AMINOALKYLIDENE AND AMINOALKYL DERIVATIVES OF 6,11-DIHYDRODIBENZO[*b,e*]THIEPIN-2- AND -9-CARBONITRILE AND 4,10-DIHYDROTHIENO[2,3-*c*]-1-BENZOTHIEPIN-6-CARBONITRILE; ANTIDEPRESSANTS WITH A NEW ACTIVITY PROFILE

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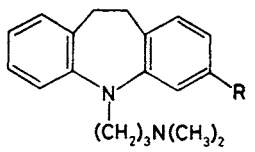
Received June 8th, 1987

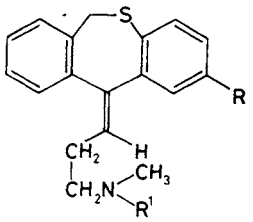
Starting from the bromo ketones *VIIc*, *XIII*, and *XXIV* and proceeding via the alcohols *VIIIc*, *IXc*, *XIV*, *XVII*, and *XXVI*, the olefinic compounds *IIc* (+ *VI*), *Xc* (+ *XI*), *XVc*, and *XIXc* (+ *XXc*), and the saturated compound *XVIc* were prepared. The pairs of geometrical isomers were separated by crystallization of salts and the individual compounds *IIc*, *Xc*, *XVc*, *XVIc*, *XIXc*, and *XXc* were transformed by treatment with cuprous cyanide in hexamethylphosphoric triamide to the corresponding cyano compounds *IIb*, *Xb*, *XVb*, *XVIb*, *XIXb*, and *XXb*. Compound *IIb* was synthesized also from the ketone *VIIc* via the cyano ketone *VIIb* and the cyano carbinol *VIIIb*. The secondary amine *IIIb* was prepared from *IIc* by partial demethylation with ethyl chloroformate, the following hydrolysis to *IIIc*, protection of NH group with butyrolactone, the following treatment with cuprous cyanide, and deprotection by mild hydrolysis. The title compounds, which are the cyano analogues of antidepressants of the prothiadene series, showed in pharmacological and biochemical tests properties of potential antidepressants and more or less selective inhibitors of the 5-hydroxytryptamine uptake in the rat brain; at the same time they are rather strong central cholinolytics.

The search after new antidepressants is still desirable because of the side effects of the classical tricyclic antidepressants, cardiotoxicity being the most serious one. It is difficult to correlate their therapeutic effects with pharmacological properties since they influence several types of receptors in the brain: adrenergic, serotonergic, histaminergic, muscarinic, and probably some further. The recent trend requires to develop antidepressants with selective effects and especially those which inhibit the uptake of 5-hydroxytryptamine (5-HT) on synaptic terminals or influence the serotonergic function by some other regulation mechanisms. At the same time they should not influence too significantly the noradrenaline (NA) uptake which is considered connected with the undesirable cardiovascular side effects. One compound, fulfilling at least partly these requirements, was derived from the classical antidepressant imipramine (*Ia*) by the simple substitution with a cyano group in position 3 of the skeleton. The obtained 3-cyano derivative of imipramine (Ro

11-2465, cianopramine) (*Ib*) was characterized as a selective inhibitor of the 5-HT uptake in some brain structures[1-3] as well as in the blood platelets[4] and the first clinical reports[5,6] on its therapeutic effect in mentally depressed patients indicated its possible usefulness. These findings attracted our attention in connection with another tricyclic antidepressant agent, prothiadene (dothiepin, dosulepin)[7-9], which consists mainly of (*E*)-N,N-dimethyl-3-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)-propylamine (*IIa*) (ref.[10]). It was considered worthwhile to investigate the cyano derivatives of compounds of the prothiadene series; the corresponding chemical and pharmacological experimental work is being described in the present article.



I

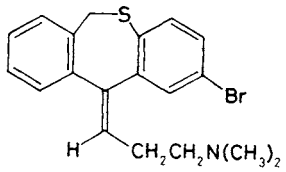


II, $R^1 = CH_3$
III, $R^1 = H$
IV, $R^1 = COOC_2H_5$
V, $R^1 = CO(CH_2)_3OH$

In formulae *I-V*, *VII-X*, *XV*, *XVI*, *XIX*, and *XX* :
a, R = H *b*, R = CN *c*, R = Br *d*, $R = CONH_2$

The first structure which was attacked was that of the 2-cyano derivative of prothiadene *IIb*. Simultaneously with our work, its synthesis has been described[11] by reaction of *IIc* with cuprous cyanide in boiling dimethylformamide. The crude product was chromatographed and the oily base, without being characterized, was transformed to the hydrobromide. The problem of geometrical isomerism was not solved and one has to assume that the product was (*E*, *Z*)-mixture. The yield of the mentioned transformation (not given in ref.[11]) must have been very low (in our hands only 10–15%). The compound was described as a selective inhibitor of 5-HT uptake in rat cerebral cortex and indicated to be a potential antidepressant. Our aim was to prepare the homogeneous (*E*)-isomer *IIb*, to settle definitely the configuration, and to develop a more substantial preparative process. Our starting material was the oily product which was obtained by the acid catalyzed dehydration of 2-bromo-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[12], i.e. the (*E*, *Z*)-mixture of N,N-dimethyl-3-(2-bromo-6,11-dihydrodibenzo[*b*,*e*]thiepin--11-ylidene)propylamines (*IIc* + *VI*). It was transformed to the mixture of hydrochlorides which was crystallized from ethanol and ether. This led to 62% of the

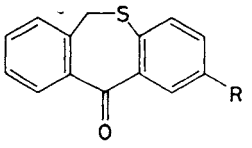
prevailing component which was identified as the hydrochloride of *IIc*. Processing of the mother liquors and crystallization from ethanol gave 2·5% of the homogeneous minor component, identified as hydrochloride of *VI*. Decomposition of the hydrochlorides with aqueous ammonia afforded the bases *IIc* (crystalline) and *VI* (oily) whose ^{1}H NMR spectra were usd to determine the configuration. Three main criteria proved useful to this end. The first was the chemical shift of the olefinic proton which is more shielded with the (*Z*)-isomer (δ 5·68) than the olefinic proton with the (*E*)-isomer (δ 5·93). The difference in the shifts (0·25 ppm) is sufficient for quantitative evaluation of the (*E*, *Z*)-mixtures. The second criterion is the signal of the CH_2 group in the ring which is dependent of the rate of inversion between the two nonplanar conformations. It is transformed from the typical AB quartet of two chemically nonequivalent protons by broadening of the signals and coalescence to a sharp singlet at elevated temperature. With regard to the fact that the volume of the substituent on the double bond, which is nearer to the flexible CH_2 group, strongly influences the energetic barrier of inversion, broadening of the CH_2 group signal occurs with the (*Z*)-isomer at room temperature already; with the (*E*)-isomer it appears as the normal AB quartet. The third and most important criterion was the comparison of the spectra of the isomers in the presence of the shift agent [$^2H_{27}$]-Eu(FOD)$_3$([$^2H_{27}$]tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium). The aromatic proton in position 1 is differently influenced by the geometrical arrangement on the double bond. In the case when the nitrogen atom, to which the shift agent is bound, is in *syn*-position to the aromatic proton, a substantially higher induced shift ($\Delta\delta$ 0·5) is apparent than with the *anti*-position ($\Delta\delta$ 0·1). In this way it was shown that the prevailing isomer *IIc* corresponds to the prevailing component of prothiadene (*IIa*).



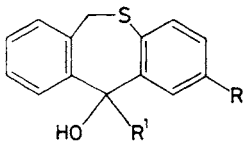
VI

Homogeneous *IIc* was subjected to treatment with cuprous cyanide in hexamethylphosphoric triamide at 150°C. This resulted in homogeneous *IIb* in high yields (80–95%). It was first isolated as the hydrochloride which was transformed to the crystalline base *IIb*, used for recording the spectra. (*E*)-Configuration remained unchanged. The hydrobromide, prepared from the base, melted at 255–256°C. This melting point is by 40°C higher than the value given by the ref.[11] (213–215°C with decomposition) which indicates the inhomogeneity of that substance. Our substance afforded also the hydrogen oxalate in two crystal modifications.

A different synthesis of *IIb* started from the ketone *VIIc* (refs[7,12]) which was subjected to treatment with cuprous cyanide in hexamethylphosphoric triamide at 150°C and gave 65% of *VIIb*. Its reaction with an insufficient amount of 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran proceeded regioselectively and afforded 60% of the amino alcohol *VIIIb*. About 40% of the starting *VIIb* were recovered which makes the yield on *VIIIb* per conversion almost theoretical. Compound *VIIIb* was dehydrated by heating with thionyl chloride in pyridine and gave 97% of *IIb* which was purified by crystallization of the hydrogen oxalate. The released base *IIb* proved identical (melting point, ^{1}H NMR spectrum) with the product obtained by the first route described.



VII

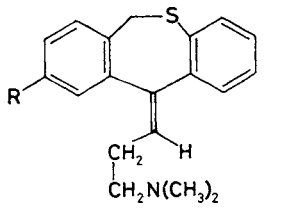


VIII, $R^1 = (CH_2)_3N(CH_3)_2$

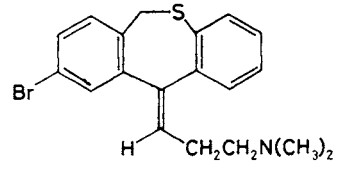
IX, $R^1 =$ 

The asymmetric structure of 6,11-dihydrodibenzo[*b*,*e*]thiepin, i.e. the carrier skeleton of the prothiadene molecule, in contradiction to the symmetric structure of 9,10-dihydrodibenz[*b*,*f*]azepine (the imipramine skeleton), necessitates to consider two cyano derivatives of prothiadene as analogues of *Ib*. In addition to the just described 2-cyano compound *IIb* it is also the 9-cyano compound *Xb* whose synthesis was also carried out. This compound was also included in the mentioned patent application[11] (without information about the configuration). We addopted a similar procedure like in the preceding case. The separation of the geometrical isomers was carried out in the stage of the 9-bromo compounds *Xc* and *XIc*; *Xc* is the heavily prevailing component of the mixture obtained by synthesis which proceeded similarly like described in literature[11]. It started from 6-bromophthalide[13] which was reacted with thiophenol in boiling sodium ethoxide solution to give 79% *XII*. Its cyclization with polyphosphoric acid at 120°C afforded 81% *XIII* which was subjected to treatment with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran. The amino alcohol *XIV* was not isolated in pure state but directly dehydrated by refluxing with 20% sulfuric acid. The obtained oily mixture of *Xc* and *XI* was transformed to the hydrochloride which corresponded to homogeneous *Xc* after two crystallizations. The mother liquors were processed by transformation to the hydrogen oxalate via the base and again, two crystallizations led to the homogeneous *Xc* oxalate. The mother liquors were further processed in the form of hydrogen maleate; a single crystallization gave the homogeneous *Xc* hydrogen maleate. Processing of the last mother liquor by evaporation and crystallization gave the homogeneous

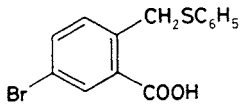
XI hydrogen maleate. The bases released from the both pure isomeric maleates were oily but their ^{1}H NMR spectra proved their homogeneity and enabled to assign the configuration. The total yield on the (*E*)-isomer (*Xc*) was 53% and that of the (*Z*)-isomer (*XI*) 1·5%. Compound *Xc* afforded by treatment with cuprous cyanide in hexamethylphosphoric triamide at 150°C the crude *Xb* which was purified by crystallization of the hydrogen oxalate. The released base *Xb* was crystalline and ts ^{1}H NMR spectrum confirmed the unchanged (*E*)-configuration.



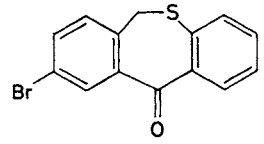
X



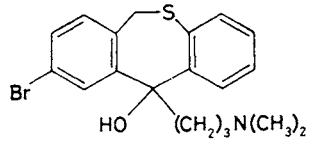
XI



XII



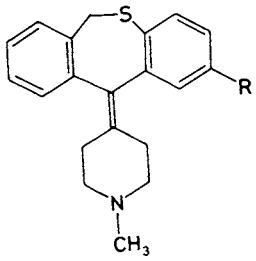
XIII



XIV

1-Methyl-4-piperidylidene analogue of prothiadene (*XVa*) (refs[9,14]) (perithiadene) possesses significant antireserpine, antihistamine, and central depressant activities. Its 2-cyano derivative *XVb* was, therefore, the further object of investigation. Its synthesis used *VIIc* (refs[7,12]) which was reacted with 1-methyl-4-piperidylmagnesium chloride[14] in tetrahydofuran to give *IXc*. Its heating with 20% sulfuric acid effected dehydration resulting in *XVc*. This case is not complicated by geometrical isomerism. Transformation of *XVc* to *XVb* was carried out similarly like in preceding cases, i.e. by heating with cuprous cyanide in hexamethylphosphoric triamide to 150°C. The crude product gave by crystallization from a mixture of benzene and light petroleum a small amount of the amide *XVd* (2 : 1 solvate with benzene) which was confirmed

by the mass and IR spectra. The mother liquor was chromatographed on aluminium oxide and elution with a mixture of benzene and chloroform afforded 31% *XVb* which crystallized in the form of the base and hydrogen oxalate (hemihydrate). The structure was corroborated by the ^{1}H NMR spectrum.

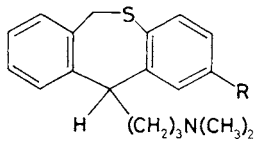


XV

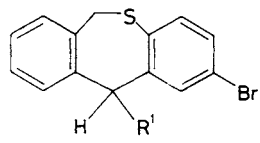
Northiadene (*IIIa*) (refs[10,15,16]), the lower homologue of prothiadene, is an effective metabolite of prothiadene[17,18]. It was, therefore, desirable to become familiar with its 2-cyano derivative *IIIb*. For preparing this compound, the homogeneous *IIc* was partially demethylated by treatment with ethyl chloroformate in boiling benzene and the uncharacterized carbamate *IVc* was hydrolyzed with a boiling concentrated solution of potassium hydroxide in ethanol. Oily *IIIc* which was obtained in a high yield, was transformed to the hydrochloride, and retention of the (*E*)-configuration was proven by the ^{1}H NMR spectrum. The secondary amino group was then protected by reaction with butyrolactone (for the method cf. ref.[19]) in boiling xylene in the presence of 2-hydroxypyridine[20] as catalyst (cf. ref.[21]). The resulting *Vc* was subjected in crude state to treatment with cuprous cyanide in hexamethylphosphoric triamide at 150°C, the obtained *Vb* was purified by chromatography and processed by hydrolysis with 10% sulfuric acid in dioxane at 90°C. The crude product was chromatograhed on aluminium oxide, the base *IIIb* was characterized by the ^{1}H NMR spectrum as consisting mainly of the (*E*)-isomer; it was transformed to the hydrogen oxalate (hemihydrate).

A further interesting substance of the prothiadene family is its dihydro derivative *XVIa* (hydrothiadene) (refs[15,22]) which, likewise, showed antidepressant activity[16,23]. Its 2-cyno derivative *XVIb* was, therefore, included into the present investigation. For its preparation we needed the bromo compound *XVIc* which was described previously[15] as the product of reduction of *XVIIIc* with hydroiodic acid and phosphorus in boiling acetic acid (characterized by the hydrochloride). We used now reduction of *IIc* with hydroiodic acid but found that this reaction is not clean at all and that the reduction of the double bond is accompanied by debromination; *XVIa* is the main product and *XVIc* was isolated only by chromatography of the mother liquors as a minor product. For obtaining the necessary amount of *XVIc* we started

from *VIIc* (refs[7,12]) which was reduced with sodium borohydride to *XVII* and this was transformed to *XVIII* by treatment with thionyl chloride. Reaction of *XVIII* with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran gave *XVIc* in moderate yield. Its reaction with cuprous cyanide in hexamethylphosphoric triamide at 150°C led to *XVIb* which was obtained as the crystalline base and characterized by the ^{1}H NMR spectrum and by the hydrogen maleate.



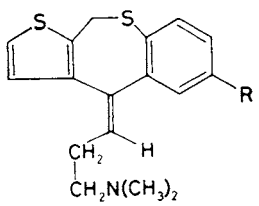
XVI



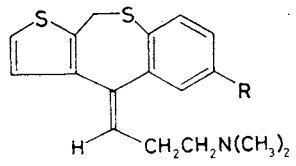
XVII, R^1 = OH
XVIII, R^1 = Cl

The last two compounds which were needed for pharmacological evaluation were *XIXb* and *XXb*, derivatives of the rather neglected 4,10-dihydrothieno[2,3-*c*]--1-benzothiepin system (cf. ref.[24]). The synthesis proceeded in the following way. 5-Bromothiosalicylic acid (*XXI*) was prepared from 5-bromoanthranilic acid[25] using the procedure described[26]. It was contaminated by the disulfide *XXII* (refs[27,28]) which could be reduced to *XXI* with triphenylphosphine in aqueous dioxane at 40°C (method, cf. ref.[29]). Compound *XXI* was reacted with 2-(chloromethyl)-thiophene[30,31] in boling aqueous ethanol in the presence of sodium hydroxide; acid *XXIII* was obtained in the yield of 90%. It was transformed by treatment with thionyl chloride to the acid chloride which was cyclized with zinc chloride in boiling benzene (diluted solution) to the ketone *XXIV*. Chromatography on silica gel was used to obtain the homogeneous product and from one of the less polar fractions *XXV* was isolated which was probably formed from *XXII*, contained as a minor contaminant in *XXIII*, by the action of zinc chloride. The formation of the similar 1,2-benzodithiole-3-one was observed when dithiosalicylic acid was treated with sulfuric acid[32]. Reaction of *XXIV* with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran gave *XXVI* which was dehydrated by boiling dilute hydrochloric acid to the mixture of *XIXc* and *XXc*. The separation started by chromatography on aluminium oxide which gave 74% of the purified mixture. It was transformed to the maleate. The released base was crystalline and was identified by the ^{1}H NMR spectrum as the (*E*)-component *XIXc*. The base, released from the mother liquors, was transformed to the hydrogen oxalate. We are dealing here with the (*Z*)-component *XXc*, contaminated by about 10% of *XIXc*. The completely pure *XXc* was obtained by chromatography of the base, prepared from this hydrogen oxalate by decomposition with aqueous ammonia. The course of the separation indicates that isomers *XIXc* and *XXc* are formed in the ratio of about 3 : 1.The final steps were transforma-

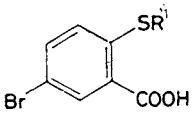
tions of *XIXc* and *XXc* by reactions with cuprous cyanide in hexamethylphosphoric triamide at 150°C to the desired *XIXb* and *XXb*. Whereas the base *XIXb* is crystalline, the base *XXb* is oily. Both afforded crystalline hydrogen oxalates.



XIX



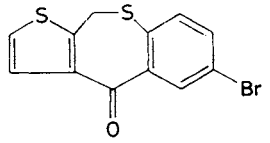
XX



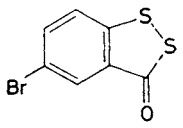
XXI, R^1 = H

XXII, R^1 = 

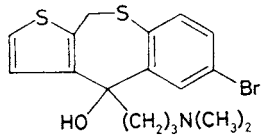
XXIII, R^1 = 



XXIV



XXV



XXVI

Compounds *IIb*, *IIIb*, *Xb*, *XVb*, *XVIb*, *XIXb*, and *XXb* were pharmacologically evaluated in the form of salts, described in the Experimental. The doses (in mg/kg) were calculated per bases. In animal tests (in vivo), the compounds were administered orally (unless stated otherwise). Acute toxicity in female mice was determined only with two compounds, LD_{50}: *XVIb*, 350 (short period of excitation followed by paresis, dyspnea, and convulsions); *XIXb*, 162 (central depression and convulsions). In the test of inhibition of the spontaneous locomotor activity in mice (Dews), the dose of 10 mg/kg was administered with all compounds; significant inhibition was observed only with *XVb*, *XIXb*, and *XXb*. In the test of reserpine ptosis in mice, significant antireserpine effect was observed with the following compounds (dose): *IIb* (10), *Xb* (10), *XVb* (25), *XVIb* (10), *XXb* (25). The ulcerogenic effect of reserpine

was significantly antagonized by 50 mg/kg of the following compounds: *XVb*, *XVIb*, *XXb*. The hypothermic effect of reserpine in mice was significantly antagonized by 10 mg/kg of *IIb* and *XVb*. The oxotremorine tremor in mice was inhibited by the following compounds (ED_{50} i.p. given): *IIb*, 15·1; *XVb*, 2·12.

The testing in the line of biochemical pharmacology was oriented towards finding selectivity in inhibition of 5-HT uptake in the brain structures in comparison with the NA uptake. The method which enables the finding of this property is the study of inhibition of the binding of [^{3}H]imipramine and [^{3}H]desipramine to the corresponding binding sites in the hypothalamus of the rat brain. Inhibition of binding of [^{3}H]imipramine corresponds to the 5-HT uptake and inhibition of [^{3}H]desipramine binding to the NA uptake; their ratios characterize the selectivity. The following medium inhibitory concentrations (IC_{50} in nmol l^{-1}) were found for the inhibition of binding of 4 nmol l^{-1} [^{3}H]imipramine in the rat hypothalamus: *IIb*, 40·28; *IIIb*, 17·49; *Xb*, 333·8; *XVb*, >100; *XVIb*, 16·23; *XIXb*, 219·2; *XXb*, 2·75. Compounds *IIIb*, *XVIb*, and especially *XXb* have high affinity to the imipramine binding sites. For inhibition of binding of 4 nmol l^{-1} [^{3}H]desipramine in rat hypothalamus the following IC_{50} (in nmol l^{-1}) were found: *IIb*, 1 936; *IIIb*, 1 967; *Xb*, 1 508; *XVb*, >100; *XVIb*, 5 233; *XIXb*, 6 316; *XXb*, 493·4. The affinity of the compounds to the desipramine binding sites is evidently much lower. The highest selectivity was shown by *IIIb*, *XVIb*, and *XXb* (index over 100).

Methods enabling to evaluate directly the influence of the compounds on the [^{3}H]5-HT uptake in the rat cerebral cortex and on the [^{3}H]NA uptake in the rat brain (both ligands were used in concentrations of 10 nmol l^{-1}) were also used. IC_{50} (in nmol l^{-1}) for inhibition of the [^{3}H]5-HT uptake: *IIb*, 36·43; *IIIb*, 842·8; *Xb*, 51·34; *XVIb*, 2 100; *XIXb*, 22·06; *XXb*, 32·85. Compounds *IIb*, *XIXb*, and *XXb* are the most powerful inhibitors. IC_{50} (in nmol l^{-1}) for inhibition of the [^{3}H]NA uptake: *IIb*, 640·9; *IIIb*, 12 997; *Xb*, 8 111; *XVIb*, 37 597; *XIXb*, 141·2; *XXb*, 84·1. Only *XIXb* and *XXb* are relatively strong inhibitors. Some agreement between the results obtained in the two types of tests can be found for compounds *IIIb* and *XVIb* which are definitely selective inhibitors of the 5-HT uptake in brain structures.

In addition to the already mentioned oxotremorine test (in vivo), the central anticholinergic activity of the compounds was evaluated by the binding study to muscarine receptors in the rat brain using 0·5 nmol l^{-1} [^{3}H]quinuclidinyl benzilate as ligand. The IC_{50} (in nmol l^{-1}) were found as follows: *IIb*, 298·2; *IIIb*, 347; *Xb*, 98·4; *XVb*, 109·6; *XVIb*, 30·5; *XIXb*, 102; *XXb*, 22·4. The compounds are rather strong central anticholinergics; this property must be considered the basis of some possible unwanted side effects. From the point of view of potential usefulness as antidepressants, compounds *XVIb* (VÚFB-17 084) and *XXb* (VÚFB-17 086) seem to be most promising: they have antireserpine activity in vivo and good selectivity for the 5-HT uptake. On the other hand, both are rather strong central anticholinergics. The only pair of geometrical isomers which was tested was that of *XIXb* and

XXb. There is clear dependence of the activity on the configuration: the (*E*)-compound was inactive in the antireserpine tests and has lower activity to the imipramine and desipramine binding sites as well as to the muscarinic receptors; the (*Z*)-compound is more interesting being active in the antireserpine tests and having high affinity to the imipramine binding sites and to muscarinic receptors.

EXPERIMENTAL

The melting points were determined in a Mettler FP-5 melting point recorder. The samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at elevated temperature. The UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8 000 spectrophotometer, the IR spectra (mostly in Nujol, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in C^2HCl_3 unless stated otherwise, δ, J in Hz) with the Tesla BS 487 C (80 MHz) spectrometer, and the mass spectra with MCH 1 320 and Varian MAT 44S spectrometers (m/z and % given). The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The column chromatography was carried out either on neutral Al_2O_3 (activity II) or on silica gel. The extracts were dried with K_2CO_3 or $MgSO_4$ and evaporated under réduced pressure in a rotating evaporator.

5-Bromothiosalicylic Acid (*XXI*)

A mixture of 35·0 g *XXII* (refs[26–28]), 250 ml dioxane, 80 ml water, and 26·0 g triphenylphosphine was stirred at 40°C for 2 h, dioxane was evaporated under reduced pressure, the residue was treated with dilute solution of NaOH, the undissolved substance (28·7 g triphenylphosphine oxide) was filtered off, and the filtrate was acidified with hydrochloric acid. The precipitated solid was filtered and crystallized from aqueous ethanol; 20·9 g (60%), m.p. 212–214°C (the block was preheated to 200°C). Ref.[26], m.p. 210–211°C.

5-Bromo-2-(phenylthiomethyl)benzoic Acid (*XII*)

A stirred solution of sodium ethoxide (3·45 g Na in 50 ml ethanol) was cooled to 40°C and treated over 5 min with 16·5 g thiophenol which was followed by 31·9 g 6-bromophthalide[13]. The mixture was refluxed for 4 h, allowed to stand overnight at room temperature. the precipitated sodium salt was dissolved by addition of 100 ml water, the solution was cooled, and acidified under stirring with 14 ml hydrochloric acid. The precipitated product was filtered after 2 h standing, washed with water, and crystallized from a mixture of 75 ml ethanol and 10 ml water; 38·2 g (79%) m.p. 141–146°C. Analytical sample, m.p. 145–148°C (aqueous ethanol). UV spectrum: inflexes at 230·5 (4·21) and 279 (3·54). IR spectrum: 690, 718, 744, 833, 860 (5 and 2 adjacent, and solitary Ar—H); 930, 1 690, 2 540, 2 640, infl. 3 100 (ArCOOH); 1 586, 3 070 (Ar). ^1H NMR spectrum: 4·50 s, 2 H ($ArCH_2S$); 7·08 d, 1 H (H-3, J = 8·5); 7·20 m, 5 H (C_6H_5); 7·50 dd, 1 H (H-4, J = 8·5; 2·0); 8·18 d, 1 H (H-6, J = 2·0); 11·25 bs, 1 H (COOH). Ref.[11], m.p. 143–145°C.

5-Bromo-2-(2-thienylmethylthio)benzoic Acid (*XXIII*)

XXI (20·9 g) was added to a stirred solution of 8·0 g NaOH in 40 ml water and 160 ml ethanol, the mixture was treated with a solution of 13·2 g 2-(chloromethyl)thiophene[30] in 20 ml ethanol, and the mixture was refluxed for 2 h. Ethanol was evaporated under reduced pressure, the

residue was dissolved in water, the solution was washed with ether and acidified with hydrochloric acid. The precipitated product was filtered after 1 h standing. washed with water and dried in vacuo; 26·5 g (90%), m.p. 166—172°C. Analytical sample, m.p. 170—173°C (benzene–ethanol). UV spectrum: 225 (4·38), 267·5 (4·14), 326 (3·66). IR spectrum: 810, 890 (2 adjacent and solitary Ar—H); 1 240, 1 690, 2 440, 2 710, infl. 3 140 (ArCOOH); 1 590, 3 010, 3 040, 3 070, 3 080 (Ar). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 4·50 s, 2 H (CH_2S); 6·80—7·50 m, 4 H (H-3 and 3 H of thienyl); 7·68 dd, 1 H (H-4, J = 9·0; 3·0); 8·00 d, 1 H (H-6, J = 3·0). For $C_{12}H_9BrO_2S_2$ (329·3) calculated: 43·78% C, 2·76% H, 24·27% Br, 19·48% S; found: 44·00% C, 2·93% H, 24·75% Br, 19·26% S.

11-Oxo-6,11-dihydrodibenzo[*b*,*e*]thiepin-2-carbonitrile (*VIIb*)

A mixture of 30·0 g *VIIc* (ref.[12]), 15 g CuCN, and 60 ml hexamethylphosphoric triamide was stirred and heated for 5·5 h to 150°C. After cooling the mixture was distributed between chloroform and dilute NH_4OH, it was filtered, the organic layer of the filtrate was separated, washed with water, dried and evaporated. Crystallization of the residue from a mixture of ethanol and benzene, and processing of the mother liquor gave 16·15 g (65%) *VIIb*, m.p. 165—166·5°C. UV spectrum: 241·5 (4·36), 286·5 (4·22). IR spectrum: 735, 770, 810, 834, 878 (4 and 2 adjacent, and solitary Ar—H); 1 591, 3 020, 3 050, 3 085 (Ar); 1 647 (Ar_2CO); 2 225 (ArCN). ^{1}H NMR spectrum: 4·05 s, 2 H ($ArCH_2S$); 7·00—7·60 m, 6 H (H_6-3,4,7,8,9,10); 8·45 d, 1 H (H-1, J = 2·0). For $C_{15}H_9NOS$ (251·3) calculated: 71·69% C, 3·61% H, 5·57% N, 12·76% S; found: 71·51% C, 3·64% H, 5·33% N, 12·60% S.

9-Bromodibenzo[*b*,*e*]thiepin-11(6*H*)-one (*XIII*)

Polyphosphoric acid was prepared from 75 ml 85% H_3PO_4 and 115 g P_2O_5 by heating to 120°C for 4 h, 37·4 g *XII* were added, and the mixture was stirred for 2 h at 120°C. After partial cooling it was decomposed by pouring into 650 g mixture of ice and water, and the product was extracted twice with 250 ml benzene. The extract was washed with 5% NaOH, dried and evaporated. The residue was crystallized from ethanol and the mother liquor was processed; 28·6 g (81%) *XIII*, m.p. 97—99°C. Ref.[11], m.p. 91—93°C.

6-Bromothieno[2,3-*c*]-1-benzothiepin-4(10*H*)-one (*XXIV*)

A suspension of 55·5 g *XXIII* in 850 ml benzene was treated with 120 ml $SOCl_2$ and the mixture was refluxed for 2 h. Volatile components were evaporated in vacuo, the remaining $SOCl_2$ was removed by addition of 150 ml benzene and its evaporation which was repeated once more. The residue (53·5 g) was the crude acid chloride which was dissolved in 740 ml benzene, 21 g freshly remelted $ZnCl_2$ were added, the mixture was diluted with further 740 ml benzene, and refluxed for 12 h. After cooling it was decomposed by pouring into 1·5 l water, the mixture was shaken, the benzene layer was separated, washed with 300 ml 10% NaOH and water, dried, and evaporated. The residue (33·5 g) was chromatographed on a column of 600 g silica gel. Elution with a mixture of benzene and light petroleum gave 0·94 g solid which was identified as 5-bromo-1,2-benzodithiole-3-one (*XXV*), m.p. 110—111°C (cyclohexane). Mass spectrum: 246 (M^+, $C_7H_3BrOS_2$, 61·9), 218 (6·3), 182 (11·1), 167 (2·4), 154 (7·9), 139 (100), 107 (11), 75 (23). UV spectrum: 239·7 (4·09), 268 (3·99), 363·4 (3·57). IR spectrum: 810, 883 (2 adjacent and solitary Ar—H); 1 571, 3 050, 3 075 (Ar); 1 659, 1 682 (ArCO—S). ^{1}H NMR spectrum: 7·46 d, 1 H (H-7, J = 9·0); 7·72 dd, 1 H (H-6, J = 2·5; 9·0); 8·05 d, 1 H (H-4, J = 2·5). For $C_7H_3BrOS_2$ (247·1) calculated: 34·02% C, 1·22% H. 32·34% Br, 25·95% S; found: 34·19% C, 1·31% H, 32·40% Br, 25·87% S.

Benzene alone eluted then 20·7 g (40%) crude *XXIV* which was crystallized from a mixture of benzene and light petroleum, m.p. 95—96°C. UV spectrum: 227 (4·28), 230 (4·28), 249 (4·27), 272 (3·98), infl. 330 (3·59). IR spectrum: 810, 820, 900 (2 adjacent and solitary Ar—H); 1 525, 1 562, 3 085, 3 100 (Ar); 1 608 (ArCOAr). ^{1}H NMR spectrum: 4·05 s, 2 H (CH_2S); 6·99 d, 1 H (H-3, J = 5·0); 7·40 m, 2 H (H_2-7, 8); 7·60 d, 1 H (H-2, J = 5·0); 8·10 d, 1 H (H-5, J = 2·5). For $C_{12}H_7BrOS_2$ (311·2) calculated: 46·31% C, 2·27% H, 25·68% Br, 20·60% S; found: 46·54% C, 2·46% H, 25·61% Br, 20·28% S.

2-Bromo-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*XVII*)

A solution of 50·0 g *VIIc* (ref.[12]) in 1 l warm ethanol was stirred and treated over 20 min with a solution of 5·0 g $NaBH_4$ in 20 ml water containing 2 drops of 20% NaOH. The mixture was refluxed for 2 h, ethanol was evaporated in vacuo, and the residue was distributed between water and chloroform. Processing of the organic layer together with the undissolved crystalline substance gave 50·3 g (theoretical) *XVII*. Recrystallization of a sample from benzene gave the homogeneous substance, m.p. 166·5—167°C. IR spectrum: 759, 808, 884 (4 and 2 adjacent, and solitary Ar—H); 1 038 (CHOH in the cycle); 1 490, 1 590, 3 055 (Ar); 3 240, 3 315 (OH). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 4·70 d, 1 H and 4·15 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·18 s, 1 H, (Ar_2CH); 6·90 d, 1 H (H-4, J = 8·5); 7·15 dd, 1 H (H-3, J = 2·5; 8·5); 7·25 m, 3 H (H_3-7,8,9); 7·45 m, 1 H (H-10); 7·72 d, 1 H (H-1, J = 2·5). For $C_{14}H_{11}BrOS$ (307·2) calculated: 54·73% C, 3·61% H, 26·01% Br, 10·44% S; found: 55·07% C, 3·82% H, 26·38% Br, 10·58% S.

2-Bromo-11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XVIII*)

A mixture of 10·0 g *XVII* and 20 ml $SOCl_2$ was refluxed for 1·5 h, undissolved substance (0·3 g, m.p. over 300°C) was filtered off, and the filtrate was evaporated in vacuo. Evaporation was repeated for removing the remaining $SOCl_2$ after the addition of 30 ml benzene. The residue was dissolved in cyclohexane and addition of light petroleum induced crystallization; 9·1 g (86%) crude *XVIII* which was recrystallized from the same mixture of solvents, m.p. 114—119°C. ^{1}H NMR spectrum: 5·28 d, 1 H and 3·70 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·05 s, 1 H (Ar_2CH); 6·90 d, 1 H (H-4, J = 9·0); 7·20 m, 5 H (H_5-3,7,8,9,10); 7·50 d, 1 H (H-1, J = 2·5). For $C_{14}H_{10}$·.BrClS (325·7) calculated: 51·63% C, 3·10% H, 24·54% Br, 10·84% Cl, 9·85% S; found: 51·77% C, 3·30% H, 24·22% Br, 10·69% Cl, 10·09% S.

11-Hydroxy-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo-[*b*,*e*]thiepin-2-carbonitrile (*VIIIb*)

The Grignard reagent was prepared by reaction of 1·0 g Mg with 4·8 g 3-dimethylaminopropyl chloride in 30 ml tetrahydrofuran (the reaction was started with a grain of iodine and several drops of 1,2-dibromoethane and finished by refluxing the mixture for 1 h). After cooling to 10°C, a solution of 6·2 g *VIIb* in 50 ml tetrahydrofuran was added, and the mixture was stirred for 2 h at 10—20°C. It was then decomposed by a slow addition of 30 ml 20% NH_4Cl, diluted with a mixture of ether, benzene, and ethyl acetate, and the basic product was extracted from the organic layer into 100 ml 10% hydrochloric acid. The acid aqueous layer was immediately made alkaline with NH_4OH, and the base was extracted with chloroform. Processing of the extract gave 5·0 g (60%) crude *VIIIb* which was crystallized from a mixture of benzene and light petroleum, m.p. 162—163°C. IR spectrum (KBr): 771, 834, 898 (4 and 2 adjacent, and solitary Ar—H); 1 130 (C—OH); 1 500, 1 590, 3 050, 3 095 (Ar); 2 220 (Ar—CN); 2 780 (N—CH_3); 3 430 (OH). For $C_{20}H_{22}N_2OS$ (338·5) calculated: 70·97% C, 6·55% H, 8·28% N, 9·47% S;

found: 70·81% C, 6·58% H, 8·24% N, 9·53% S. Evaporation of the organic layer (after the extraction of the base with dilute hydrochloric acid) recovered 2·5 g starting *VIIb*.

2-Bromo-11-(1-methyl-4-piperidyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*IXc*)

The Grignard reagent was prepared from 1·85 g Mg and 10·0 g 4-chloro-1-methylpiperidine[14] in 40 ml tetrahydrofuran. The reaction was started with a small amount of iodine and 10 drops of 1,2-dibromoethane. After the exothermic reaction was over, the mixture was refluxed for 2 h. After cooling to room temperature, the reagent was stirred and treated over 5 min with a solution of 12·2 g *VIIc* (ref.[12]) in 40 ml tetrahydrofuran. The mixture was refluxed for 2 h, allowed to stand overnight, and decomposed by a slow addition of 100 ml 20% NH_4Cl. After filtration the organic layer of the filtrate was separated and the basic product was extracted into 50 ml ice-cold 10% hydrochloric acid. The aqueous acid layer was immediately made alkaline with NH_4OH, the base was extracted with chloroform, and the extract was processed. The residue (15 g) was crystallized from a mixture of benzene and light petroleum; 6·0 g (37%) 6 : 1 solvate of *IXc* with benzene, m.p. 196·5—199·5°C. IR spectrum (KBr): 760, 800, 883, 900 (4 and 2 adjacent, and solitary Ar—H); 1 147, 1 165 (C—OH); 1 640, 3 060, 3 085 (Ar); 2 795 (N—CH_3); 3 390 (OH). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 2·18 s, 3 H (NCH_3); 4·65 d, 1 H and 4·05 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 7·03 d, 1 H (H-4, J = 8·5); 7·25 m, 4 H (H_4-3, 7, 8, 9); 7·80 m, 1 H (H-10); 7·98 d, 1 H (H-1, J = 2·5). For $C_{20}H_{22}BrNOS + 1/6\ C_6H_6$ (417·4) calculated: 60·43% C, 5·55% H, 19·15% Br, 3·36% N, 7·68% S; found: 60·47% C, 5·62% H, 19·10% Br, 3·37% N, 8·12% S.

6-Bromo-4-(3-dimethylaminopropyl)-4,10-dihydrothieno[2,3-*c*]-1-benzothiepin-4-ol (*XXVI*)

Grignard reagent was prepared by reaction of 4·15 g Mg and 20·7 g 3-dimethylaminopropyl chloride in 55 ml tetrahydrofuran similarly like in the preceding cases. It was cooled to 10°C and treated under stirring at 10—15°C with a solution of 26·4 g *XXIV* in 125 ml tetrahydrofuran, added dropwise. The mixture was stirred for 2 h at room temperature and allowed to stand overnight. Under stirring it was decomposed by a solution of 36 g NH_4Cl in 150 ml water, the organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were dried and evaporated. The residue (35·8 g) was dissolved in 350 ml ethanol, the undissolved substance (2·5 g) was filtered off, and the filtrate was evaporated to crystallization; 26·1 g (77%) *XXVI*, m.p. 137—139°C (ethanol). IR spectrum: 823, 846, 891 (2 adjacent and solitary Ar—H); 1 095 (C—OH); 1 500, 1 542, 1 566, 3 050, 3 088 (Ar); 2 660, infl. 3 100 (O—H···N). ^{1}H NMR spectrum: 2·18 s, 6 H (2 NCH_3); 4·00 s, 2 H (CH_2S); 6·98 d, 1 H (H-3, J = 5·0); 7·20—7·50 m, 3 H (H_3-2, 7, 8); 8·20 d, 1 H (H-5, J = 2·5). For $C_{17}H_{20}BrNOS_2$ (398·4) calculated: 51·25% C, 5·06% H, 20·06% Br, 3·52% N, 16·09% S; found: 51·42% C, 5·05% H, 20·14% Br, 3·41% N, 16·25% S.

(*E*)- and (*Z*)-N,N-Dimethyl-3-(2-bromo-6,11-dihydrodibenzo[*b*,*e*]-thiepin-11-ylidene)propylamine (*IIc* and *VI*)

According to our previous procedure[7,12], 91·6 g *VIIc* was reacted with an excess of 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran and gave 103 g (88%) crude *VIIIc* which was dehydrated by refluxing with 1 l 20% H_2SO_4 for 40 min. Processing gave 91·3 g of the oily mixture of *IIc* and *VI*. It was dissolved in ethanol and transformed by treatment with a solution of HCl in ether to the mixture of hydrochlorides (72·5 g). Crystallization from a mixture of ethanol and ether, evaporation of the mother liquors and crystallization of the 2nd and 3rd

product from ethanol–ether gave totally 55·5 g (62%) homogeneous hydrochloride of *IIc*, m.p. 260–261°C. Ref.[12], m.p. 260–261°C. Treatment of this product with NH_4OH, extraction with ether, and processing of the extract gave the homogeneous base *IIc*, m.p. 64–68°C (cyclohexane–light petroleum). UV spectrum: 232·5 (4·35), 277 (4·01), 312 (3·34). IR spectrum: 763, 810, 819, 841, 866 (4 and 2 adjacent, and solitary Ar—H); 1 489, 1 505, 3 015, 3 050 (Ar); 1 632 (C=C in conjugation); in CS_2 : 868 and 875 (corresponding to the solitary Ar—H in the (*E*)-isomer). ^{1}H NMR spectrum: 2·10 s, 6 H ($N(CH_3)_2$); c. 2·30 m, 4 H (NCH_2CH_2); 4·90 d, 1 H and 3·34 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 5·95 t, 1 H (C=CH, J = 7·0); 6·80 d, 1 H (H-4, J = 8·5); c. 7·20 m, 5 H (H_5-3, 7, 8, 9, 10); 7·40 d, 1 H (H-1, J = 2·5; in the presence of 20 mg [$^2H_{27}$] $Eu(FOD)_3$ per 50 mg substance $\Delta\delta$ = 0·07). For $C_{19}H_{20}BrNS$ (374·3) calculated: 60·96% C, 5·39% H, 21·35% Br, 3·74% N, 8·56% S; found: 61·25% C, 5·33% H, 21·35% Br, 3·49% N, 8·58% S.

Evaporation of the mother liquor after the 3rd product of *IIc*. HCl and crystallization of the residue from ethanol gave 1·8 g (2·5%) homogeneous hydrochloride of *VI*, m.p. 215–222°C. For $C_{19}H_{21}BrClNS$ (410·8) calculated: 55·55% C, 5·15% H, 19·45% Br, 8·63% Cl, 3·41% N, 7·80% S; found: 55·39% C, 5·14% H, 19·12% Br, 8·33% Cl, 3·80% N, 7·94% S. Decomposition of this hydrochloride with NH_4OH and extraction with ether gave the homogeneous oily base *VI*. ^{1}H NMR spectrum: 2·20 s, 6 H ($N(CH_3)_2$); 2·40 m, 4 H (NCH_2CH_2); 4·86 bd, 1 H and 3·40 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 5·68 m, 1 H (C=CH); 6·90 d, 1 H (H-4, J = 8·5); c. 7·15 m, 5 H (H_5-3, 7, 8, 9, 10); 7·25 d, 1 H (H-1, J = 2·5; in the presence of 20 mg [$^2H_{27}$] $Eu(FOD)_3$ per 50 mg substance $\Delta\delta$ = 0·45).

(*E*)- and (*Z*)-N,N-Dimethyl-3-(9-bromo-6,11-dihydrodibenzo[*b*,*e*]-thiepin-11-ylidene)propylamine (*Xc* and *XI*)

Grignard reagent was prepared by reaction of 3·4 g Mg with 17·1 g 3-dimethylaminopropyl chloride in 45 ml boiling tetrahydrofuran. After cooling to 10°C, the stirred reagent was treated over 30 min at 10–15°C with a solution of 28·3 g *XIII* in 125 ml tetrahydrofuran. The mixture was stirred for 30 min at room temperature, cooled, and decomposed under stirring with a solution of 29 g NH_4Cl in 110 ml water. The organic layer was separated, the aqueous one was extracted with ether, the organic layers were combined, and evaporated. The residue (crude *XIV*) was treated with 250 ml 20% H_2SO_4, the suspension was extracted with ether to remove the neutral solid, and the aqueous layer (with some precipitated sulfate) was refluxed with stirring for 40 min. After cooling it was made alkaline with 40% NaOH and the bases were isolated by extraction with chloroform. Processing of the extract gave 23·8 g oily mixture of *Xc* and *XI*. It was dissolved in 140 ml ether and treatment with an excess of HCl in ether precipitated 28·6 g mixture of hydrochlorides. Two crystallizations from ethanol–ether gave 6·5 g homogenous hydrochloride of *Xc*, m.p. 182·5–185·5°C. For $C_{19}H_{21}BrClNS$ (410·8) calculated: 55·55% C, 5·15% H, 19·45% Br, 8·63% Cl, 3·41% N, 7·80% S; found: 55·74% C, 5·13% H, 19·46% Br, 8·54% Cl, 3·45% N, 8·04% S. A sample of this salt was decomposed with NH_4OH and the oily homogeneous base *Xc* was isolated by extraction with ether. ^{1}H NMR spectrum: 2·13 s, 6 H ($N(CH_3)_2$); 2·30 m, 4 H (NCH_2CH_2); 4·90 d, 1 H and 3·30 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 5·91 t, 1 H (C=CH, J = 7·0); c. 7·00 m, 4 H (H_4-1,2,3,4); 7·12 d, 1 H (H-7, J = 8·0); 7·25 d, 1 H (H-10, J = 2·0; in the presence of 20 mg [$^2H_{27}$] $Eu(FOD)_3$ per 50 mg substance $\Delta\delta$ = 0·42); 7·39 dd, 1 H (H-8, J = 8·0; 2·0).

The combined mother liquors after the hydrochloride were evaporated in vacuo, the residue was treated with NH_4OH, and the bases were extracted with chloroform. Evaporation gave 18·1 g mixture of bases which was dissolved in 50 ml acetone and the solution was neutralized with a solution of 6·1 g oxalic acid dihydrate in 25 ml acetone. Standing overnight led to crystal-

lization of 20·5 g mixture of hydrogen oxalates which was crystallized twice from a mixture of 80% aqueous ethanol and ether; 13·2 g homogeneous hydrogen oxalate of *Xc*, m.p. 209 to 211·5°C. For $C_{21}H_{22}BrNO_4S$ (464·4) calculated: 54·31% C, 4·78% H, 17·21% Br, 3·02% N, 6·90% S; found: 54·71% C, 4·82% H, 17·38% Br, 2·97% N, 7·16% S.

The combined mother liquors were evaporated again in vacuo, the mixture of bases was released with NH_4OH, and extracted with ether. The extract was dried, partly evaporated, and neutralized with a solution of maleic acid in ether. The oily maleate was isolated by decantation of ether and crystallized from acetone; 2·8 g homogeneous *Xc* hydrogen maleate, m.p. 186—189°C (ethanol). For $C_{23}H_{24}BrNO_4S$ (490·4) calculated: 56·33% C, 4·93% H, 16·29% Br, 2·86% N, 6·54% S; found: 56·34% C, 5·16% H, 16·39% Br, 2·78% N, 6·69% S. The total yield on isolated *Xc* was thus 53%.

Evaporation of the acetonic mother liquor gave 2·3 g glassy hydrogen maleate which was crystallized from ethanol and gave 0·6 g (1·5%) homogeneous *XI* hydrogen maleate, m.p. 152·5 to 154°C. For $C_{23}H_{24}BrNO_4S$ (490·4) calculated: 56·33% C, 4·93% H, 16·29% Br, 2·86% N, 6·54% S; found: 56·54% C, 5·03% H, 16·32% Br, 2·87% N, 6·69% S. The released oily base was used for recording the ^{1}H NMR spectrum: 2·18 s, 6 H ($N(CH_3)_2$); 2·40 m, 4 H (NCH_2CH_2); 4·82 bd, 1 H and 3·40 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 5·70 m, 1 H (C=CH); 6·90—7·50 m, 7 H (7 ArH).

2-Bromo-11-(1-methyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XVc*)

A solution of 5·8 g *IXc* in 100 ml 20% H_2SO_4 was stirred and heated for 2 h to 100—120°C. After cooling it was made alkaline with 20% NaOH, the base was isolated by extraction with benzene, and the extract was processed. The residue crystallized from ether; 3·75 g (70%) *XVc* which was recrystallized from a mixture of benzene and light petroleum, m.p. 167·5—169°C. ^{1}H NMR spectrum: 2·20 s, 3 H (NCH_3); 1·90—2·70 m, 8 H (4 CH_2 of piperidine); 4·84 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·70—7·30 m, 7 H (7 ArH). For $C_{20}H_{20}BrNS$ (386·4) calculated: 62·17% C, 5·22% H, 20·68% Br, 3·63% N, 8·30% S; found: 62·61% C, 5·32% H, 20·79% Br, 3·56% N, 8·51% S.

(*E*)-N-Methyl-3-(2-bromo-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propylamine (*IIIc*)

A solution of 12·6 g *IIc* in 40 ml benzene was added dropwise to a stirred solution of 4·73 g ethyl chloroformate in 20 ml benzene at 75°C and the mixture was refluxed for 1 h. After cooling it was washed with 50 ml 10% H_2SO_4 and with water, it was dried with solid KOH, and evaporated. The oily residue (12·6 g crude *IVc*) was treated with a solution of 9·0 g KOH in 11 ml ethanol and the mixture was heated for 2 h under reflux in a bath of 125—130°C. After cooling the mixture was diluted with 50 ml water and extracted with benzene. From the extract the basic product was transferred by shaking into 50 ml 10% hydrochloric acid, the aqueous solution was made alkaline with 20% NaOH, and the product was isolated by extraction with benzene. Processing of the extract gave 8·3 g (68%) homogeneous oily *IIIc* which was dissolved in ethanol and transformed by a slight excess of HCl in ether to the solid hydrochloride (7·5 g). Crystallization of this substance from chloroform gave the homogeneous compound melting at 273—277°C. Mass spectrum: 359 (M^+, $C_{18}H_{18}BrNS$, 0·01), 282 (0·03), 235 (0·5), 221 (0·6), 203 (1), 202 (1), 44 (100). UV spectrum: 231 (4·34), 276 (4·01), 315 (3·34). IR spectrum: 765, 810, 868 (4 and 2 adjacent, and solitary Ar—H); 1 484, 1 585, 3 040 (Ar); 1 659 (C=C in conjugation); 2 440 (NH_2^+). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 2·40 m, 2 H (=C—CH_2); 2·52 s, 3 H (NCH_3); 3·02 bt, 2 H (CH_2N, J = 7·0); 4·80 d, 1 H and 3·72 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·04 t, 1 H (C=CH, J = 7·0); 6·93 d, 1 H (H-4, J = 9·0); 7·30 m, 5 H (H_5-3, 7, 8, 9, 10); 7·10 d, 1 H,

(H-1, $J = 2{\cdot}5$). For $C_{18}H_{19}BrClNS$ (396·8) calculated: 54·48% C, 4·83% H, 20·14% Br, 8·94% Cl, 3·53% N, 8·08% S; found: 54·74% C, 4·91% H, 20·09% Br, 8·92% Cl, 3·41% N, 8·25% S. The released base was used for the further step.

(±)-N,N-Dimethyl-3-(2-bromo-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)propylamine (*XVIc*)

A) A mixture of 50 ml 55% hydroiodic acid, 1 g NaH_2PO_2, 6·2 g red P, and 20·0 g crude hydrochloride of *IIc* was stirred and treated over 15 min with 50 ml acetic anhydride. The mixture was heated for 4 h under reflux and in nitrogen atmosphere in a bath of 120°C, filtered, and allowed to crystallize; 14·9 g (72%) *XVIa* hydroiodide, m.p. 202—205°C (aqueous ethanol–ether). Mass spectrum: 297 (M^+, $C_{19}H_{23}NS$, 1), 264 (2), 178 (3·5), 128 (7·5), 127 (4), 86 (16), 58 (100). For $C_{19}H_{24}INS$ (425·4) calculated: 53·64% C, 5·69% H, 29·84% I, 3·29% N, 7·54% S; found: 53·26% C, 5·74% H, 29·47% I, 3·22% N, 7·92% S. The released oily base *XVIa* was used for recording the ^1H NMR spectrum: 1·60 m, 2 H (CH_2 in the middle of the propane chain); 2·21 s, 6 H ($N(CH_3)_2$); c. 2·20 m, 2 H (CH_2 in position 1 of the propane chain); 2·38 t, 2 H (CH_2N); 4·45 bt, 1 H (Ar_2CH, $J = 7{\cdot}0$);4·66 bd, 1 H and 3·90 bd, 1 H (ABq, $ArCH_2S$, $J = 13{\cdot}0$); 6·90—7·40 m, 7 H (7 ArH). A sample of the base was transformed to the hydrogen oxalate, m.p. 171·5—173·5°C (aqueous ethanol–ether). For $C_{21}H_{25}NO_4S$ (387·5) calculated: 65·09% C, 6·50% H, 3·61% N, 8·28% S; found: 64·92% C, 6·64% H, 3·58% N, 8·70% S.

The mother liquor after *XVIa*.HI was evaporated, the base was released with 10% NaOH and isolated by extraction with chloroform. It was chromatographed on 200 g silica gel. Elution with a mixture of chloroform and ethanol gave 1·0 g (6%) crude *XVIc* which was transformed to the hydrogen oxalate, m.p. 129—132°C (ethanol–ether). Mass spectrum: 375 (M^+, $C_{19}H_{22}BrNS$, 0·2), 342 (0·4), 297 (0·4), 86 (10), 73 (15), 58 (100). For $C_{21}H_{24}BrNO_4S$ (466·4) calculated: 54·08% C, 5·19% H, 17·13% Br, 3·00% N, 6·88% S; found: 54·04% C, 5·40% H, 16·65% Br, 2·87% N, 7·39% S.

B) Grignard reagent was prepared from 1·65 g Mg and 8·2 g 3-dimethylaminopropyl chloride in 60 ml tetrahydrofuran similarly like in the preceding cases. Under stirring at room temperature it was treated over 3 min with a solution of 9·0 g *XVIII* in 40 ml tetrahydrofuran, the mixture was refluxed for 2 h, cooled, diluted with ether, and decomposed by addition of 100 ml 20% NH_4Cl. From the organic layer the basic components were extracted into dilute hydrochloric acid, the aqueous solution was made alkaline with NH_4OH, and the crude product was extracted with ether. Processing of the extract gave 6·4 g mixture which was chromatographed on 300 g Al_2O_3. Benzene eluted 2·38 g (23%) homogeneous oily *XVIc*, identical with the minor product obtained under *A*) (TLC, hydrogen oxalate melting at 130—132°C).

(*E*)- and (*Z*)-N,N-Dimethyl-3-(6-bromo-4,10-dihydrothieno[2,3-*c*]-1-benzothiepin-4-ylidene)propylamine (*XIXc* and *XXc*)

A mixture of 8·3 g *XXVI* and 90 ml 1 : 1 dilute hydrochloric acid was refluxed for 1 h. After cooling it was made alkaline with 20% NaOH, and the product was isolated by extraction with benzene. Evaporation of the extract gave the residue which was shown (TLC) to be a mixture of two substances. It was chromatographed on a column of 400 g Al_2O_3 giving 5·9 g (74%) mixture of *XIXc* and *XXc* (elution with benzene). Neutralization with maleic acid in ethanol and addition of ether gave 3·6 g maleate which was homogeneous after two recrystallizations from ethanol–ether (3·0 g, 29%), m.p. 169—171°C. The released base crystallized from ether and melted at 58—63°C. It was shown to be the homogeneous *XIXc*. UV spectrum: 260 (3·97). IR spectrum: 700 (thiophene Ar—H); 815, 900 (2 adjacent and solitary Ar—H); 1 542, 1 570, 3 000, 3 020, 3 068 (Ar); 2 760, 2 810 (N—CH_3); in CS_2: 707, 810, 890. ^1H NMR spectrum:

2·12 s, 6 H ($N(CH_3)_2$); 2·30 m, 4 H (NCH_2CH_2); 3·98 bs, 2 H (CH_2S); 6·02 bt, 1 H (C=CH); 6·90 d, 1 H (H-3, J = 5·0); 7·03 d, 1 H (H-2, J = 5·0); 7·40 m, 3 H (remaining 3 ArH). For $C_{17}H_{18}BrNS_2$ (380·4) calculated: 53·68% C, 4·77% H, 21·01% Br, 3·68% N, 16·86% S; found: 53·84% C, 4·69% H, 21·29% Br, 3·69% N, 16·78% S.

Hydrochloride, m.p. 189—194°C (ethanol). For $C_{17}H_{19}BrClNS_2$ (416·8) calculated: 48·98% C, 4·59% H, 19·17% Br, 8·51% Cl, 3·36% N, 15·38% S; found: 49·13% C, 4·48% H, 19·07% Br, 8·73% Cl, 3·36% N, 15·00% S.

The mother liquors after the crystallization of the maleate were combined, evaporated, the residue was decomposed with NH_4OH, the bases were extracted with ether, and the extract was evaporated. The residue was neutralized with oxalic acid dihydrate in acetone and ether which led to 2·75 g mixture of hydrogen oxalates melting at 163—169°C. Three crystallizations from ethanol–ether gave 1·5 g hydrogen oxalate of *XXc* (containing still about 10% of the salt of *XIXc*), m.p. 170—176°C. For $C_{19}H_{20}BrNO_4S_2$ (470·4) calculated: 48·51% C, 4·29% H, 16·99% Br, 2·98% N, 13·63% S; found: 48·42% C, 4·16% H, 17·20% Br, 2·86% N, 13·79% S. The base (7·5 g), released from the oxalate of a similar quality was chromatographed on 190 g silica gel. Chloroform eluted 0·3 g of a less polar component. Mixture of chloroform and ethyl acetate gave first 2·0 g mixture of *XIXc* and *XXc* (about 1 : 1) and 3·6 g homogeneous oily *XXc* which was used for the final step and also for recording the ^{1}H NMR spectrum: 2·28 s, 6 H ($N(CH_3)_2$); 2·50 m, 4 H (NCH_2CH_2); 4·10 s, 2 H (CH_2S); 5·75 m, 1 H (C=CH); 6·85 d, 1 H (H-3, J = 5·0); 7·05 d, 1 H (H-2, J = 5·0); 7·30 m, 3 H (remaining 3 ArH).

(*E*)-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin-2-carbonitrile (*IIb*)

A) *IIc* (released from 10·1 g homogeneous hydrochloride) was dissolved in 20 ml hexamethylphosphoric triamide, 5·0 g CuCN were added, and the mixture was stirred and heated for 14 h to 150°C in nitrogen atmosphere. After cooling it was distributed between 15% NH_4OH and a 1 : 1 mixture of benzene and ether, filtered, the organic layer was washed with water, dried, and evaporated. The residue was dissolved in ether and transformed by treatment with HCl in ether to the hydrochloride; 8·3 g (95%). After crystallization from ethanol, the compound is homogeneous and melts at 256—258·5°C. For $C_{20}H_{21}ClN_2S$ (356·9) calculated: 67·30% C, 5·93% H, 9·93% Cl, 7·85% N, 8·98% S; found: 67·42% C, 5·95% H, 10·21% Cl, 7·86% N, 9·14% S. This hydrochloride was treated with 20% NaOH and the base was extracted with ether. It crystallized from a mixture of cyclohexane and light petroleum, m.p. 87·5—88·5°C. ^{1}H NMR spectrum: 2·10 s, 6 H ($N(CH_3)_2$); 2·30 m, 4 H (NCH_2CH_2); 5·00 d, 1 H and 3·35 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 5·98 t, 1 H (C=CH, J = 6·5); 6·95 d, 1 H (H-8, J = 8·5); c. 7·20 m, 5 H (H_5-3,4, 8, 9, 10); 7·50 d, 1 H (H-1, J = 2·5; in the presence of [$^2H_{27}$] Eu(FOD)$_3$ $\Delta\delta$ = 0·15). For $C_{20}H_{20}N_2S$ (320·5) calculated: 74·96% C, 6·29% H, 8·74% N, 10·01% S; found: 75·32% C, 6·33% H, 8·84% N, 10·05% S.

Hydrobromide, m.p. 255—256°C (ethanol–ether). For $C_{20}H_{21}BrN_2S$ (401·4) calculated: 59·85% C, 5·27% H, 19·91% Br, 6·98% N, 7·99% S; found: 59·47% C, 5·28% H, 20·17% Br, 6·70% N, 8·07% S. Ref.[11], m.p. 213—215°C with decomposition.

Hydrogen oxalate, crystal form A, m.p. 210—213°C (ethanol–ether). For $C_{22}H_{22}N_2O_4S$ (410·5) calculated: 64·37% C, 5·40% H, 6·82% N, 7·81% S; found: 63·76% C, 5·56% H, 6·37% N, 7·82% S. Crystal form B, m.p. 229·5—230·5°C (aqueous ethanol). For $C_{22}H_{22}N_2O_4S$ (410·5) calculated: 64·37% C, 5·40% H, 6·82% N, 7·81% S; found: 64·22% C, 5·48% H, 6·64% N, 8·12% S.

B) A solution of 4·15 g *VIIIb* in 20 ml pyridine was treated with 1·3 ml $SOCl_2$ and the mixture was heated for 5 h under reflux. After cooling it was distributed between ether and dilute NH_4OH, the organic layer was dried and evaporated; 3·8 g (97%) homogeneous oily *IIb*. Its neutralization

with oxalic acid dihydrate in a mixture of acetone and ether gave 4·5 g form A of hydrogen oxalate, m.p. 208—212°C. Its crystallization from aqueous ethanol gave form B of hydrogen oxalate, m.p. 229·5—230·5°C. The released base melted at 82—86°C and its ^{1}H NMR spectrum was identical with that of the base described under *A*). The hydrochloride, prepared from this base, was crystallized from 95% ethanol and proved to be the hemihydrate, m.p. 250—255°C with decomposition. UV spectrum: 245 (4·23), 301 (4·21). IR spectrum: 760, 769, 824, 830, 860, 874, 890 (4 and 2 adjacent, and solitary Ar—H); 1 480, 1 600, 3 010, 3 030, 3 070 (Ar); 1 640 (C=C in conjugation), 2 220 (Ar—CN); 2 420, 2 513, 2 600 (NH^+); 3 400 (H_2O). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 2·40 m, 2 H (CH_2 in the middle of the propylidene chain); 2·75 s, 6 H ($N(CH_3)_2$); 3·25 bt, 2 H (CH_2N); 4·90 d, 1 H and 3·80 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·11 t, 1 H (C=CH, J = 7·0); 7·20 d, 1 H (H-4, J = 8·5); c. 7·45 m, 5 H (H_5-3, 7, 8, 9, 10); 7·88 d, 1 H (H-1, J = 2·0). For $C_{20}H_{21}ClN_2S + 0{\cdot}5\,H_2O$ (365·9) calculated: 65·65% C, 6·06% H, 9·69% Cl, 7·66% N, 8·76% S; found: 66·17% C, 5·90% H, 10·22% Cl, 7·42% N, 8·97% S.

(*E*)-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin-9-carbonitrile (*Xb*)

A mixture of 5·65 g *Xc*, 3·3 g CuCN, and 15 ml hexamethylphosphoric triamide was stirred and heated for 14 h in nitrogen atmosphere to 150°C (bath temperature). After cooling, the mixture was diluted with 200 ml 1 : 1 mixture of benzene and ether, and shaken with 100 ml dilute NH_4OH. After filtration the organic layer was washed with water, dried and evaporated. The residue (3·9 g, 81% of the oily base *Xb*) was dissolved in ether and neutralized with a solution of 1·7 g oxalic acid dihydrate in acetone; 4·95 g homogeneous *Xb* hydrogen oxalate crystallizing from a mixture of aqueous ethanol and ether as the monohydrate, m.p. 99·5—101·5°C. For $C_{22}H_{22}N_2O_4S + H_2O$ (428·5) calculated: 61·66% C, 5·64% H, 6·54% N, 7·48% S; found: 61·06% C, 5·27% H, 6·43% N, 7·38% S.

Treatment of this salt with dilute NH_4OH and extraction with ether gave the homogeneous base *Xb* crystallizing from cyclohexane and melting at 117·5—119°C. ^{1}H NMR spectrum: 2·12 s, 6 H ($N(CH_3)_2$); 2·20 m, 4 H (NCH_2CH_2); 4·98 d, 1 H and 3·38 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·02 t, 1 H (C=CH, J = 7·0); 6·90—7·20 m, 4 H (H_4-1, 2, 3, 4); 7·34 d, 1 H (H-7, J = 8·5); 7·40 d, 1 H (H-10, J = 2·0); 7·55 dd, 1 H (H-8, J = 8·5; 2·0). For $C_{20}H_{20}N_2S$ (320·5) calculated: 74·96% C, 6·29% H, 8·74% N, 10·01% S; found: 74·61% C, 6·26% H, 8·80% N, 10·26% S.

11-(1-Methyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin-2-carbonitrile (*XVb*)

A mixture of 3·55 g *XVc*, 1·8 g CuCN, and 10 ml hexamethylphosphoric triamide was stirred and heated for 14 h to 150°C. After cooling, the mixture was distributed between benzene and dilute NH_4OH, filtered, the benzene layer of the filtrate was separated, washed with water, dried, and evaporated. The residue was dissolved in ether and the insoluble polymers were filtered off. Evaporation gave 2·0 g residue which was dissolved in a mixture of benzene and light petroleum; there crystallized 0·3 g 11-(1-methyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin-2-carboxamide (*XVd*) in the form of 2 : 1 solvate with benzene, m.p. 233—238°C (benzene). Mass spectrum: 350 (M^+, $C_{21}H_{22}N_2OS$, 5), 317 (40), 96 (25), 70 (100), 58 (27), 57 (24), 44 (75).
UV spectrum: infl. 245 (4·11), 297 (4·12). IR spectrum: 749, 768, 770, 853 (4 and 2 adjacent, and solitary Ar—H); 1 543, 1 588, 1 610, 3 040 (Ar); 1 640 ($CONH_2$); 2 770 (N—CH_3); 3 190, 3 220, 3 390 (N—H). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): 2·18 bs, 3 H (NCH_3); 2·40 m, 8 H, (4 CH_2 of piperidine); 4·85 d, 1 H and 3·68 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·90—7·70 m: 7 H (7 ArH). For $C_{21}H_{22}N_2OS + 0{\cdot}5\,C_6H_6$ (389·5) calculated: 7·19% N, 8·23% S; found. 6·85% N, 8·16% S.

The mother liquor was chromatographed on a column of 200 g Al_2O_3. Elution with benzene removed a less polar component and elution with a mixture of benzene and chloroform gave 0·96 g (31%) *XVb* which crystallized from a mixture of benzene and light petroleum, m.p. 171 to 172°C. UV spectrum: 247 (4·14), 302 (4·18). IR spectrum: 729, 772, 810, 860 (4 and 2 adjacent, and solitary Ar-H); 1 481, 1 587, 3 010, 3 050, 3 075 (Ar); 2 225 (Ar—CN); 2 780 (N—CH_3). ^{1}H NMR spectrum: 2·21 s, 3 H (NCH_3); 2·00—2·80 m, 8 H (4 CH_2 of piperidine); 4·90 d, 1 H and 3·35 d, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·90—7·30 m, 7 H (7 ArH). For $C_{21}H_{20}N_2S$ (332·5) calculated: 75·87% C, 6·06% H, 8·43% N, 9·64% S; found: 75·91% C, 6·23% H, 8·17% N, 9·46% S.

Neutralization with oxalic acid dihydrate in acetone and ether gave the hydrogen oxalate hemihydrate, m.p. 169—171°C (acetone–ether). For $C_{23}H_{22}N_2O_4S + 0{\cdot}5\ H_2O$ (431·5) calculated: 64·02% C, 5·37% H, 6·49% N, 7·43% S; found: 64·10% C, 5·35% H, 6·47% N, 7·48% S.

(*E*)-11-(3-Methylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin-2-carbonitrile (*IIIb*)

A mixture of 9·65 g *IIIc*, 5·7 g 2-hydroxypyridine[20], 13 ml butyrolactone, and 50 ml xylene was refluxed for 4 h. The mixture was filtered and the filtrate was distributed between benzene and dilute NH_4OH. The benzene layer was dried and evaporated. The residue was chromatographed on a column of 250 g silica gel. The less polar components of the mixture were washed out with benzene and then with chloroform. A mixture of chloroform and ethanol eluted 10·0 g crude *Vc*. It was dissolved in 20 ml hexamethylphosphoric triamide, 4·5 g CuCN were added, and the mixture was stirred and heated in nitrogen atmosphere for 12 h to 150°C. After cooling it was distributed between benzene and dilute NH_4OH, the benzene layer was washed with water, dried and evaporated. The residue was chromatographed on 300 g Al_2O_3. The chloroform fraction afforded 3·85 g crude *Vb* which was subjected to hydrolysis without characterization. It was dissolved in 100 ml dioxane, 100 ml 10% H_2SO_4 were added, and the mixture was heated for 4 h to 90°C. Dioxane was evaporated, the aqueous solution was washed with benzene and made alkaline with NH_4OH. The released base was extracted with benzene, the extract was processed, and the residue was chromatographed on 100 g Al_2O_3. Benzene and then chloroform eluted 2·24 g (27%) oily *IIIb*. Its neutralization with oxalic acid dihydrate in ethanol afforded 2·15 g hydrogen oxalate hemihydrate, m.p. 202—204°C (ethanol). For $C_{21}H_{20}N_2O_4S + 0{\cdot}5\ H_2O$ (405·5) calculated: 62·21% C, 5·22% H, 6·91% N, 7·91% S; found: 62·54% C, 5·03% H, 6·45% N, 7·65% S. The base, released from this salt, was used for recording the spectra. IR spectrum (film): 754, 819, 876 (4 and 2 adjacent, and solitary Ar—H); 1 540, 1 587, 3 015, 3 053 (Ar); 1 637 (C=C in conjugation); 2 222 (Ar—CN); 2 790 (N—CH_3); 3 320 (N—H). ^{1}H NMR spectrum: 1·10 bs, 1 H (NH); 2·38 s, 3 H (NCH_3); 4·95 bd, 1 H and 3·35 bd, 1 H (ABq, $ArCH_2S$); 5·98 t, 1 H (C=CH); 6·80—7·50 m, 7 H (7 ArH); the presence of weak signals at 2·32 (s) and 5·71 (m) ppm indicated the presence of a small amount of the (*Z*)-isomer.

(±)-11-(3-Dimethylaminopropyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-2-carbonitrile (*XVIb*)

A mixture of 7·1 g *XVIc*, 4·5 g CuCN, and 20 ml hexamethylphosphoric triamide was stirred and heated (N_2 atmosphere) for 28 h to 150°C. After cooling it was diluted with benzene and the solution was washed with dilute NH_4OH. The mixture was filtered, the benzene layer of the filtrate was washed with water, dried and evaporated. The residue (3·7 g) was dissolved in ether and the undissolved substance (0·5 g) was filtered off. The filtrate was evaporated and the residue (3·2 g) was chromatographed on 150 g Al_2O_3. Elution with benzene removed 0·75 g of the less polar component and a mixture of benzene and chloroform eluted then 1·7 g of *XVIb*. Its neutralization with maleic acid in ethanol gave 1·85 g (22%) hydrogen maleate, m.p. 187—191°C (ethanol). For $C_{24}H_{26}N_2O_4S$ (438·6) calculated: 65·73% C, 5·98% H, 6·39% N, 7·31% S; found: 65·05% C, 5·98% H, 6·14% N, 7·41% S.

Decomposition of a sample of this salt with NH_4OH and extraction with ether gave the homogeneous base which crystallized on standing; m.p. 79–82°C (ether). IR spectrum (KBr): 725, 761, 832, 881 (4 and 2 adjacent, and solitary Ar—H); 1 489, 1 598, 3 020, 3 060 (Ar); 2 218 (Ar—CN); 2 780, 2 810 (N—CH_3). ^{1}H NMR spectrum: 1·50 m, 2 H (CH_2 in the middle of the propane chain); 2·18 s, 6 H ($N(CH_3)_2$); c. 2·30 m, 4 H (CH_2-1 and CH_2-3 of the propane chain); 4·42 t, 1 H (Ar_2CH, J = 8·0); 4·74 bd, 1 H and 3·85 bd, 1 H (ABq, $ArCH_2S$, J = 13·0); 6·90 to 7·30 m, 6 H (H_6-3, 4, 7, 8, 9, 10); 7·40 bs, 1 H (H-1). For $C_{20}H_{22}N_2S$ (322·5) calculated: 74·49% C, 6·88% H, 8·69% N, 9·94% S; found: 74·31% C, 6·80% H, 8·67% N, 9·49% S.

(*E*)-4-(3-Dimethylaminopropylidene)-4,10-dihydrothieno[2,3-*c*]-
-1-benzothiepin-6-carbonitrile (*XIXb*)

A mixture of 6·8 g *XIXc*, 4·5 g CuCN, and 20 ml hexamethylphosphoric triamide was stirred for 13 h at 150°C in the nitrogen atmosphere. After cooling it was distributed between benzene and diluted NH_4OH, the mixture was filtered, and the benzene layer of the filtrate was evaporated. The residue (6·4 g) was chromatographed on 100 g Al_2O_3. Benzene eluted 3·93 g (67%) *XIXb* which crystallized from methanol, m.p. 105·5–106·5°C. UV spectrum: 218 (4·53), 292 (3·80). IR spectrum: 830, 850, 880 (2 adjacent and solitary Ar—H); 1 500, 1 585, 3 040, 3 110 (Ar); 2 230 (Ar—CN); 2 755, 2 780 (N—CH_3); in CS_2: 710, 822, 904. ^{1}H NMR spectrum (Tesla BS 567 A, 100 MHz): 2·18 s, 6 H ($N(CH_3)_2$); c. 2·20 m, 4 H (NCH_2CH_2); 4·08 s, 2 H ($ArCH_2S$); 6·12 t, 1 H (C=CH, J = 6·0); 6·98 d, 1 H (H-3, J = 5·0); 7·10 d, 1 H (H-2, J = 5·0); 7·50 to 7·80 m, 3 H (remaining 3 ArH). For $C_{18}H_{18}N_2S_2$ (326·5) calculated: 66·22% C, 5·56% H, 8·58% N, 19·64% S; found: 66·72% C, 5·39% H, 8·57% N, 19·74% S.

Neutralization with oxalic acid dihydrate in ethanol afforded the hydrogen oxalate, m.p. 205–206·5°C (ethanol). For $C_{20}H_{20}N_2O_4S_2$ (416·5) calculated: 57·67% C, 4·84% H, 6·73% N, 15·40% S; found: 57·78% C, 5·02% H, 6·62% N, 15·50% S.

(*Z*)-4-(3-Dimethylaminopropylidene)-4,10-dihydrothieno[2,3-*c*]-
-1-benzothiepin-6-carbonitrile (*XXb*)

The reaction of 4·6 g *XXc* (containing 10% *XIXc*) with 3·0 g CuCN in 15 ml hexamethylphosphoric triamide was carried out similarly like in the preceding case. Chromatography of the crude product on 120 g Al_2O_3 gave 2·77 g (70%) oily *XXb* (containing about 10% *XIXb*). ^{1}H NMR spectrum: 2·25 s (and 2·22 s), 6 H ($N(CH_3)_2$); 2·30 m, 4 H (NCH_2CH_2); 4·20 s (and 4·03 s), 2 H ($ArCH_2S$); 5·91 t (and 6·00 t), 1 H (C=CH); 6·89 d (and 7·01 d), 1 H (H-3, J = 5·0); 7·11 d (and 7·13 d), 1 H (H-2, J = 5·0); 7·29 bs, 2 H (H-7 and H-8); 7·58 d, 1 H (H-5, J = 2·0).

Hydrogen oxalate, m.p. 200–203°C (aqueous ethanol–ether). For $C_{20}H_{20}N_2O_4S_2$ (416·4) calculated: 57·67% C, 4·84% H, 6·73% N, 15·40% S; found: 57·64% C, 4·78% H, 6·74% N, 15·29% S.

*The authors wish to thank their colleagues at the Research Institute for Pharmacy and Biochemistry for their contributions to the present study: Drs M. Ryska and I. Koruna (mass spectra), Dr J. Metyš, Mrs E. Šulcová, Mrs J. Ezrová, Miss A. Vykulilová, Mrs A. Kargerová, Mrs S. Schubertová (pharmacology and biochemical pharmacology), Mrs J. Komancová, Mrs V. Šmídová, and Mrs R. Svatošová (elemental analyses), and Mr B. Schneider, Mrs A. Hrádková, and Mrs Z. Janová (*UV *and* IR *spectra).*

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Translated by the author (M.P.).