m.p. 192–194°C (95% ethanol). For $C_{21}H_{22}N_2O_4S$ (398·1) calculated: 63·29% C, 5·57% H, 7·03% N, 8·05% S; found: 63·81% C, 5·58% H, 6·99% N, 8·20% S.

10-(3-Dimethylaminopropyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-carbonitrile (*XXI*)

A similar alkylation of 11·35 g *IVa* with 8·9 g 3-dimethylaminopropyl chloride in 50 ml dimethylformamide in the presence of 2·35 g 80% NaH gave 14·8 g (96%) crude oily base which was transformed by neutralization with oxalic acid in acetone and by treatment with ether to 16·3 g (78%) hydrogen oxalate, m.p. 127–129°C (ethanol–ether). For $C_{24}H_{26}N_2O_4S$ (438·5) calculated: 65·73% C, 5·98% H, 6·40% N, 7·31% S; found: 65·63% C, 5·73% H, 6·16% N, 7·42% S.

10-[2-(Tetrahydro-2-pyranyloxy)ethyl]-10,11-dihydrodibenzo[*b,f*]thiepin-10-carbonitrile (*XXII*)

A mixture of 16·4 g *IVa*, 70 ml dimethylformamide and 2·30 g 80% NaH (suspension in oil) was stirred under nitrogen for 10 min at room temperature, it was then treated with 15·2 g 2-(tetrahydro-2-pyranyloxy)ethyl chloride[26] and the stirring was continued for 30 min (exothermic reaction). The mixture was poured into water and extracted with benzene. The extract was dried with K_2CO_3, evaporated and the residue crystallized after mixing with 50 ml light petroleum; 24·7 g (98%) mixture of stereoisomeric bases *XXII*, m.p. 117–133°C (after a single recrystallization from a mixture of benzene and light petroleum). This mixture was used for further work. IR spectrum: 770 (4 adjacent Ar—H), 1 025, 1 125 (R—O—R'), 2 225 cm^{-1} (CN). ^1H NMR spectrum: δ 7·00–7·60 (m, 8 H, Ar—H), 4·58 (bs, 1 H, O—CH—O), 4·40 + + 4·38 and 3·40 (ABq, J = 13·0 Hz, 2 H, $ArCH_2$), 3·30–4·10 (m, 4 H, 2 CH_2O), 2·40 (bt, 2 H, remaining CH_2 in the chain), 1·60 (m, 6 H, remaining 3 CH_2 in the ring). For $C_{23}H_{23}NO_2S$ (365·5) calculated: 72·29% C, 6·34% H, 3·83% N, 8·77% S; found: 72·33% C, 6·43% H, 3·68% N, 8·98% S.

The mother liquor after the first crop of crystals (light petroleum) was evaporated and the residue was crystallized from a mixture of benzene and light petroleum until reaching a constant melting point of 106–107·5°C; 0·87 g of a homogeneous racemic *XXII*. IR spectrum: 752, 765 (4 adjacent Ar—H), 1 025, 1 125 (R—O—R'), 2 220 cm^{-1} (R—CN). ^1H NMR spectrum: δ 7·00–7·60 (m, 8 H, ArH), 4·58 (bs, 1 H, O—CH—O), 4·38 and 3·40 (ABq, J = 13·0 Hz, 2 H, $ArCH_2$), 3·30–4·10 (m, 4 H, 2 CH_2O), 2·40 (bt, 2 H, remaining CH_2 in the chain), *c.* 1·60 (m, 6 H, remaining 3 CH_2 in the ring). For $C_{23}H_{23}NO_2S$ (365·5) calculated: 72·29% C, 6·34% H, 3·83% N, 8·77% S; found: 72·76% C, 6·56% H, 3·73% N, 8·40% S.

10-(2-Bromoethyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-carbonitrile (*XXIV*)

XXII (24·5 g mixture of stereoisomers) was dissolved in 200 ml methanol, the solution was treated with 10 drops conc. hydrochloric acid and refluxed for 10 h. The solution was evaporated under reduced pressure, the residue was dissolved in 150 ml benzene, the solution was washed with water, dried with $MgSO_4$ and evaporated; 18·3 g (97%) almost homogeneous (TLC) oily 10-(2-hydroxyethyl)-10,11-dihydrodibenzo[*b,f*]thiepin-10-carbonitrile (*XXIII*) which was, without characterization, dissolved in 100 ml benzene and the stirred solution was treated over 10 min with 6·7 g PBr_3, added dropwise. It was stirred for 2 h, allowed to stand for 48 h at room temperature, heated for 2 h to 70°C and cooled. The precipitated solid was filtered off; 10·9 g (46%) *XXX* hydrobromide, m.p. 230–232°C (for its characterization see the next paragraph). The filtrate was washed with water and 15% Na_2CO_3, dried and evaporated. The residue was chromatographed on 200 g silica gel. Elution with benzene gave 2·69 g (12%) of *XXIV*, m.p. 132–132·5°C

(ether–light petroleum). IR spectrum: 750 (4 adjacent Ar—H), 2 235 (R—CN), 3 015 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·00—7·80 (m, 8 H, ArH), 4·21 and 3·30 (ABq, J = 13·0 Hz, 2 H, $ArCH_2$), 3·40 (m, 2 H, CH_2Br), 2·60 (m, 2 H, remaining CH_2). For $C_{17}H_{14}BrNS$ (344·3) calculated: 59·31% C, 4·10% H, 23·21% Br, 4·07% N, 9·31% S; found: 59·74% C, 4·09% H, 23·55% Br, 4·02% N, 9·26% S. Continued elution with benzene yielded 0·31 g nitrile *IVa*, m.p. 95—96·5°C (cyclohexane–light petroleum).

Acidification of the aqueous and alkaline washings with hydrochloric acid gave 5·2 g (23%) 2-(10-cyano-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)ethyl dihydrogen phosphite (*XXV*), m.p. 117·5—120·5°C (acetone). IR spectrum: 745, 765 (4 adjacent Ar—H), 1 000, 1 015, 1 035, 1 125 (P—O—C, P—OH), 2 230 (R—CN), 2 600—2 700 cm^{-1} (P—OH). ^1H NMR spectrum (C^2H_3·SOC^2H_3): δ 7·00—7·90 (m, 8 H, ArH), 4·29 and 3·45 (ABq, J = 13·0 Hz, 2 H, $ArCH_2$), 4·00 (bm, 2 H, CH_2O), *c.* 2·50 (bm, 2 H, remaining CH_2). For $C_{17}H_{16}NO_3PS$ (345·5) calculated: 59·12% C, 4·67% H, 4·06% N, 9·28% S; found: 59·10% C, 4·77% H, 3·67% N, 9·50% S.

2′-Imino-4′,5′-dihydrospiro[dibenzo[*b*,*f*]thiepin-10(11*H*),3′(2′*H*)-furan] (*XXX*)

A) The main product of the preceding experiment was identified as *XXX* hydrobromide. IR spectrum: 750, 765 (4 adjacent Ar—H), 1 642 (C=NH_2^+), 2·730 (NH_2^+), 3 060 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 11·7 (bs, 2 H, =NH_2^+), 7·00—7·90 (m, 8 H, ArH), 5·12 (bm, 2 H, CH_2O), 4·10 and 3·60 (ABq, J = 13·0 Hz, 2 H, $ArCH_2$), *c.* 2·50 (bm, 2 H, remaining CH_2). When recorded in [$^2H_5$]pyridine solution, the most typical signals in the ^1H NMR spectrum were 2 t at 5·03 (2 H, CH_2O) and 2·47 ppm (2 H, CH_2) belonging to the methylene groups in the five-membered ring, and the ABq at 4·20 and 3·63 ppm (J = 13·7 Hz) belonging to the $ArCH_2$ group; after 2 h standing the spectrum in [$^2H_5$]pyridine changes greatly due to the transformation of the hydrobromide to the base: ABq of $ArCH_2$ at 4·32 and 4·00 ppm (J = = 13·7 Hz), m at 3·09 ppm (2 H) corresponding to one CH_2 group of the five-membered ring. For $C_{17}H_{16}BrNOS$ (362·3) calculated: 56·36% C, 4·45% H, 22·06% Br, 3·87% N, 8·85% S; found: 56·18% C, 4·47% H, 22·12% Br, 3·69% N, 8·95% S.

A sample was decomposed with 10% NaOH and the base was isolated by extraction with chloroform. Processing of the extract gave the oily base *XXX* which was transformed by treatment with HCl in ether to the hydrochloride, m.p. 195—198°C with softening from 184°C (ethanol). Mass spectrum, *m/z* (%): 281 (M^+ corresponding to $C_{17}H_{15}NOS$, 39%), 220 ($C_{12}H_{14}NOS$, 55), 197 ($C_{13}H_9S$, 35), 172 ($C_{11}H_{10}NO$, 100). IR spectrum: 750, 770 (4 adjacent Ar—H), 1 120 (R—O—C=N^+), 1 657 (O—C=NH_2^+), 2 620, 2 725 cm^{-1} (NH_2^+). ^{13}C NMR spectrum ($C^2H_3SOC^2H_3$): 186·2 (quaternary carbon of OC=NH_2^+), 139·0; 136·7; 135·3; 132·7 (4 aromatic quaternary carbons), 54·8 (quaternary spiro-carbon), 132·3; 131·5; 131·1; 130·2; 128·9; 128·4; 128·0; 127·1 (8 aromatic methine carbons), 75·5 (CH_2O), 37·6 ppm (1 methylene carbon atom; the other is covered by the strong signal of [$^2H_6$]dimethyl sulfoxide). In pyridine the first signal is shifted to 177·8 ppm (due to the loss of the charge on the nitrogen atom by transformation to the base); the signals of the all four remaining aliphatic carbons are apparent: 58·9 (CH_2O), the shift by 16·6 ppm upfield indicates its presence in the imidic ester group), 54·3 (spiro-carbon), 43·4; 42·1 ppm (2 CH_2). For $C_{17}H_{16}ClNOS$ (317·8) calculated: 64·24% C, 5·07% H, 11·16% Cl, 4·41% N, 10·09% S; found: 63·83% C, 5·33% H, 11·01% Cl, 4·35% N, 10·03% S.

B) A solution of 4·5 g *XXV* in 50 ml warm acetic acid was cooled to 20°C and saturated under external cooling over 1·5 h with HBr. The mixture was allowed to stand overnight at room temperature, diluted with 70 ml water and the precipitated solid was filtered, washed with water and benzene and recrystallized from a mixture of benzene, chloroform and ethanol; 4·0 g (85%) *XXX* hydrobromide, m.p. 235—239°C. The identity with the compound described sub *A* was established by direct comparison.

2'-Oxo-4',5'-dihydrospiro[dibenzo[*b*,*f*]thiepin-10(11*H*),3'(2'*H*)-furan] (*XXXI*)

A mixture of 3·3 g *XXX* hydrochloride and 50 ml 1 : 1 dilute hydrochloric acid was refluxed for 3·5 h, allowed to stand for 2 days at room temperature and the precipitated solid was filtered, washed with water and dried; 1·12 g (38%) crude *XXXI*. Crystallization from a mixture of benzene and hexane gave a 2 : 1 solvate with benzene, m.p. 70–80°C and after resolidification 120·5 to 122°C. Mass spectrum, *m/z* (%): 282 (M^+ corresponding to $C_{17}H_{14}O_2S$, 100), 254 (23), 237 (16), 223 (22), 197 (92), 176 (27). IR spectrum: 760 (4 adjacent Ar—H), 1 163, 1 178 (C—O in lactone), 1 750 cm^{-1} (COO of lactone). ^1H NMR spectrum: δ 6·90–7·70 (m, 8 H, ArH), 7·30 (s, 3 H, 0·5 C_6H_6), 4·40 (t, J = 7·0 Hz, 2 H, CH_2O), 4·10 and 3·15 (ABq, J = 13·0 Hz, 2 H, $ArCH_2$), 2·30 (t, J = 7·0 Hz, 2 H, remaining CH_2). ^{13}C NMR spectrum (C^2HCl_3): 179·7 (CO of lactone, typical for a five-membered ring), 139·8; 139·4; 136·1; 133·5 (4 aromatic quaternary carbons), 51·1 (spiro-carbon), 131·5; 131·0 (2 C); 130·5; 128·3; 127·5 (3 C) (8 aromatic methine carbons), 65·1 (CH_2O), 39·4 and 39·1 ppm (remaining 2 CH_2). For $C_{17}H_{14}O_2S + 0·5\ C_6H_6$ (321·4) calculated: 74·74% C, 5·33% H, 9·98% S; found: 74·86% C, 5·42% H, 9·97% S.

10-(3-Bromopropyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-carbonitrile (*XXVIII*)

A mixture of 8·2 g *IVa*, 35 ml dimethylformamide and 1·15 g 80% NaH (suspension in oil) was stirred under nitrogen for 10 min at 40°C and treated with 8·2 g 3-(tetrahydro-2-pyranyloxy)-propyl chloride[30]. The mixture was stirred for 30 min, poured into water and extracted with benzene. Processing of the extract gave an inhomogeneous product which was chromatographed on 250 g silica gel. Benzene eluted the less polar impurities and chloroform eluted 13·0 g (99%) homogeneous oily *XXVI* which was used without characterization. The product was dissolved in 100 ml methanol, 6 drops of hydrochloric acid were added and the mixture was refluxed for 6 h. Methanol was evaporated, the residue was dissolved in benzene, the solution washed with water, dried with $MgSO_4$ and evaporated; 10·1 g (99%) homogeneous oily *XXVII*. It was dissolved without characterization in 50 ml benzene, the solution was stirred and treated over 10 min at 5–10°C with 3·3 g PBr_3. The mixture was stirred for 5 h at room temperature, allowed to stand for 2 days, washed with water and 15% Na_2CO_3, dried with $MgSO_4$ and evaporated. The residue was chromatographed on 200 g silica gel. Elution with benzene yielded 7·46 g (61%) homogeneous *XXVIII* which was crystallized from a mixture of ether and light petroleum, m.p. 106·5–108°C. IR spectrum: 762 (4 adjacent Ar—H), 2 225 cm^{-1} (R—CN). ^1H NMR spectrum: δ 7·00–7·60 (m, 8 H, ArH), 4·20 and 3·38 (ABq, J = 13·0 Hz, 2 H, $ArCH_2$), 3·30 (m, 2 H, CH_2Br), *c.* 2·15 (m, 4 H, remaining CH_2CH_2). For $C_{18}H_{16}BrNS$ (358·3) calculated: 60·34% C, 4·50% H, 22·30% Br, 3·91% N, 8·95% S; found: 60·85% C, 4·49% H, 22·10% Br, 3·71% N, 8·78% S.

Acidification of the aqueous and alkaline washings with hydrochloric acid gave 3·25 g (26%) 3-(10-cyano-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)propyl dihydrogen phosphite (*XXIX*), m.p. 134–136°C (acetone). IR spectrum (KBr): 748, 761 (4 adjacent Ar—H), 1 018, 1 105, 1 187 (P—O—C, P—OH), 3 045 (Ar), 3 400 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·10–7·70 (m, 8 H, ArH), 4·20 and 3·40 (ABq, J = 13·0 Hz, 2 H, $ArCH_2$), 3·90 (m, 2 H, CH_2O), 1·50–2·30 (m, 4 H, remaining CH_2CH_2). For $C_{18}H_{18}NO_3PS$ (359·4) calculated: 60·16% C, 5·05% H, 3·90% N, 8·62% P, 8·92% S; found: 60·41% C, 5·18% H, 3·91% N, 8·48% P, 9·34% S.

1,3-Bis(10-cyano-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)propanes (*XXXII*)

A mixture of 7·1 g *IVa*, 30 ml dimethylformamide and 1·0 g 80% NaH was stirred under nitrogen for 10 min, heated to 50°C and treated with 9·1 g 1,3-dibromopropane. Exothermic reaction took place with a rise of temperature to 80°C. The mixture was stirred for 20 min, diluted with 300 ml

benzene, washed with water, dried with $MgSO_4$ and evaporated. The residue was mixed with a small quantity of benzene and filtered; 5·4 g (70%) mixture of stereoisomeric *XXXII*, m.p. 187—192°C. Repeated crystallization from benzene gave 1·68 g homogeneous isomer considered to be the *meso-XXXII*, m.p. 215·5—217°C. Mass spectrum, *m/z* (%): 514 (M^+ corresponding to $C_{33}H_{26}N_2S_2$, 16·9%), 278 (10·6), 251 (13·7), 250 (14·0), 236 (87·7), 210 (9·3), 204 (7·8), 203 (18·7), 197 (100), 165 (10·1), 77 (9·8). IR spectrum: 738, 760, 770 (4 adjacent Ar—H), 2 218 cm^{-1} (R—CN). ^1H NMR spectrum: δ 7·00—7·60 (m, 16 H, ArH), 4·08 and 3·40 (ABq, J = 14·0 Hz, 4 H, 2 $ArCH_2$), 1·80 (bs, 6 H, 3 CH_2). ^{13}C NMR spectrum (C^2HCl_3): 138·6; 137·4; 136·6; 133·5 (aromatic quaternary carbon atoms), 123·2 (CN), 45·4 (quaternary carbon atoms in positions 10,10'), 132·2; 131·9; 131·5; 130·4; 129·2; 128·1; 127·9 (aromatic methine carbon atoms), 43·7 (2 methylene carbon atoms of the propane chain adjacent to $C_{(10)}$ of the skeleton), 41·7 (2 methylene carbon atoms adjacent to Ar), 19·9 ppm (methylene carbon atom in the middle of the propane chain). For $C_{33}H_{26}N_2S_2$ (514·7) calculated: 77·01% C, 5·09% H, 5·44% N, 12·46% S; found: 76·96% C, 5·10% H, 5·14% N, 12·58% S.

Processing of the mother liquors and repeated crystallization of a fraction from ethanol led to 0·90 g of the other homogeneous stereoisomer considered to be (±)-*XXXII*, m.p. 187—190°C. Mass spectrum, *m/z* (%): 514 (M^+ corresponding to $C_{33}H_{26}N_2S_2$, 22·4%), 278 (11·2), 251 (13·8), 250 (15·0), 236 (100), 210 (11·4), 204 (11·0), 203 (22·1), 197 (98·6), 165 (11·4), 77 (12·1). IR spectrum: 737, 756, 768, 773 (4 adjacent Ar—H), 2 210 cm^{-1} (CN). ^1H NMR spectrum: δ 7·00—7·60 (m, 16 H, ArH), 4·07, 4·03, 3·40 and 3·35 (4 d in ABq, J = 14·0 Hz, 4 H, 2 $ArCH_2$), 1·80 (bs, 6 H, 3 CH_2). For $C_{33}H_{26}N_2S_2$ (514·7) calculated: 77·01% C, 5·09% H, 5·44% N, 12·46% S; found: 77·17% C, 5·30% H, 5·05% N, 12·32% S.

2-(2-Fluorophenylthio)benzoic Acid (*XXXV*)

2-Fluorothiophenol[41] (59·2 g) was added to a solution of 79·9 g KOH in 775 ml water, the mixture was stirred for 10 min at 50°C, treated with 114 g 2-iodobenzoic acid and 7·4 g Cu catalyst and refluxed for 10 h. After cooling to 50°C it was filtered with charcoal and the filtrate was acidified with hydrochloric acid. The precipitated product was filtered after standing overnight, washed with water and crystallized from ethanol; 107 g (93%), m.p. 184—186°C. Analytical sample, m.p. 186·5—188·5°C (ethanol). UV spectrum: λ_{max} 253 nm (log ε 3·97), 313 nm (3·66), infl. at 275 nm (3·70). IR spectrum: 750, 760 (4 adjacent Ar—H), 920, 1 260, 1 676, 2 520, 2 560, 2 650, infl. 3 150 (ArCOOH), 1 561, 1 590, 3 055 cm^{-1} (Ar). For $C_{13}H_9FO_2S$ (248·3) calculated: 62·89% C, 3·65% H, 7·65% F, 12·92% S; found: 62·97% C, 3·69% H, 7·88% F, 13·02% S.

2-(2-Fluorophenylthio)benzyl Alcohol (*XXXVI*)

A suspension of 62·0 g *XXXV* in 100 ml tetrahydrofuran was stirred and treated at 20—30°C with 10·6 g $NaBH_4$, added in small portions. The mixture was treated under nitrogen with 31 ml boron trifluoride etherate, added dropwise over 35 min at 20—30°C, diluted with 50 ml tetrahydrofuran and stirred for 4 h at room temperature. After standing overnight, the mixture was decomposed under cooling with diluted hydrochloric acid and the product was isolated by extraction with benzene. The extract was washed with 5% NaOH and water, dried with Na_2SO_4 and distilled; 56·6 g (97%), b.p. 172°C/97 Pa. The distillate crystallized on standing and was crystallized from hexane, m.p. 49—51°C. IR spectrum: 750 (4 adjacent Ar—H), 1 029, 1 070 (CH_2OH), 1 570, 1 590, 3 060 (Ar), 3 340 cm^{-1}(OH). ^1H NMR spectrum: δ 6·80—7·60 (m, 8 H, ArH), 4·75 (bs, 2 H, $ArCH_2O$), 2·40 (bs, 1 H, OH). For $C_{13}H_{11}FOS$ (234·3) calculated: 66·64% C, 4·73% H, 8·11% F, 13·69% S; found: 66·77% C, 4·76% H, 8·23% F, 13·80% S.

2-(2-Fluorophenylthio)benzyl Chloride (*XXXVII*)

A mixture of 56·7 g *XXXVI* and 25 ml pyridine was stirred and treated dropwise over 1·5 h with 24 ml $SOCl_2$ at 20°C. It was then stirred for 1 h at room temperature and for 2 h at 30—40°C. After standing overnight, the stirred mixture was decomposed by a slow addition of 200 ml water and the product was extracted with benzene. The extract was washed with 1M-HCl and water, dried with $CaCl_2$ and distilled; 55·9 g (91%), b.p. 156°C/0·1 kPa. ^{1}H NMR spectrum: δ 6·90 to 7·60 (m, 8 H, ArH), 4·80 (s, 2 H, $ArCH_2Cl$). For $C_{13}H_{10}ClFS$ (252·7) calculated: 61·77% C, 3·99% H, 14·03% Cl, 7·52% F, 12·69% S; found: 61·91% C, 4·09% H, 14·13% Cl, 7·63% F, 12·88% S.

Diethyl 2-(2-Fluorophenylthio)benzylmalonate (*XXXVIII*)

Diethyl malonate (10·1 g) was added to a solution of 1·4 g Na in 30 ml ethanol, the mixture was stirred for 25 min and treated over 30 min with 15·9 g *XXXVII*, added dropwise. The mixture was stirred for 30 min at room temperature and refluxed for 10 h. Ethanol was then evaporated under reduced pressure, the residue diluted with water and extracted with benzene. The extract was washed with water, dried with Na_2SO_4 and distilled; 14·8 g (63%), b.p. 220°C/1·3 kPa. IR spectrum (film): 755 (4 adjacent Ar—H), 1 153, 1 222, 1 262 (C—O of ester), 1 574, 1 590, 3 040 (Ar), 1 732 cm^{-1} (RCOOR'). ^{1}H NMR spectrum: δ 6·90—7·40 (m, 8 H, ArH), 4·15 (q, J = 7·0 Hz, 4 H, 2 CH_2O), 3·91 (t, 1 H, COCHCO), 3·29 (d, 2 H, $ArCH_2$), 1·21 (t, J = 7·0 Hz, 6 H, 2 CH_3). For $C_{20}H_{21}FO_4S$ (376·4) calculated: 63·81% C, 5·62% H, 5·05% F, 8·52% S; found: 63·96% C, 5·60% H, 5·01% F, 8·43% S.

Ethyl 2-(2-Fluorophenylthio)benzylcyanoacetate (*XXXIX*)

Ethyl cyanoacetate (10·2 g) was added to a solution of sodium ethoxide (from 2·08 g Na and 45 ml ethanol), the mixture was stirred for 10 min, diluted with 25 ml ethanol and treated with 22·7 g *XXXVII*. It was then stirred for 30 min without heating and refluxed for 6·5 h. After cooling ethanol was evaporated, the residue was decomposed with 60 ml water and extracted with a mixture of benzene and ether. The extract was dried with Na_2SO_4 and distilled; 12·9 g (44%), b.p. 206—208°C/0·12 kPa. IR spectrum: 753 (4 adjacent Ar—H), 1 220, 1 259 (C—O of ester), 1 470, 1 570, 1 590, 3 058 (Ar), 1 740 (RCOOR'), 2 225 cm^{-1} (R—CN). ^{1}H NMR spectrum: δ 6·90—7·40 (m, 8 H, Ar—H), 4·25 (q, J = 7·0 Hz, 2 H, CH_2O), 4·02 (dd, J = 9·5; 5·5 Hz, 1 H, COCHCN), 3·60 and 3·21 (2 dd, J = 13·5; 5·5 and 13·5; 9·5 Hz, 2 H, $ArCH_2$), 1·30 (t, J = = 7·0 Hz, 3 H, CH_3). For $C_{18}H_{16}FNO_2S$ (329·4) calculated: 65·63% C, 4·90% H, 5·77% F, 4·25% N, 9·74% S; found: 65·88% C, 4·85% H, 6·08% F, 3·67% N, 9·98% S.

2-(2-Fluorophenylthio)benzylmalonic Acid (*XL*)

XXXVIII (2·4 g, recovered from an attempt at its cyclization) was dissolved in 7 ml ethanol, the solution was treated with a solution of 1·3 g KOH in 1·2 ml water, the mixture was refluxed for 10 h and evaporated under reduced pressure, the residue was dissolved in 20 ml water, the solution was washed with ether, filtered with charcoal and the filtrate was acidified with hydrochloric acid. The oily product was isolated by extraction with benzene; 1·7 g (83%). Chromatography on a column of 50 g silica gel (elution with benzene and a mixture of benzene and ether) gave *XL*, m.p. 125—128°C (benzene–light petroleum). IR spectrum (KBr): 750 (4 adjacent Ar—H), 945, 1 220, 1 260, 1 705, 1 717, 2 610, infl. 3 140 (COOH), 1 470, 1 570, 1 587 cm^{-1} (Ar). For $C_{16}H_{13}FO_4S$ (320·3) calculated: 59·99% C, 4·09% H, 5·93% F, 10·01% S; found: 60·00% C, 4·13% H, 5·91% F, 10·00% S.

3-]2-(2-Fluorophenylthio)phenyl]propionic Acid (*XLI*)

Crude *XL*, obtained from another attempt at cyclization of 7·52 g *XXXVIII* with NaH in dimethylformamide, was heated to 160—180°C for 1 h; 1·6 g crystals which were crystallized from a mixture of cyclohexane and hexane, m.p. 78—82°C. IR spectrum: 750 (4 adjacent Ar—H), 940, 1 218, 1 320, 1 695, 2 620, infl. 3 160 (COOH), 1 470, 1 570, 1 584, 1 594 cm^{-1} (Ar). ^1H NMR spectrum: δ 11·25 (bs, 1 H, COOH), 6·90—7·40 (m, 8 H, ArH), 3·18 (bt, 2 H, $ArCH_2$), 2·72 (bt, 2 H, CH_2CO). For $C_{15}H_{13}FO_2S$ (276·3) calculated: 65·19% C, 4·74% H, 6·88% F, 11·61% S; found: 65·13% C, 4·71% H, 7·03% F, 11·00% S.

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