POTENTIAL ANTIDEPRESSANTS: SATURATED SIDE CHAIN AMINES DERIVED FROM 6,11-DIHYDRODIBENZO[*b*,*e*]THIEPIN AND 4,9-DIHYDROTHIENO[2,3-*c*]-2-BENZOTHIEPIN

Zdeněk POLÍVKA[a], Vladimír VALENTA[a], Karel ŠINDELÁŘ[a], Jiří HOLUBEK[a], Miloš BUDĚŠÍNSKÝ[b], Miroslav RYSKA[a], Ivan KORUNA[a], Jitka KOHOUTOVÁ[b], Jan METYŠ[a], Jiřina METYŠOVÁ[a], Martin VALCHÁŘ[a] and Miroslav PROTIVA[a]

[a] *Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3*
[b] *Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6*

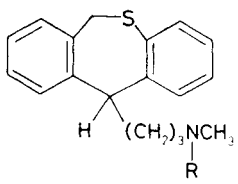
Received March 25th, 1988
Accepted April 17th, 1988

Dedicated to Prof. G. Snatzke on the occasion of his 60th birthday.

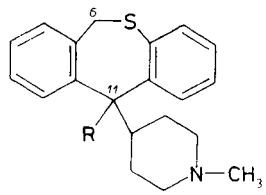
Reduction of *IV* with hydroiodic acid afforded almost quantitatively the spirocyclic amino sulfide *VII*, evidently via *V* and *VI*. The carbamate *II* was chlorinated with N-chlorosuccinimide, the product (*XII*) was reacted with phenylmagnesium bromide and then reduced with $LiAlH_4$ to give the 6-phenyl derivative *X* of the antidepressant agent hydrothiadene (*I*). Treatment of 11-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XIII*) with butyllithium followed by alkylation with 3-dimethylaminopropyl chloride resulted in 6-(3-dimethylaminopropyl) derivative *XIV*. Reaction of *XIV* with ethyl chloroformate and the following alkaline hydrolysis gave the 6-(3-methylaminopropyl) derivative *XV* (mixture of stereoisomers). Reduction of the corresponding olefinic amine and the tertiary alcohol with hydroiodic acid gave the saturated side chain amines derived from 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin *XVIII* and *XIX*. The dihydro derivative of dithiadene *XVIII* (VÚFB-17 031) proved very effective in a series of tests predictive of antidepressant activity.

The saturated side chain amines, derived from 6,11-dihydrodibenzo[*b*,*e*]thiepin (refs[1-5]), were found in pharmacological experiments[6,7] to possess the thymoleptic pharmacological profile and hydrothiadene (*I*) proved even in clinical trials[8,9] antidepressant activity. Tertiary amines of this type with the side chain in position 11 of the skeleton were prepared by three methods: (a) reduction of the corresponding tertiary alcohols, e.g. 11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol, with hydroiodic acid[1-3]; (b) similar reduction of the olefinic amines, e.g. N,N-dimethyl-3-(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propylamine[2], and (c) reaction of 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepins with 3-(tert.amino)propylmagnesium chlorides[2,10]. The present paper deals with attempts at preparing the 11-(1-methyl-4-piperidinyl) compound *III* by methods (a) and (c), with the synthesis of a derivative of hydrothiadene (*I*) substituted in position 6 with a phenyl group,

with compounds having the aminoalkyl side chain in position 6 of the skeleton, and finally with saturated side chain amines derived from 4,9-dihydrothieno[2,3-*c*]-2--benzothiepin.

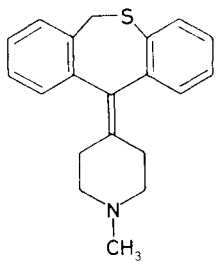


I, R = CH_3
II, R = $COOC_2H_5$

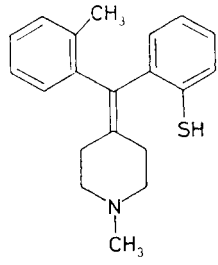


III, R = H
IV, R = OH

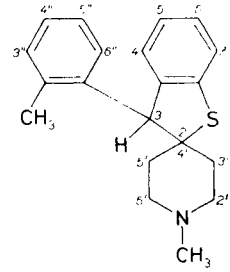
Compound *IV* (ref.[11]) was reduced with hydroiodic acid in boiling acetic acid in the presence of red phosphorus and the course of the reaction was checked by TLC. After 10 min boiling the starting *IV* was no more present in the mixture; the main component, however, was the product of dehydration, i.e. *V* (ref.[11]); dehydration of *IV* is thus the first step of the reaction sequence. The intermediate *V* was slowly reduced and after 5 h boiling almost disappeared. For its complete removal, the crude product was chromatographed on silica gel; the completely homogeneous and crystalline product of the expected composition $C_{20}H_{23}NS$ (analysis and mass spectrum) was obtained in the yield of almost 90% and was transformed to the hydrogen maleate and hydrochloride. The ^1H NMR spectrum (80 MHz), however, did not confirm the expected structure *III*: there were two signals of methyl groups (singlets at δ 2·27 and 2·47 corresponding to $ArCH_3$ and NCH_3) and the typical signal of the $ArCH_2S$ fragment was missing. The presence of an $ArCH_3$ group made clear that reduction of *V* proceeded by cleavage of the $ArCH_2SAr$ bridge under the formation of the thiol *VI*, which, in turn, could undergo an intramolecular cyclization (addition of the thiol group to the system $Ar_2C{=}C$) under the formation of the spirocyclic compound *VII*.



V



VI

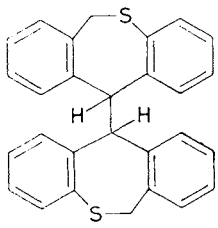


VII

The assigned structure *VII* was confirmed by means of the ^1H and ^{13}C NMR spectra (complete data see in Experimental). The ^{13}C NMR spectrum showed the presence of two disubstituted aromatic rings (8 —CH= and 4 >C=), of two methyl groups (C—CH_3 at δ 20·62, N—CH_3 at δ 53·78), of five carbon atoms of the piperidine ring (4 CH_2 and 1 —C—), and finally of the tertiary carbon connecting both aromatic nuclei (>CH— at δ 59·31). ^1H NMR spectrum (200 MHz) confirmed the presence of both methyl groups (singlets at δ 2·26 and 2·45), of eight hydrogen atoms of the piperidine residue (in the region of δ 1·5–2·81), of the isolated methine proton (a broadened singlet at δ 4·68), and of eight aromatic protons of two *o*-disubstituted benzene rings (in the range of δ 6·89–7·23). A detailed analysis of the spectrum enabled identification and structural assignment of all hydrogen atoms of the piperidine ring whose symmetrical equivalence is completely destroyed by the different orientation towards the aromatic ring, attached to C-3. The signals of the aromatic protons of both *o*-disubstituted benzene rings could be structurally assigned by means of the long-range couplings of the sp^2-methyl group and the bridge hydrogen H-3. The selective decoupling of protons of the methyl group effected the narrowing of the lines of multiplets of four out of eight aromatic protons, which hence have to belong to the hydrogens of the ring, substituted with methyl. This line-narrowing effect, in agreement with the expectation, decreases in the series *o*-, *m*-, and *p*-hydrogen (towards methyl) and the observed values 0·8, 0·25, and 0·1 Hz, together with the characteristic splitting of the signals, enabled thus the unequivocal structural assignment of the hydrogens H-3″ to H-6″. On the other hand, the selective decoupling of the bridge hydrogen H-3 did not influence the signals of any of the mentioned hydrogens H-3″ to H-6″ (the mobility of the methyl-substituted ring does not form suitable conditions for their long-range couplings) but eliminated the fine splitting of the signals (0·5–0·9 Hz) of three out of four remaining aromatic protons. This enabled the structural assignment of the remaining hydrogens H-4 to H-7, out of which only the most distant H-6 does not present any long-range couplings with the bridge hydrogen H-3. The mass spectrum (HR) is also in agreement by its fragmentation pattern with the suggested structure *VII*. The only surprising and not completely explained fact is the low abundancy of the fragment with *m/z* 91 (C_7H_7), i.e. the tropylium cation. Anyway we have to conclude that the formation of *VII* from *IV* represents an unprecedented transformation of the dibenzo[*b*,*e*]thiepin system to the new spiro[benzo[*b*]thiophene-2(3*H*),4′-piperidine] system which was determined on the one hand by the lability of the CH_2—S bridge, and by the specific constellation in structures of the precursors *V* and *VI* on the other. It is worth mentioning that we are describing in this paper (last paragraph of Experimental) a very similar case in which the reduction proceeded normally, i.e. with retention of the CH_2—S bridge.

An attempt to prepare *III* by reaction of 11-chloro-6,11-dihydrodibenzo[*b*,*e*]-

thiepin[2] with 1-methyl-4-piperidylmagnesium chloride[11] in a boiling mixture of tetrahydrofuran and benzene was unsuccessful. The main product was a neutral substance $C_{28}H_{22}S_2$ (analysis and mass spectrum), insoluble in common solvents and having a high melting point, to which the structure *VIII* is assigned (cf.refs[12,13]). The basic product was chromatographed but none of the fractions did afford crystalline salts.

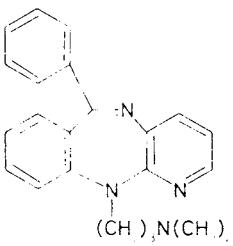


VIII

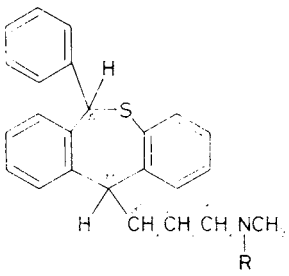
The antidepressant properties of tampramine (AHR-9377) (*IX*) (refs[14–18]), a tricyclic compound with an additional phenyl substituent (the increaed lipophility is evidently balanced by the presence of three nitrogen atoms in the skeleton) induced us to pay attention to a similar compound in the series of antidepressant 6,11-dihydrodibenzo[*b*,*e*]thiepins; our choice was the 6-phenyl derivative of hydrothiadene, i.e. compound *X*. The intention was to introduce the additional phenyl by reaction of a suitable 6-chlorinated intermediate with phenylmagnesium bromide. N-Chlorosuccinimide is a recommended agent for chlorination of benzylic sulfides[19,20] and was, therefore, used. Its reaction with *I* in benzene led, however, to a mixture which was unsuitable to a further processing (the α-chlorosulfides are unstable and it is necessary to use them "in situ", i.e. without isolation and characterization). The second experiment was carried out with the carbamate *II* (ref.[2]); after the reaction with N-chlorosuccinimide in benzene, the separated succinimide was filtered off, and the filtrate (containing *XII*) was added to a solution of phenylmagnesium bromide in ether. The mixture formed was separated by chromatography and the obtained homogeneous fraction was characterized by the ^{1}H NMR spectrum as the desired *XI*. It was reduced with lithium aluminium hydride in boiling ether and the crude oily base was chromatographed. The homogeneous oily base was transformed to the hydrogen oxalate, purified and analyzed in this form. Its mass spectrum confirmed the composition of the desired base *X*. The ^{1}H NMR spectrum of the released base indicated homogeneity: signals of H-6 and of $N(CH_3)_2$ appear as sharp singlets. After the purification procedures the product is probably the predominating racemate of the two possible.

For enabling the selective introduction of a saturated aminoalkyl into position 6 of the 6,11-dihydrodibenzo[*b*,*e*]thiepin skeleton, the Japanese authors[21,22] blocked

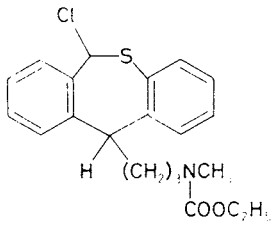
position 11 either with methylene of with methyl and hydroxyl and prepared the corresponding 6-(3-dimethylaminopropyl) derivatives. We tried to block position 11 only with one methyl group and prepared compound *XIII* by reduction of the known 11-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[21,23] with hydroiodic acid



IX



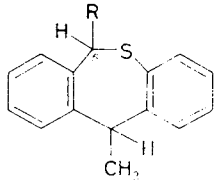
X, R = CH_3
XI, R = $COOCH_2CH_3$



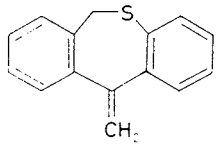
XII

in boiling acetic acid. The use of sodium hydride in benzene did not lead in this case to the formation of the anion at C-6 and/or C-11 because after the following treatment with 3-dimethylaminopropyl chloride and hydrolysis the starting *XIII* was recovered almost quantitatively. According to our experience[24], sodium hydride (in benzene) was able to form the anion at C-11 in the case of 6,11-dihydrodibenzo-[*b*,*e*]thiepin 5,5-dioxide and the anion at C-6 in the case of dibenzo[*b*,*e*]thiepin-11-(6*H*)-one 5,5-dioxide. For *XIII* it was necessary to use butyllithium in a mixture of ether and hexane; the following treatment with 3-dimethylaminopropyl chloride led to the formation of a basic product which was isolated as hydrochloride, corresponding analytically to the expected $C_{20}H_{25}NS$. The released base did not crystallize which indicates that we are dealing here with a mixture of stereoisomers. Its ^{1}H NMR spectrum showed unequivocally that the formation of the anion and the following aminoalkylation took place at C-6 which means structure *XIV* for our product. This contains two centers of chirality which explains the inhomogeneity. Thin-layer chromatography on silica gel showed two main components with R_F 0·6 and 0·7. Column chromatography on silica gel separated the strongly predominating fraction with R_F 0·6, but even then the base did not crystallize. It was transformed to the hydrogen maleate which was used for pharmacological testing. Because of the potential interest of secondary amines in the series of tricyclic antidepressants (cf. refs[2,4,5,7]), partial demethylation of *XIV* to *XV* was carried out. The crude base *XIV* was treated with ethyl chloroformate in boiling benzene and the oily *XVI* formed was hydrolyzed without characterization with a concentrated solution of potassium hydroxide in ethanol. The crude product afforded a crystalline hydrogen maleate from which the oily base was released. Its ^{1}H NMR spectrum showed clearly the

inhomogeneity by several splitted signals; it was possible to determine that the mixture consists in 35% of *XV-A* with equatorial H-6 and 65% *XV-B* with axial H-6. This mixture in the form of hydrogen maleate was used for phamacological testing. 11-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[21,23] was dehydrated to *XVII* by heating with sulfuric acid in methanol. The product obtained was found identical with the product of Japanese authors[23] who carried out the dehydration wit hydrogen chloride in dichloromethane.



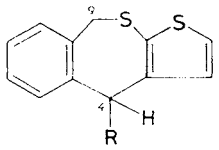
XIII, R = H
XIV, R = $(CH_2)_4N(CH_3)_2$
XV, R = $(CH_2)_3NHCH_3$
XVI, R = $(CH_2)_3NCH_3$
$COOC_2H_5$



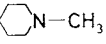
XVII

In the 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin series the saturated side chain amines have not been known yet. The corresponding unsaturated amines, viz 4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin[1,25] and 4-(1-methyl-4-piperidylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin[26,27] showed very useful pharmacodynamic properties: the first is being used as a very active antihistamine agent "dithiadene" (refs[28,29]) and the second is in the final stage of promising clinical trials as the anti-migraine agent "pipethiadene" (refs[30,31]). After unsuccessful attempts at preparing *XVIII* either from 4-(3-dimethylaminopropyl)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol[1] by treatment with methanesulfonyl chloride in pyridine or N,N-di(2-propyl)ethylamine and by redudtion of the supposed methanesulfonic ester with lithium aluminium hydride, or from 4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin[1] by catalytic hydrogenation on palladium, the reduction of 4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]--2-benzothiepin[1,25] with hydroiodic acid in boiling acetic acid led to the desired result. After chromatography of the crude product the homogeneous oily base *XVIII* was obtained in the yield of 50%, its identity was confirmed by spectra, and the base was transformed to the hydrochloride, necessary for pharmacological testing. Compound *XIX* was obtained similarly by reduction of 4-(1-methyl-4-piperidyl)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol[26,27] with hydroiodic acid. Chromatography of the crude product afforded 63% of the homogeneous oily base *XIX* which was transformed to the hydrochloride. Recording of its spectra confirmed the structure. Hydrogen maleate was prepared for pharmacological testing.

Compounds *VII*, *X*, *XIV*, *XV*, *XVIII*, and *XIX* were pharmacologically tested in the form of salts, described in Experimental, Unless stated otherwise, they were administered in the in vivo tests orally and the doses given (in mg/kg) were calculated per bases. Acute toxicity in female mice, LD_{50} in mg/kg: *VII*, 202 (toxic symptoms:



XVIII, R = $(CH_2)_3N(CH_3)_2$

XIX, R = 

central depression and then convulsions); *X*, 451 (convulsions); *XIV*, >500 (no central depressant effect); *XV*, 47·4 on intravenous administration (toxic symptoms: ataxia and paresis); *XVIII*, 28·2 on i.v. administration (toxic symptoms: convuliions and dyspnea), *XIX*, 136 (convulsions). Incoordinating activity in the rotarod test in mice, ED_{50} in mg/kg: *VII*, 9·6 (maximum effect after 45 min), *X*, 83 (maximum effect after 90 min); *XIV*, 35; *XV*, ataxia appears after the i.v. dose of 10 mg/kg and is common after 30 mg/kg i.v., the state was repaired in 30 min after the administration); *XVIII*, 60 (maximum effect after 15 min, repair in 2 h); *XIX*, 25–50 (mild excitation, maximum effect in 30–45 min, repair in 2 h). Potentiation of the thiopental sleeping time in mice: *VII* in the dose of 2 mg/kg prolongs the sleeping time to 200% of the control value. Influence on the spontaneous locomotor activity of mice evaluated by the photo-cell method of Dews: *X*, doses of 5 and 20 mg/kg do not influence the spontaneous locomotor activity; *XVIII*, the dose of 10 mg/kg increases mildly the activity; *XIX*, mild inhibition of the activity after the dose of 10 mg/kg. Inhibition of the reserpine-induced ulcer formation in rats: *VII*, mild effect at 50 mg/kg; *X*, ineffective in doses of 20 and 50 mg/kg; *XIV*, significant effect at 100 mg/kg; *XV*, significant effect at 50 mg/kg; *XVIII*, significant inhibition starting with the dose of 10 mg/kg; *XIX*, inactive at 50 mg/kg. Inhibition of the reserpine-induced hypothermia in mice: *VII* and *XIV*, significant effects at 10 mg/kg; *XVIII*, ED_{50} = = 17·5 mg/kg. Inhibition of the reserpine-induced ptosis in mice: *XIV*, significant inhibition at 50 mg/kg; *XVIII*, significant inhibition starting with 10 mg/kg: *XIX*, inactive at 30 mg/kg. Antagonism against perphenazine-induced catalepsy in rats (anticataleptic effect): *VII*, *X*, *XV*, and *XIX*, inactive at 50 mg/kg; *XVIII*, intensive anticataleptic action at 40 mg/kg, mild action at 20 mg/kg. Potentiation of the toxicity of yohimbine in mice, ED_{50} in mg/kg: *X*, 148; *XVIII*, 10·8. Inhibition of binding of 4 nmol l^{-1} [^{3}H]imipramine and 4 nmol l^{-1} [^{3}H]desipramine in the rat hypothalamus in vitro, IC_{50} in nmol l^{-1}: *X*, 534, 1 073; *XVIII*, 169·4, 512. The antihistamine activity of the compounds is very low: *VII* in doses of 10 mg/kg

protects 25% of the guinea pigs in the histamine detoxication as well as histamine aerosol test; *X*, *XV* and *XIX* in the same doses are inactive in both tests. The compounds lack the peripheral antiserotonin action (test of oedema of the rat paws): *VII*, *XV* and *XVIII* are inactive in doses of 10 mg/kg.

In conclusion, the compounds prepared show (with the exception of *XIX*) a more or less pronounced thymoleptic character of actions. The most interesting appears the dihydro derivative of dithiadene VÚFB-17 031 (*XVIII*) which is very active in the antireserpine tests, has intensive anticataleptic action, potentiates effectively the toxicity of yohimbine, and inhibits the binding of [^{3}H]imipramine and [^{3}H]desipramine to their binding sites in the brain; it is well comparable with imipramine.

The compounds were screened for antimicrobial activity in vitro (microorganisms and minimum inhibitory concentrations in μg/ml are given, unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *VII* 50, *X* 128, *XV* 50, *XIX* 32; *Streptococcus faecalis*, *VII* 50, *X* 16, *XV* 100, *XIX* 32; *Staphylococcus pyogenes aureus*, *VII* 25, *X* 128, *XIV* 100, *XV* 50, *XIX* 32; *Pseudomonas aeruginosa*, *XIX* 64; *Escherichia coli*, *VII* 50, *XIV* 50, *XV* 50, *XIX* 64; *Proteus vulgaris*, *VII* 100, *X* 128, *XIV* 100, *XV* 100, *XIX* 64; *Trichophyton mentagrophytes*, *VII* 50, *X* 50, *XIV* 50, *XIX* 50.

EXPERIMENTAL

The melting points of analytical samples were determined mostly in the Kofler block (are not corrected), partly in the 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 a suitably elevated temperature. UV spectra (in methanol, λ_{max} (log ε)) were recorded with a Unicam SP 8 000 spectrophotometer, IR spectra (in Nujol, ν in cm^{-1}) partly with the Unicam SP 200G and mostly with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in $CDCl_3$ unless stated otherwise, δ, J in Hz) mostly with the CW-NMR spectrometer Tesla BS 487C (80 MHz) and partly with the FT-NMR spectrometer Tesla BS 567A (^{1}H at 100 MHz; ^{13}C at 25·15 MHz) or the FT-NMR spectrometer Varian XL-200 (200 MHz), and the mass spectra (m/z and %) mostly with Varian MAT 44S (GC-MS) spectrometer and in one case with a ZAB-EQ (VG Analytical) (HR) spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$, Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotating evaporator.

1′-Methyl-3-(2-tolyl)-spiro[benzo[*b*]thiophene-2(3*H*),4′-piperidine] (*VII*)

A mixture of 30 ml acetic acid, 28 ml 57% HI, 3·5 g red P, and 8·1 g *IV* (ref.[11]) was stirred and refluxed under nitrogen for 5 h. After cooling the mixture was filtered, the solid was washed with acetic acid, and the filtrate was evaporated in vacuo. The residue was diluted with 100 ml water, made alkaline with 40% NaOH, and the base was extracted with dichloromethane. Processing of the extract gave 7·5 g residue which was chromatographed on 70 g silica gel (Merck 40). Elution with chloroform gave 6·9 g (89%) of homogeneous *VII* which crystallized; m.p. 95–98°C (cyclohexane–benzene). Mass spectrum (HR): 309 (M^+, $C_{20}H_{23}NS$, 64), 294 ($C_{19}H_{20}NS$, 21), 238 ($C_{16}H_{14}S$, 31), 217 ($C_{13}H_{15}NS$, 20), 211 ($C_{14}H_{11}S$, 11), 202 ($C_{12}H_{12}NS$, 15), 197 ($C_{13}H_9S$, 16), 178 ($C_{14}H_{10}$, 18), 165 ($C_{13}H_9$, 18), 160 ($C_{10}H_8S$, 18), 147 (C_9H_7S, 18), 109 ($C_7H_{11}N$, 27), 96

($C_6H_{10}N$, 100), 91 (C_7H_7, 12), 70 (C_4H_8N, 67), 57 (C_3H_7N, 67), 44 (C_2H_6N, 65). UV spectrum: 251 (3·84), infl. 263 (3·72), 286·5 (3·20), infl. 297 (3·11). IR spectrum: 745, 759 (4 adjacent Ar—H), 1 483, 1 572, 1 585, 1 600, 3 010, 3 060, 3 070 (Ar); 2 735, 2 760, 2 795 (N—CH_3, N—CH_2). ^{1}H NMR spectrum (200 MHz): 1·50 dq, 1 H (H-5′ eq, J(5′ eq, 5′ ax) = 13·6; J(5′ eq, 6′ eq) = = 2·8; J(5′ eq, 6′ ax) = 3·2; J(5′ eq, 3′ eq) = 2·8; 1·64 ddd, 1 H (H-5′ ax, J(5′ ax, 6′ ax) = = 11·6; J(5′ ax, 6′ eq) = 4·0); 1·99 ddd, 1 H (H-3′ ax, J(3′ ax, 3′ eq) = 13·3; J(3′ ax, 2′ ax) = = 11·8; J(3′ ax, 2′ eq) = 4·0); 2·11 dt, 1 H (H-6′ ax, J(6′ ax, 6′ eq) = 11·8); 2·17 dq, 1 H (H-3′ eq, J(3′ eq, 2′ ax) = 2·8; J(3′ eq, 2′ eq) = 2·7); 2·26 s, 3 H (C—CH_3); 2·38 dt, 1 H (H-2′ ax, J(2′ ax, 2′ eq) 11·8); 2·45 s, 3 H (N—CH_3); 2·68 dm, 1 H (H-6′ eq, J(6′ eq, 2′ eq) = 1·8); 2·81 dm, 1 H (H-2′ eq); 4·68 bs, 1 H (H-3, J(3, 6″) = 0·9; J(3, 4) < 0·5); 6·89 m, 1 H (H-7, J(7, 6) = = 7·5; J(7, 5) = 1·7; J(7, 4) = 0·7; J(7, 3) = 0·9); 6·96 ddd, 1 H (H-6, J(6, 5) = 6·8; J(6, 4) = = 1·4); 7·02 ddd, 1 H (H-4″, J(4″, 5″) = 8·0; J(4″, 6″) = 2·1; J(4″, 3″) = 6·6); 7·07 ddd, 1 H (H-5″, J(5″, 6″) = 6·5; J(5″, 3″) = 2·8); 7·13 m, 1 H (H-5, J(5, 4) = 7·7; J(5, 3) = 0·7); 7·14 bdd, 1 H (H-6″); 7·18 bdd, 1 H (H-3″); 7·23 m, 1 H (H-4). ^{13}C NMR spectrum: 143·94 s, 140·35 s, 136·99 s, and 136·32 s (4 aromatic =C<); 130·57 d, 130·12 d, 127·65 d, 126·98 d, 126·31 d, 125·94 d, 124·59 d, and 122·43 d (8 aromatic =CH—); 65·06 s (spirane C-2(4′)); 59·31 d (C-3); 53·78 t (C-2′ and C-6′); 46·09 q (N—CH_3); 39·59 t and 33·91 t (C-3′ and C-5′); 20·62 q (2″—CH_3). For $C_{20}H_{23}NS$ (309·5) calculated: 77·62% C, 7·49% H, 4·53% N, 10·36% S; found: 77·63% C, 7·73% H, 4·36% N, 10·28% S.

Hydrogen maleate, m.p. 206—208°C (ethanol–ether). Mass spectrum: 309 (M^+, $C_{20}H_{23}NS$, 6), 250 (5·5), 238, 217 (5·4), 160 (6), 96 (100), 70 (47), 57 (55). For $C_{24}H_{27}NO_4S$ (425·6) calculated: 67·74% C, 6·40% H, 3·29% N, 7·53% S; found: 67·43% C, 6·60% H, 3·22% N, 7·77% S.

Hydrochloride, m.p. 253—255°C (ethanol–ether). For $C_{20}H_{24}ClNS$ (345·9) calculated: 69·44% C, 6·99% H, 10·25% Cl, 4·05% N, 9·27% S; found: 69·54% C, 7·10% H, 10·23% Cl, 4·36% N, 9·30% S.

Bis(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl) (*VIII*)

Grignard reagent was prepared from 0·76 g Mg and 4·26 g 4-chloro-1-methylpiperidine[11] in 20 ml tetrahydrofuran (reaction was started with a grain of *I* and 0·6 g 1,2-dibromoethane) and was treated under stirring with a solution of 5·92 g 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[2] in 24 ml benzene, added dropwise over 30 min. The mixture was stirred and refluxed for 6·5 h and after cooling decomposed at 0—5°C with 100 ml 10% NH_4Cl, stirred for 3 h, and extracted with benzene. The undissolved solid was filtered, washed with benzene, and dried; 2·9 g (57%) of *VIII*, m.p. 295—304°C. A sample of 0·40 g was crystallized from 20 ml acetophenone; m.p. 295–297°C with decomposition. Mass spectrum: 422 (M^+, $C_{28}H_{22}S_2$, 1·5), 211 (100), 178. For $C_{28}H_{22}S_2$ (422·6) calculated: 79·57% C, 5·25% H, 15·18% S; found: 79·23% C, 5·26% H, 14·88% S.

From the benzene extract the basic components were isolated but their processing by chromatography on 120 g neutral Al_2O_3 (activity II) and neutralization with various acids did not lead to any characterized product.

N,N-Dimethyl-3-(6-phenyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl)propylamine (*X*)

A stirred solution of 14·1 g *II* (ref.[2]) in 150 ml benzene was treated with 5·3 g N-chlorosuccinimide and the mixture was stirred for 1 h (temperature rose spontaneously from 25 to 38°C). The precipitated succinimide was filtered off and the solution of *XII* was added to a stirred solution of phenylmagnesium bromide, prepared from 2·5 g Mg and 15·7 g bromobenzene in 100 ml ether. The mixture was stirred for 3 h at room temperature, allowed to stand overnight, de-

composed with 20% NH_4Cl, the organic layer was washed with dilute hydrochloric acid, dried with K_2CO_3, and evaporated. The residue was chromatographed on a column of 200 g silica gel. Benzene eluted first 1·73 g of biphenyl, m.p. 67°C (ethanol) which was followed by 0·4 g mixture, and then by 9·5 g (55%) homogeneous *XI* which was characterized by the ^1H NMR spectrum (100 MHz): 1·21 t, 3 H (CH_3 in ethyl); c. 1·20 bm, 2 H (CH_2 in position 3′ of propyl); 2·20 bm, 2 H (CH_2 in position 2′ of propyl); 2·75 s, 3 H (NCH_3); 3·18 bt, 2 H (CH_2N); 4·10 q, 2 H ($COOCH_2$, $J = 7·0$); 4·40 bt, 1 H (H-11); 5·64 s, 1 H (H-6); 7·00–7·50 m, 13 H (13 ArH).

A solution of 9·5 g *XI* in 60 ml ether was added dropwise to a stirred solution of 6·0 g $LiAlH_4$ in 100 ml ether and the mixture was refluxed for 6 h under nitrogen. After cooling it was decomposed by 30 ml 10% NaOH, the mixture was stirred for 30 min, the solid was filtered off and washed with ether, the filtrate was dried and evaporated. The residue (6·66 g) was chromatographed on a column of 100 g neutral Al_2O_3 (activity II). Benzene eluted 4·63 g (56%) of almost homogeneous *X* which was neutralized with oxalic acid in a mixture of acetone and ether to give 5·1 g of hydrogen oxalate, m.p. 159–163°C (acetone–ethanol–ether). Mass spectrum: 373 (M^+, $C_{25}H_{27}NS$, 1), 340 (2), 295 (0·5), 254 (3), 178 (1), 165 (1), 86 (10), 58 (100), 44 (10). For $C_{27}H_{29}NO_4S$ (463·6) calculated: 69·95% C, 6·31% H, 3·02% N, 6·92% S; found: 69·38% C, 6·40% H, 2·90% N, 7·05% S.

A sample of the oxalate was decomposed with NH_4OH and the purified base was isolated by extraction with ether and used for recording the ^1H NMR spectrum (100 MHz): 1·25 m, 2 H (CH_2 in position 2′ of propyl); 2·12 s, 6 H ($N(CH_3)_2$); c. 2·20 m, 4 H (2 CH_2 in positions 1′ and 3′ of propyl); 4·40 bt, 1 H (H-11); 5·63 s, 1 H (H-6); c. 7·20 m, 13 H (13 ArH).

Hydrogen oxalate monohydrate, m.p. 118–122°C (aqueous acetone). For $C_{27}H_{29}NO_4S + H_2O$ (481·6) calculated: 67·33% C, 6·49% H, 2·91% N, 6·66% S; found: 67·73% C, 6·38% H, 3·41% N, 6·38% S.

11-Methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XIII*)

A mixture of 25 ml 55% HI and 0·4 g $NaH_2PO_2.H_2O$ was stirred for 15 min at 80°C, diluted with 25 ml acetic acid, treated with 3·1 g red P and 7·25 g 11-methyl-6,11-dihydrodibenzo[*b*,*e*]-thiepin-11-ol[21,23]. The mixture was refluxed under stirring for 3 h under nitrogen, cooled, diluted at 50°C with 50 ml benzene, filtered with charcoal, and evaporated in vacuo. The residue was extracted with benzene, the extract was washed with 5% $NaHSO_3$ and water, dried, and evaporated. Crystallization of the residue from 80 ml ethanol gave 6·3 g (93%) of *XIII*, m.p. 66–67·5°C (ethanol). ^1H NMR spectrum: 1·67 d, 3 H (CH_3, $J = 7·0$); 3·70 d, 1 H and 4·69 d, 1 H (2 H-6, $J = 13·5$); 4·60 q, 1 H (H-11); 6·70–7·30 m, 8 H (ArH). For $C_{15}H_{14}S$ (226·3) calculated: 79·59% C, 6·23% H, 14·17% S; found: 79·56% C, 6·21% H, 14·01% S.

N,N-Dimethyl-3-(11-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-6-yl)propylamine (*XIV*)

A solution of 3·4 g *XIII* in 35 ml ether was stirred and treated over 45 min with 8·5 g 15% 1-butyllithium in hexane, added dropwise at 14–18°C. The red mixture was stirred for 1·5 h at room temperature, then slowly treated with 7·3 g 3-dimethylaminopropyl chloride, stirred for 3·5 h, and allowed to stand overnight. After dilution with 50 ml ether, the stirred and cooled mixture was decomposed by a slow addition of 15 ml water, the organic layer was washed with water, and the bases were extracted into 75 ml 1M-HCl (3 × 25 ml). The aqueous layer deposited by standing for 1 h 3·6 g (100% per conversion) of *XIV* hydrochloride monohydrate, m.p. 116 to 120°C (2-propanol). For $C_{20}H_{28}ClNOS$ (366·0) calculated: 9·69% Cl, 3·82% N, 8·76% S; found: 9·61% Cl, 3·69% N, 8·89% S. Evaporation of the organic layer after the extraction of the basic components recovered 1·2 g starting *XIII*, m.p. 63°C.

The hydrochloride of crude *XIV* (2·6 g) was suspended in 20 ml water, the suspension was treated with 1·5 ml 2·5M-NaOH, and the bases were extracted with ether. Evaporation of the extract gave 1·9 g of inhomogeneous base *XIV* (according to TLC mixture of the major component with R_F 0·6 and minor component with R_F 0·7) which was chromatographed on a column of 100 g silica gel. Elution with a mixture of 97% chloroform and 3% methanol afforded 1·7 g of almost homogeneous oily base *XIV* (R_F 0·6) which was used for recording the ^{1}H NMR spectrum: 1·50—2·30 m, 6 H (3 CH_2 of the propyl chain); 1·79 d, 3 H (CH_3 in position 11, J = 7·0); 2·18 s, 6 H ($N(CH_3)_2$); 4·35 t, 1 H (H-6, J = 7·0); 4·85 q, 1 H (H-11); 6·90—7·40 m, 8 H (8 ArH).

Hydrogen maleate, m.p. 115—116·5°C (ethanol–ether). For $C_{24}H_{29}NO_4S$ (427·6) calculated: 67·42% C, 6·83% H, 3·27% N, 7·50% S; found: 67·74% C, 6·91% H, 3·22% N, 7·64% S.

N-Methyl-3-(11-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-6-yl)propylamine (*XV*)

A stirred solution of 1·9 g ethyl chloroformate in 6 ml benzene was treated over 30 min with a solution of 3·1 g *XIV* in 10 ml benzene and the mixture was refluxed for 2·5 h. After standing overnight the mixture was diluted with 50 ml benzene, the solution was washed with 25 ml 1M-HCl and water, dried, and evaporated. The residue (3·5 g of oily *XVI*) was diluted with 10 ml ethanol, 8·0 g KOH were added and the mixturé was stirred and refluxed for 2 h (bath temperature 115°C). After standing overnight it was diluted with 30 ml water and extracted with benzene. Processing of the extract gave 2·7 g (91%) of oily *XV* which was neutralized with 1·2 g maleic acid in 25 ml ethanol. Addition of 30 ml ether gave 3·1 g of hydrogen maleate, m.p. 160—162°C (ethanol–ether). For $C_{23}H_{27}NO_4S$ (413·5) calculated: 66·80% C, 6·58% H, 3·39% N, 7·76% S; found: 66·43% C, 6·51% H, 3·28% N, 7·50% S.

A sample of the purified hydrogen maleate was decomposed with 1M-NaOH and the base *XV* was isolated by extraction with ether; oil which was shown by ^{1}H NMR spectrum to be a mixture of 35% *XV—A* with equatorial H-6 and 65% *XV—B* with axial H-6: 1·74 d and 1·75 d, Σ 3 H (CH_3 in position 11); 2·31 s and 2·41 s, Σ 3 H (NCH_3); 4·81 bq, 1 H (H-11); 4·30 bt and 5·14 bt, Σ 1 H (H-6); 6·80—7·50 m, 8 H (8 ArH).

11-Methylene-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XVII*)

A solution of 7·2 g 11-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[21,23] in 80 ml methanol was treated with 4 ml H_2SO_4, the mixture was refluxed for 2 h, after cooling diluted with 100 ml benzene and 100 ml water, and neutralized with 20% NaOH. The organic layer was dried and evaporated. The residue crystallized from a mixture of cyclohexane and light petroleum; 5·8 g (86%), m.p. 54—56°C (light petroleum). UV spectrum: 222 (4·31), infl. 265 (3·81), 310 (3·34). IR spectrum: 713, 734, 780 (4 adjacent Ar—H); 920, 1 615 ($Ar_2C{=}CH_2$); 1 489, 1 590, 3 028, 3 072 (Ar). ^{1}H NMR spectrum: 4·15 s, 2 H (2 H-6); 5·21 d and 5·59 d, 1 + 1 H ($C{=}CH_2$, J = 1·8); 6·90—7·50 m, 8 H (8 ArH). Ref.[23], m.p. 54—54·5°C.

N,N-Dimethyl-3-(4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-yl)propylamine (*XVIII*)

A mixture of 120 ml acetic acid, 75 ml 55% HI, 13·9 g red P, and 33·8 g N,N-dimethyl-3-(4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ylidene)propylamine hydrochloride[1,25] was stirred and refluxed under nitrogen for 3 h. The cooled mixture was filtered, diluted with 400 ml water, under cooling made alkaline with 25% NaOH, and extracted with dichloromethane. Processing of the extract gave the inhomogeneous residue which was chromatographed on a column of 120 g silica gel (Merck 60). Elution with chloroform gave 14·9 g (49%) of homogeneous oily base *XVIII*. Neutralization with HCl in a mixture of ethanol and ether gave the hydrochloride, m.p.

172—173°C (ethanol–ether). Mass spectrum: 303 (M^+, $C_{17}H_{21}NS_2$, 0·5), 270 (2), 217 (3), 184 (8), 58 (100), 42 (18). IR spectrum: 760 (4 adjacent Ar—H); 1 595, 3 070, 3 100 (Ar); 2 450, 2 565 (NH^+). For $C_{17}H_{22}ClNS_2$ (340·0) calculated: 60·06% C, 6·52% H, 10·43% Cl, 4·12% N, 18·86% S; found: 59·81% C, 6·43% H, 10·48% Cl, 4·50% N, 18·30% S.

The released base was used for recording the ^{1}H NMR spectrum: 1·00—2·50 m, 7 H (Ar_2CH. .$CH_2CH_2CH_2N$); 2·18 s, 6 H ($N(CH_3)_2$); 4·25 s, 2 H (2 H-9); 7·15 m, 6 H (6 ArH).

4-(1-Methyl-4-piperidyl)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*XIX*)

A mixture of 45 ml acetic acid, 45 ml 57% HI, 5·6 g red P, and 13·3 g 4-(1-methyl-4-piperidyl)--4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol[26,27] was stirred and refluxed for 3·5 h. Similar processing like in the preceding case gave 13·5 g of inhomogeneous base which was chromatographed on 80 g silica gel (Merck 40). Elution with chloroform removed first 0·9 g mixture which was followed by 8·0 g (63%) of homogeneous oily base *XIX*. Treatment withHCl in a mixture of ethanol and ether gave the hydrochloride, m.p. 287—290°C (ethanol).Mass spectrum: 315 (M^+, $C_{18}H_{21}NS_2$, 6), 217 (35), 184 (17), 98 (100), 55 (20), 45 (25). UV spectrum: 272 (3·54), 303 (3·29). IR spectrum: 742 (4 adjacent Ar—H); 790 (2 adjacent thiophene Ar—H); 1 582, 3 020, 3 060 (Ar); 2 380, 2 450, 2 610 (NH^+). ^{1}H NMR spectrum ($(CD_3)_2SO$: 1·20—3·50 m, 10 H (4 CH_2 and CH of piperidyl and H-4); 2·68 s, 3 H (NCH_3); 4·10 d and 4·38 d, 1 + 1 H (2 H-9, J = 13·0); 7·00—7·70 m, 6 H (6 ArH). For $C_{18}H_{22}ClNS_2$ (352·0) calculated: 61·43% C, 6·30% H, 10·07% Cl, 3·98% N; found: 60·71% C, 6·49% H, 9·65% Cl, 3·76% N.

Hydrogen maleate, m.p. 151—153°C (ethanol–ether). For $C_{22}H_{25}NO_4S_2$ (431·6) calculated: 61·23% C, 5·84% H, 3·25% N, 14·86% S; found: 61·17% C, 5·85% H, 3·34% N, 14·58% S.

The authors wish to thank their colleagues at the Research Institute for Pharmacy and Biochemistry for their contributions to the present study: Dr O. Matoušová (mass spectra); Drs E. Svátek and B. Schneider, Mrs A. Hrádková and Mrs Z. Janová (UV and IR spectra); Mrs M. Vlková and Mr Z. Šedivý (help with the synthesis); Mrs J. Komancová, Mrs V. Šmídová, Mrs J. Kropáčová, Mrs A. Svatošová, Mrs Z. Volková, and Mr M. Čech (elemental analyses); Drs J. Turinová and V. Holá (microbiological screening); Mrs M. Jandová, Mrs L. Horáková, Mrs E. Šulcová, Mrs S. Schubertová, and Mrs J. Ezrová (pharmacology and biochemical pharmacology).

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Translated by the author (M.P.).