POTENTIAL ANTIDEPRESSANTS: 6-(AMINOALKOXY)DIBENZO-[*b,f*]THIEPIN-10(11*H*)-ONES AND 6-(AMINOALKOXY)-10,11--DIHYDRODIBENZO[*b,f*]THIEPIN-10-OLS

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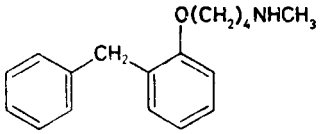
Received September 20, 1988
Accepted October 31, 1988

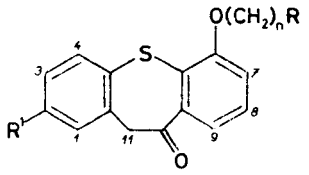
Sodium salts of 6-hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one and its 2-chloro derivative were reacted with hydrochlorides of 2-dimethylaminoethyl chloride, 2-(piperidino)ethyl chloride, 3-dimethylaminopropyl chloride, and 3-(piperidino)propyl chloride in ethanol in the presence of sodium ethoxide which resulted in the title compounds *IIa*, *IIb*, *IVa*, *Va*, *Vb*, and *VIIa*. The tertiary amines *IIa*, *IIb*, and *Va* were partially demethylated via the carbamates *VIIIa*, *VIIIb*, and *IXa* to the secodary amines *IIIa*, *IIIb*, and *VIa*. The amino ketones *IIa* and *Va* were reduced to the amino alcohols *XII* and *XIII*. With the exception of compound *Va* (hydrochloride VÚFB--15515), the products lacked completely the expected pharmacological profile of potential antidepressants.

In two previous communications[1,2] we have described our efforts to find new antidepressants within series of tricyclic analogues of the atypical antidepressant and cerebral activator „bifemelane" (*I*) (refs[3-5]): 4-(aminoalkoxy)dibenzo[*b,e*]thiepin--11(6*H*)ones[1], 4-(aminoalkoxy)xanthones[2], and 4-(aminoalkoxy)thioxanthones[2]. In the present paper we are describing in the first line the synthesis of similar 6-(aminoalkoxy)dibenzo[*b,f*]theipin-10(11*H*)-ones *IIa* – *VIIa* and of two of the 2-chloro derivatives (*IIb*, *IIIb*).

The basic starting product was 6-hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one[6] which was transformed with sodium ethoxide in ethanol to the sodium salt which was reacted with 2-dimethylaminoethyl chloride, 2-(piperidino)ethyl chloride, 3-dimethylaminopropyl chloride, and 3-(piperidino)propyl chloride, used in the form of hydrochlorides, to give *IIa*, *IVa*, *Va*, and *VIIa*. 2-Chloro-6-hydroxydibenzo[*b.f*]-thiepin-10(11*H*)-one[7] gave similarly *IIb*. With the exception of *Va*, all bases were crystalline, and all of them afforded crystalline hydrochlorides. Their identity was corroborated by spectra. For preparing the secondary amines *IIIa*, *IIIb*,and *VIa*, the correspoding tertiary amines *IIa*, *IIb*, and *Va* were subjected to partial demethylation. Their reactions with ethyl chloroformate in boiling benzene gave in good yields as the neutral products the carbamates *VIIIa*, *VIIIb*, and *IXa*. Only *IXa* was oily



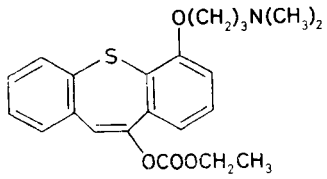
I



II, n = 2 ; R = $N(CH_3)_2$ *VII*, n = 3 , R = N⬡
III, n = 2 ; R = $NHCH_3$ *VIII*, n = 2 ; R = N(CH3)COOC2H5
IV, n = 2 ; R = N⬡ *IX*, n = 3 ; R = N(CH3)COOC2H5
V, n = 3 ; R = $N(CH_3)_2$ *X*, n = 4 ; R = Br
VI, n = 3 ; R = $NHCH_3$

In formulae *II*–*X*: *a*, R^1 = H *b*, R^1 = Cl

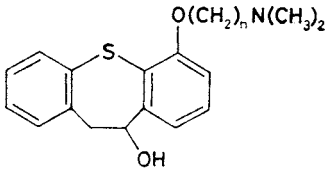
and was further used without characterization; *VIIIa* and *VIIIb* were crystalline and their spectra were recorded. In one experiment aiming at *IXa*, there was an important basic fraction, separated from *IXa* on the basis of its solubility in dilute hydrochloric acid. It was isolated as the hydrochloride corresponding to $C_{22}H_{25}NO_4S$. HCl (analysis and mass spectrum). It contains the untouched dimethylamino group (in the ^{1}H NMR spectrum singlet at δ 2·80 corresponding to 6 H) and at the same time the ethoxycarbonyloxy group (corresponding signals of OCH_2CH_3 in the ^{1}H NMR spectrum and the band at 1 755 cm^{-1} in the IR spectrum interpreted as corresponding to C=C–O–COOR). On the basis of the data available, the structure of the mixed enol carbonate *XI* is proposed for this product. Hydrolysis of the carbamates *VIIIa*, *VIIIb*, and *IXa* with boiling concentrated solutions of potassium hydroxide in ethanol afforded the secondary amines *IIIa*, *IIIb*, and *VIa*. Bases *IIIa* and *IIIb* were crystalline and afforded crystalline hydrochlorides; base *VIa* was oily and was purified in the form of the neutral oxalate (the released base was used for recording the ^{1}H NMR spectrum).



XI

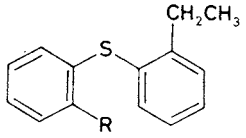
Treatment of the potassium salt of 6-hydroxydibenzo[*b*,*f*]thiepin-10(11*H*)-one[6] with 1,4-dibromobutane in boiling methanol gave *Xa*. Ketones *IIa* and *Va* were

reduced with sodium borohydride in ethanol to the alcohols *XII* and *XIII* which were identified by spectra and transformed to the hydrogen succinates.



XII, n = 2
XIII, n = 3

In connection with a different previous investigation in the dibenzo[*b*,*f*]thiepin series[8], a new synthesis of 2-(2-(2-ethylphenylthio)phenyl)acetic acid (*XVIII*) was carried out. 2-Iodobenzoic acid was reacted with 2-ethylthiophenol[9] in a boiling aqueous solution of potassium hydroxide in the presence of copper which resulted in *XIV*. This was reduced with sodium dihydridobis(2-methoxyethoxy)aluminate in a mixture of benzene and toluene to give *XV* which was transformed by tratment with thionyl chloride in the presence of pyridine to *XVI*. The following reaction with sodium cyanide in boiling aqueous ethanol gave the impure *XVII* containing (according to the ^{1}H NMR spectrum) 73% of the desired substance. Processing of a sample on a GC-MS instrument led first to separation of three main components which were identified by the mass spectra as the desired *XVII*, *XV* (formed by hydrolysis of *XVI*), and 2-(2-ethylphenylthio)benzyl ethyl ether (formed by ethanolysis of *XVI*). Hydrolysis of the crude *XVII* with potassium hydroxide in boling aqueous ethanol afforded the theoretical amount of *XVIII* which was found identical with the compound, prepared previously[8] differently.



XIV, R = COOH
XV, R = CH_2OH
XVI, R = CH_2Cl
XVII, R = CH_2CN
XVIII, R = CH_2COOH

Most of the compounds prepared were tested as potential antidepresants and/or subjected to general pharmacological screening. They were tested in the form of salts, described in the Experimental; the doses given were calculated per bases. Unless stated otherwise, they were administered orally. Acute toxicity in mice on intravenous administration, LD_{50} in mg/kg: *IIa*, 56 (257 orally); *IIIa*, 63·8; *IVa*, 33;

Va, 29·9 (324 orally); *VIa*, 54 (877 orally); *VIIa*, 40; *IIb*, 75; *IIIb*, 88·4; *XII*, 27·5; *XIII*, 18·9. Doses used in the screening, D in mg/kg (i.v.): *IVa*, 4; *VIa*, 10; *IIb*, 15.

Ataxic activity in the rotarod test in mice, ED_{50} in mg/kg (i.v.): *IIa*, 18·4; *IIIa*, 23·2; *IVa*, 10; *Va*, 15·0; *VIIa*, 12·2; *XII*, 5·7; *XIII*, 7·2. Inhibition of the locomotor activity of mice in the test of Dews; dose in mg/kg and effect: *IIa*, 50, insignificant effect; *IIIa*, 10, inactive; *IVa*, 10 and 50, inactive; *Va*, 50, significant inhibition; *VIIa*, 10 and 50, inactive; *XII*, 10 and 50, inactive; *XIII*, 10 and 50, inactive. Inhibition of the reserpine-induced gastric ulcer formation in rats: at 50 mg/kg only *Va* (VÚFB-15515) had mild but significant activity; *IIa*–*IVa*, *VIa*, *VIIa*, *XII*, and *XIII* were inactive. Inhibition of the reserpine-induced hypothermia in mice: *IIa* and *Va* in i.p. doses of 4 mg/kg were inactive. Anticataleptic effect towards perphenazine-induced catalepsy in rats: in doses of 50 mg/kg *IIa*–*VIIa*, *IIIb*, *XII*, and *XIII* were inactive. Compounds *IIa*–*Va*, *VIIa*, *XII*, and *XIII* proved inactive in the test for antiserotonin action (rat paw oedema) in oral doses of 10 mg/kg, in the test for antihistamine activity (aerosol) in guinea pigs, and in the same doses s.c. in the further test for antihistamine activity (detoxication in guinea pigs).

Blood pressure of normotensive anaesthetized rats: *IIb* and *VIa*, brief and deep drops after the doses D. Spasmolytic effect on the isolated rat duodenum against acetylcholine contractions (concentrations in mg/l reducing the contractions to 50%): *IIb*, 10; *VIa*, 1–10. Similar spasmolytic effect against barium chloride contractions: *VIa*, 10. Antiarrhythmic effect against aconitine-induced arrhythmia in rats (ED in mg/kg i.v.): *VIa*, 2·5. Antitussive action in guinea pigs (reduction of the cough attacks elicited by the aerosol of citric acid solution in % of the control value (100%)): *IVa*, 20 mg/kg, 48%; *VIa*, 50 mg/kg, 52%. Anorectic effect in mice (dose in mg/kg reducing the food consumption to 50%): *IIb*, 25–75.

In conclusion: Only *Va* showed indication of the pharmacological profile of a potential antidepressant with a central depressant component of activity.

The compounds prepared were also tested for antimicrobial activity in vitro (microorganisms and the minimum inhibitory concentraions in mg/l were given unless they exceed 100 mg/l): *Streptococcus β-haemolyticus*, *IIa*, 100, *IIb* 50, *IIIb* 25, *IVa* 100; *Streptococcus faecalis*, *IIIb* 25, *IVa* 100, *VIa* 100, *VIIa* 100; *Staphylococcus pyogenes aureus*. *IIa* 100, *IIb* 25, *IIIb* 25, *IVa* 50, *VIIa* 50; *Pseudomonas aeruginosa*, *VIIa* 50; *Proteus vulgaris*, *IIa* 100, *IIIb* 100; *Trichophyton mentagrophytes*, *IIb* 50, *IVa* 50, *VIIa* 12·5; *Candida albicans*, *IIa* 50.

EXPERIMENTAL

The melting points were determined in Kofler block and were not corrected; the samples were dried in vacuo of about 60 Pa over P_2O_5 at room temperature or at a suitably elevated temperature. The UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded with a Unicam SP 8 000 spectrophotometer, IR spectra (in Nujol unless stated otherwise, ν in cm^{-1}) with Perkin–Elmer

298 spectrophotometer, ^{1}H NMR spectra (mostly in $CDCl_3$, δ, J in Hz) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra (m/z, fragment and/or %) with MCH 1320 and/or Varian MAT 44S (GC-MS) spectrometers. The homogeneity of the substances and compositions of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with $MgSO_4$ (Na_2SO_4) or K_2CO_3 and were evaporated under eeduced pressure on a rotating evaporator.

6-(2-Dimethylaminoethoxy)dibenzo[*b,f*]thiepin-10(11*H*)-one (*IIa*)

6-Hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one[6] (12·12 g) and 10·8 g 2-dimethylaminoethyl chloride hydrochloride were added to a solution of sodium ethoxide, prepared from 3·0 g Na and 350 ml ethanol, and the mixture was stirred and refluxed for 9 h. After standing overnight, the precipitated NaCl was filtered off, the filtrate was slightly acidified with dilute hydrochloric acid and evaporated in vacuo. The residue was dissolved in water, the solution was washed with benzene, made alkaline with NH_4OH, and the base was isolated by extraction with benzene: 10·4 g (66%) of oily *IIa* which crystallized from cyclohexane, m.p. 69–71°C. UV spectrum: 240 (4·25), infl. 265 (3·93), infl. 277 (3·77), infl. 285 (3·62), 345 (3·66). IR spectrum (KBr): 704, 750, 769, 787 (4 and 3 adjacent Ar–H); 1 035, 1 255 (Ar–O–R); 1 560, 1 582, 3 060 (Ar); 1 665 (ArCO); 2 765, 2 820 (N–CH_3). ^{1}H NMR spectrum: 2·46 s, 6 H ($N(CH_3)_2$); 2·91 t, 2 H (CH_2N, J = 6·0); 4·23 t, 2 H (CH_2O, J = 6·0); 4·30 s, 2 H ($ArCH_2CO$); 7·00–7·90 m, 7 H (ArH). For $C_{18}H_{19}NO_2S$ (313·4) calculated: 68·98% C, 6·11% H, 4·47% N, 10·23% S; found: 69·17% C, 6·22% H, 4·52% N, 10·18% S.

Hydrochloride, m.p. 176–179°C (ethanol–ether). Mass spectrum: 313 (M^+, $C_{18}H_{19}NO_2S$), 184 ($C_{12}H_8S$), 152 ($C_{12}H_8$), 72, 58. For $C_{18}H_{20}ClNO_2S$ (349·9) calculated: 61·79% C, 5·76% H, 10·13% Cl, 4·00% N, 9·17% S; found: 61·76% C, 5·83% H, 10·30% Cl, 4·02% N, 9·25% S.

2-Chloro-6-(2-dimethylaminoethoxy)dibenzo*b,f*]thiepin-10(11*H*)-one (*IIb*)

A similar reaction of 3·1 g 2-chloro-6-hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one[7], 2·6 g 2-dimethylaminoethyl chloride hydrochloride and sodium ethoxide (from 0·7 g Na and 40 ml ethanol) (refluxing for 11·5 h) gave 2·5 g (64%) of solid *IIb* which was recrystallized from cyclohexane, m.p. 101–103°C. UV spectrum: 237·5 (4·44), 267 (4·07), 342 (3·77). IR spectrum: 720, 775, 803, 820, 886 (3 and 2 adjacent and solitary Ar–H); 1 025, 1 263 (Ar—O—R); 1 564, 1 586, 3 070, 3 085 (Ar); 1 672 (ArCO); 2 725, 2 770, 2 805, 2 815 (N—CH_3). ^{1}H NMR spectrum: 2·42 s, 6 H ($N(CH_3)_2$); 2·88 t, 2 H (CH_2N, J = 6·0); 4·20 t, 2 H (CH_2O, J = 6·0); 4·25 m, 2 H ($ArCH_2CO$); 7·03 dd, 1 H (H-7, J = 8·0; 2·0); 7·18 dd, 1 H (H-3, J = 8·0; 2·5); 7·23 t, 1 H (H-8, J = 8·0); 7·44 d, 1 H (H-1, J = 2·5); 7·59 d, 1 H (H-4, J = 8·0); 7·80 dd, 1 H (H-9, J = 8·0; 2·0). For $C_{18}H_{18}ClNO_2S$ (347·8) calculated: 62·15% C, 5·21% H, 10·19% Cl, 4·03% N, 9·22% S; found: 62·59% C, 5·20% H, 9·86% Cl, 3·76% N, 9·06% S.

Hydrochloride hemihydrate, m.p. 197–199°C (ethanol). For $C_{18}H_{19}Cl_2NO_2S$ + 0·5 H_2O (393·3) calculated: 54·96% C, 5·13% H, 18·03% Cl, 3·56% N, 8·15% S; found: 55·01% C, 4·91% H; 17·84% Cl, 3·42% N, 8·17% S.

6-(2-(Piperidino)ethoxy)dibenzo[*b,f*]thiepin-10(11*H*)-one (*IVa*)

A similar reaction of 12·1 g 6-hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one[6], 12·9 g 2-(piperidino)ethyl chloride hydrochloride and sodium ethoxide (from 3·0 g Na and 250 ml ethanol) (refluxing for 7 h) gave 14·6 g (83%) of practically homogeneous oily *IVa* which crystallized from a mixture of cyclohexane and hexane, m.p. 55–58°C. ^{1}H NMR spectrum: 1·55 bs, 6 H (3 CH_2 in posi-

tions 3, 4, 5 of piperidine); 2·60 bm, 4 H (CH_2NCH_2 of piperidine); 2·90 t, 2 H (remaining CH_2N, $J = 6·0$); 4·21 t, 2 H (CH_2O, $J = 6·0$); 4·25 s, 2 H ($ArCH_2CO$); 6·90—7·90 m, 7 H (ArH). For $C_{21}H_{23}NO_2S$ (353·5) calculated: 71·35% C, 6·56% H, 3·96% N, 9·07% S; found: 71·59% C, 6·71% H, 3·76% N, 8·93% S.

Hydrochloride hemihydrate, m.p. 186—189°C (ethanol–ether). Mass spectrum: 353 (M^+, $C_{21}H_{23}NO_2S$, 1), 112 ($C_7H_{14}N$, 2), 98 ($C_6H_{12}N$, 100). UV spectrum: 241 (4·22), infl. 265 (3·89), 342 (3·62). IR spectrum (KBr): 722, 748, 763, 794 (4 and 3 adjacent Ar—H); 1 255, 1 300 (Ar—O—R); 1 470, 1 560, 1 582, 3 040 (Ar); 1 665 (ArCO); 2 395, 2 500, 2 540, 2 560, 2 610, 2 640 (NH^+). For $C_{21}H_{24}ClNO_2S + 0·5\ H_2O$ (398·9) calculated: 63·22% C, 6·32% H, 8·89% Cl, 3·51% N, 8·04% S; found: 63·57% C, 6·41% H, 9·19% Cl, 3·45% N, 7·81% S.

6-(3-Dimethylaminopropoxy)dibenzo[*b,f*]thiepin-10(11*H*)-one (*Va*)

A similar reaction of 6·7 g 6-hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one[6], 6·6 g 3-dimethylaminopropyl chloride hydrochloride and sodium ethoxide (from 1·73 g Na and 200 ml ethanol) (refluxing for 10 h) gave 6·4 g (71%) of almost homogeneous oily *Va* which was transformed by treatment with HCl in a mixture of ethanol and ether to the hydrochloride, m.p. 181—183°C (ethanol–ether). Mass spectrum: 327 (M^+, $C_{19}H_{21}NO_2S$, 2), 184 ($C_{12}H_8S$, <1), 152 ($C_{12}H_8$, 1), 86 ($C_5H_{12}N$, 7), 58 (C_3H_8N, 100). UV spectrum: 239 (4·27), infl. 263 (3·96), infl. 276 (3·78), infl. 284 (3·63), 343 (3·68). IR spectrum: 765, 798 (4 and 3 adjacent Ar—H); 1 050, 1 230 (Ar—O—R); 1 552, 1 575, 3 040 (Ar); 1 650 (ArCO); 2 410 (NH^+). For $C_{19}H_{22}ClNO_2S$ (363·9) calculated: 62·71% C, 6·09% H, 9·74% Cl, 3·85% N, 8·81% S; found: 62·67% C, 6·04% H, 9·92% Cl, 3·94% N, 8·68% S.

A sample of the purified hydrochloride was decomposed with NH_4OH and the released base *Va* (homogeneous, oily) was isolated by extraction with ether and used for recording the spectra. UV spectrum: 239 (4·28), infl. 247 (4·24), 340 (3·68). IR spectrum: 720, 750, 765, 790 (4 and 3 adjacent Ar—H); 1 040, 1 060, 1 255, 1 310 (Ar—O—R), 1 560, 1 580, 3 055 (Ar); 1 670 (ArCO); 2 760 (N—CH_3). ^{1}H NMR spectrum: 2·12 m, 2 H (CH_2 in position 2 of propyl); 2·30 s, 6 H ($N(CH_3)_2$); 2·60 t, 2 H (CH_2N, $J = 6·0$); 4·15 t, 2 H (CH_2O, $J = 6·0$); 4·29 s, 2 H ($ArCH_2CO$); 6·90—7·80 m, 7 H (ArH).

6-(3-(Piperidino)propoxy)dibenzo[*b,f*]theipin-10(11*H*)-one (*VIIa*)

A similar reaction of 10·9 g 6-hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one[6], 12·5 g 3-(piperidino)-propyl chloride hydrochloride, and sodium ethoxide (from 2·5 g Na and 200 ml ethanol) (refluxing for 8·5 h) gave 14·0 g (85%) of crystalline *VIIa*, m.p. 78—80°C (cyclohexane). UV spectrum: 240 (4·26), infl. 263 (3·96), infl. 278 (3·76), infl. 285 (3·63), 345 (3·66). IR spectrum (KBr): 706, 720, 750, 755, 768, 790 (4 and 3 adjacent Ar—H); 1 043, 1 255, 1 265 (Ar—O—R); 1 560, 1 580, 3 065 (Ar); 1 665 (ArCO); 2 690, 2 770, 2 800 (N—CH_2). ^{1}H NMR spectrum: 1·60 m, 6 H (3 CH_2 in positions 3, 4, 5 of piperidine); 2·15 m, 2 H (CH_2 in position 2 of propyl); 2·50 m, 4 H (CH_2NCH_2 of piperidine); 2·68 t, 2 H (remaining CH_2N, $J = 6·0$); 4·20 t, 2 H (CH_2O, $J = 6·0$); 4·30 s, 2 H ($ArCH_2CO$); 7·00—7·90 m, 7 H (ArH). For $C_{22}H_{25}NO_2S$ (367·5) calculated: 71·90% C, 6·86% H, 3·81% N, 8·72% S; found: 71·74% C, 6·76% H, 3·84% N, 8·70% S.

Hydrochloride, m.p. 166—169°C (acetone). For $C_{22}H_{26}ClNO_2S$ (404·0) calculated: 65·40% C, 6·49% H, 8·78% Cl, 3·47% N, 7·94% S; found: 65·14% C, 6·71% H, 8·90% Cl, 2·98% N, 8·07% S.

Ethyl N-Methyl-N-(2-(10-oxo-11*H*-dibenzo[*b,f*]thiepin-6-yloxy)ethyl)carbamate (*VIIIa*)

A stirred solution of 7·8 g *IIa* in 50 ml benzene was treated dropwise with a solution of 5·4 g ethyl chloroformate in 20 ml benzene, the mixture was stirred for 30 min at 60—70°C and refluxed

for 3 h. After cooling the reaction mixture was filtered, the filtrate was washed with 3M-HCl and water, dried, and evaporated. The neutral residue (7·4 g, 80%) represents the crude *VIIIa* which crystallized from ethanol, m.p. 103—106°C. UV spectrum: 240 (4·25), infl. 265 (3·92), infl. 278 (4·01), infl. 285 (3·62), 345 (3·63). IR spectrum: 705, 719, 750, 765, 770, 785 (3 and 4 adjacent Ar—H); 1 175, 1 255, 1 310 (Ar—O—R, NCOOR); 1 487, 1 560, 1 583, 3 060 (Ar); 1 667 (ArCO), 1 700 (NCOOR). ^{1}H NMR spectrum: 1·30 t, 3 H (CH_3 of ethyl, J = 7·0); 3·25 s, 3 H (NCH_3); 3·80 t, 2 H (CH_2N, J = 6·0); 4·20 q, 2 H (CH_2O of ethoxycarbonyl, J = 7·0); 4·25 t, 2 H (remaining CH_2O, J = 6·0); 4·30 s, 2 H ($ArCH_2CO$); 6·90—7·90 m, 7 H (ArH).

Ethyl N-(2-(2-Chloro-10-oxo-11*H*-dibenzo[*b*,*f*]thiepin-6-yloxy)ethyl)-N-methylcarbamate (*VIIIb*)

A similar reaction of 6·96 g *IIb* and 4·6 g ethyl chloroformate in 60 ml benzene gave 5·1 g (63%) of crude *VIIIb* which crystallized from ethanol ,m.p. 152—154°C. UV spectrum: 236·5 (4·32), 266·5 (4·02), 344 (3·75). IR spectrum (KBr): 720, 775, 805, 815, 880, 900 (3 and 2 adjacent and solitary Ar–H); 1 020, 1 265 (Ar—O—R); 1 164, 1 179 (C—O of ester); 1 569, 1 590, 3 080 (Ar); 1 668 (ArCO); 1 703 (NCOOR). ^{1}H NMR spectrum: 1·25 t, 3 H (CH_3 of ethyl J = 7·0); 3·18 s, 3 H (NCH_3); 3·75 bt, 2 H (CH_2N, J = 5·0); 4·80 t, 2 H (CH_2OAr, J = 5·0); 4·18 q, 2 H (CH_2O of ethoxycarbonyl, J = 7·0); 4·21 s, 2 H ($ArCH_2CO$); 7·10 m, 3 H (H-3, 7, 8); 7·40 d, 1 H (H-1, J = 2·5); 7·52 d, 1 H (H-4, J = 8·0); 7·75 dd, 1 H (H-9, J = 2·0; 8·0). For $C_{20}H_{20}ClNO_4S$ (405·9) calculated: 59·18% C, 4·97% H, 8·73% Cl, 3·45% N, 7·90% S; found: 59·15% C, 5·08% H, 8·67% Cl, 3·55% N, 8·02% S.

10-(Ethoxycarbonyloxy)-6-(3-dimethylaminopropoxy)dibenzo[*b*,*f*]thiepin (*XI*)

A stirred solution of 8·2 g *Va* in 50 ml benzene was treated dropwise with a solution of 5·5 g ethyl chloroformate in 20 ml benzene. The mixture was stirred for 30 min at room temperature and for 2·5 h under reflux in a bath of 70—80°C. The warm benzene solution was decanted from the heavy insoluble oil, was shaken with excessive 3M-HCl, 1 : 1 dilute hydrochloric acid and with water. The benzene layer was dried and evaporated giving 2·7 g (28%) of crude, oily *IXa*. The acid aqueous solutions were combined, made alkaline with NH_4OH and extracted with benzene. Processing of the extract gave 4·2 g (42%) of crude *XI* which was converted to the hydrochloride, m.p. 167—170°C (ethanol–ether). Mass spectrum: 399 (M^+, $C_{22}H_{25}NO_4S$), 310 ($C_{19}H_{20}NOS$), 86 ($C_5H_{12}S$), 58 (C_3H_8N). UV spectrum: 259 (4·26); 304 (3·89). IR spectrum: 754, 778, 805 (4 and 3 adjacent Ar—H); 1 015, 1 243, 1 255, 1 274 (Ar—O—R and OCOOR); 1 565, 3 040 (Ar); 1 640 (C=C), 1 755 (C=C—O—COOR); 2 410, 2 510 (NH^+). ^{1}H NMR spectrum: 1·23 t, 3 H (CH_3 of ethyl, J = 7·0); 2·35 bm, 2 H (CH_2 in position 2 of propyl); 2·80 s, 6 H ($N(CH_3)_2$); 3·30 bt, 2 H (CH_2N); 4·00 t, 2 H (CH_2O of ethoxycarbonyl, J = 7·0); 6·70—7·60 m, 8 H (Ar and H-11); 12·30 flat band, 1 H (NH^+). For $C_{22}H_{26}ClNO_4S$ (436·0) calculated: 60·61% C, 6·01% H, 8·13% Cl, 3·21% N, 7·36% S; found: 60·91% C, 6·13% H, 8·25% Cl, 3·13% N, 7·42% S.

6-(2-Methylaminoethoxy)dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*IIIa*)

A stirred mixture of 3·7 g *VIIIa*, 2·8 g KOH and 3·5 ml ethanol was refluxed for 4 h. Ethanol was evaporated, the residue was diluted with water and extracted with benzene. Processing of the extract gave 2·8 g (94%) of oily *IIIa* which crystallized from light petroleum, m.p. 61—64°C (light petroleum–ether). UV spectrum: 240 (4·25), 342 (3·65). IR spectrum: 703, 719, 754, 763, 785 (4 and 3 adjacent Ar—H); 1 045, 1 255 (Ar—O—R); 1 556, 1 580, 3 050 (Ar); 1 665 (ArCO); 2 790 (N—CH_3); 3 280 (NH). ^{1}H NMR spectrum: 1·80 bs, 1 H (NH); 2·53 s, 3 H (NCH_3); 3·02 t, 2 H (CH_2N, J = 6·0); 4·15 t, 2 H (CH_2O, J = 6·0); 4·20 s, 2 H ($ArCH_2CO$); 6·80 to

7·80 m, 7 H (ArH). For $C_{17}H_{17}NO_2S$ (299·4) calculated: 68·20% C, 5·72% H, 4·68% N; found: 68·45% C, 5·85% H, 4·66% N.

Hydrochloride, m.p. 208—212°C (methanol). For $C_{17}H_{18}ClNO_2S$ (335·8) calculated: 60·79% C, 5·40% H, 10·56% Cl, 4·17% N, 9·55% S; found: 60·39% C, 5·61% H, 10·80% Cl, 4·15% N, 9·81% S.

2-Chloro-6-(2-methylaminoethoxy)dibenzo[*b,f*]thiepin-10(11*H*)-one (*IIIb*)

A stirred mixture of 3·3 g *VIIIb*, 2·5 g KOH and 5·0 ml ethanol was refluxed for 10 h (some *VIIIb* was still present). After evaporation of ethanol, the residue was diluted with water and extracted with benzene. From the benzene solution the basic product was extracted into excessive 3M-HCl, the aqueous solution of the hydrochloride was treated with NH_4OH and the base was isolated by extraction with benzene; 1·9 g (70%) of homogeneous, crystalline *IIIb*, m.p. 101 to 103°C (benzene–hexane). UV spectrum: 235·5 (4·35), 265 (4·00), 339 (3·69). IR spectrum: 725, 778, 808, 827, 872 (3 and 2 adjacent and solitary Ar—H); 1 018, 1 260 (Ar—O—R); 1 569, 1 580, 3 040, 3 080 (Ar); 1 680 (ArCO); 2 790 (N—CH_3); 3 290, 3 330 (NH). ^{1}H NMR spectrum: 1·75 bs, 1 H (NH); 2·54 s, 3 H (NCH_3); 3·02 t, 2 H (CH_2N, J = 5·0); 4·16 t, 2 H (CH_2O, J = 5·0); 4·19 s, 2 H ($ArCH_2CO$), 6·99 dd, 1 H (H-7, J = 2·0; 8·0); 7·11 dd, 1 H (H-3, J = 2·5; 8·0); 7·20 t, 1 H (H-8, J = 8·0); 7·38 d, 1 H (H-1, J = 2·5); 7·52 d, 1 H (H-4, J = 8·0); 7·75 dd, 1 H (H-9, J = 2·0; 8·0). For $C_{17}H_{16}ClNO_2S$ (333·8) calculated: 61·16% C, 4·83% H, 4·20% N, 9·61% S; found: 61·06% C, 4·78% H, 4·04% N, 9·53% S.

Hydrochloride, m.p. 193—195°C (ethanol). For $C_{17}H_{17}Cl_2NO_2S$ (370·3) calculated: 55·14% C, 4·63% H, 19·15% Cl, 3·78% N, 8·66% S; found: 54·78% C, 4·76% H, 19·19% Cl, 3·71% N, 8·80% S.

6-(3-Methylaminopropoxy)dibenzo[*b,f*]thiepin-10(11*H*)-one (*VIa*)

A solution of 7·9 g *Va* in 42 ml benzene was added dropwise to a stirred solution of 5·2 g ethyl chloroformate in 20 ml benzene over 10 min, the mixture was refluxed for 3 h. After cooling the mixture was washed with 3M-HCl and water, dried, and evaporated; 7·2 g (77%) of almost homogeneous *IXa* which could not be obtained in crystalline state even after chromatography on neutral Al_2O_3; it was used without further characterization.

Oily *IXa* (2·0 g), 1·5 g KOH, and 2 ml ethanol were stirred and refluxed for 11 h. After cooling the mixture was diluted with water and extracted with benzene. Processing of the extract gave 1·4 g (86%) of oily *VIa* which was neutralized with 0·5 g oxalic acid dihydrate in 2 ml boiling ethanol; neutral oxalate hemihydrate, m.p. 198—201°C ((80% ethanol–ether). For $C_{19}H_{20}NO_4S$ + 0·5 H_2O (367·4) calculated: 62·10% C, 5·76% H, 3·81% N, 8·73% S; found: 62·13% C, 5·75% H, 3·84% N, 8·76% S.

A sample of the purified salt was decomposed with NH_4OH and the homogeneous oily base *VIa* was used for recording the ^{1}H NMR spectrum: 1·75 bs, 1 H (6H); 2·12 m, 2 H (CH_2 in position 2 of propyl); 2·52 s, 3 H (NCH_3); 2·90 t, 2 H (CH_2N, J = 7·0); 4·19 t, 2 H (CH_2O, J = 7·0); 4·29 s, 2 H ($ArCH_2CO$); 7·00—7·50 m, 5 H (H-1, 2, 3, 7, 8); 7·65 bd, 1 H (H-4, J = 8·5); 7·79 dd, 1 H (H-9, J = 8·5; 2·0).

6-(4-Bromobutoxy)dibenzo[*b,f*]thiepin-10(11*H*)-one (*Xa*)

6-Hydroxydibenzo[*b,f*]thiepin-10(11*H*)-one[6] (4·8 g) and 9·0 g 1,4-dibromobutane were added to a stirred solution of 1·4 g KOH in 55 ml methanol and the mixture was refluxed for 6 h. Methanol

was evaporated in vacuo, the residue was distributed between water and benzene, the benzene layer was washed with 10% NaOH and water, dried, and evaporated; 7·1 g (96%) of crude *Xa* which crystallized from ethanol, m.p. 73–75°C. UV spectrum: 239 (4·26), infl. 242 (3·97), 285 (3·67), 346 (3·66). IR spectrum: 720, 753, 767, 784 (4 and 3 adjacent Ar—H); 1040, 1 255 (Ar—O—R); 1 472, 1 558, 1 579, 3 045, 3 060 (Ar). ^{1}H NMR spectrum: 2·15 m, 4 H (2 CH_2 in positions 2 and 3 of butyl); 3·61 bt, 2 H (CH_2Br); 4·14 bt, 2 H (CH_2O); 4·28 s, 2 H ($ArCH_2CO$); 6·90–8·00 m, 7 H (ArH). For $C_{18}H_{17}BrO_2S$ (377·3) calculated: 57·30% C, 4·54% H, 21·18% Br, 8·50% S; found: 57·61% C, 4·74% H, 21·32% Br, 8·66% S.

6-(2-Dimethylaminoethoxy)-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XII*)

A stirred solution of 6·5 g *IIa* in 70 ml ethanol was treated dropwise with a solution of 2·0 g $NaBH_4$ in 20 ml water containing 0·5 ml 10% NaOH and the mixture was refluxed for 4·5 h. The volatile components were evaporated in vacuo, the residue was distributed between water and benzene, the benzene layer was dried and evaporated; 5·9 g (90%) of *XII* which crystallized from ethanol, m.p. 123–125°C. IR spectrum: 675, 760, 785 (4 and 3 adjacent Ar—H); 1 020, 1 275 (Ar—O—R); 1 045, 1 067 (CHOH); 1 465, 1 570, 3 050 (Ar); 2 720, 2 780 (N—CH_3); 3 110 (OH). ^{1}H NMR spectrum: 2·24 s, 6 H ($N(CH_3)_2$); 2·68 t, 2 H (CH_2N, J = 6·0); 3·20 dd and 3·52 dd, 1 + 1 H (2 H-11, J = 13·0; 8·0 and 13·0; 4·0); 3·90 t, 2 H (CH_2O, J = 6·0); 4·20 bs, 1 H (OH); 5·48 dd, 1 H (Ar—CH—O, J = 8·0; 4·0); 6·50–7·50 m, 7 H (ArH). For $C_{18}H_{21}NO_2S$ (315·4) calculated: 68·54% C, 6·71% H, 4·44% N, 10·17% S; found: 68·63% C, 6·77% H, 4·62% N, 10·36% S.

Hydrogen maleate, m.p. 157–159°C (ethanol). For $C_{22}H_{25}NO_6S$ (431·5) calculated: 61·23% C, 5·84% H, 3·25% N; found: 61·36% C, 5·87% H, 3·28% N.

6-(3-Dimethylaminopropoxy)-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIII*)

Similar reduction of 6·6 g *Va* with 2·0 g $NaBH_4$ in a mixture of 50 ml ethanol, 20 ml benzene, and 20 ml water gave 4·8 g (73%) of crude *XIII* which crystallized from methanol, m.p. 166 to 169°C. IR spectrum: 732, 750, 792 (4 and 3 adjacent Ar—H); 1 042 (CHOH); 1 042, 1 265 (Ar—O—R); 1 570, 3 040, 3 060 (Ar); 2 730, 2 765, 2 790, 2 820 (N—CH_3); 3 110 (OH). ^{1}H NMR spectrum (CD_3SOCD_3, 80°C): 1·95 m, 2 H (CH_2 in position 2 of propyl); 2·20 s, 6 H ($N(CH_3)_2$); 2·52 t, 2 H (CH_2N, J = 7·0); 3·22 dd and 3·48 dd, 1 + 1 H (2 H-11, J = 13·0; 8·0 and 13·0; 4·0); 4·03 t, 2 H (CH_2O, J = 7·0); 5·40 dd, 1 H (Ar—CH—O, J = 8·0; 4·0); 6·80–7·50 m, 7 H (ArH). For $C_{19}H_{23}NO_2S$ (329·5) calculated: 69·26% C, 7·04% H, 4·25% N, 9·73% S; found: 69·01% C, 7·28% H, 4·45% N, 9·67% S.

Hydrogen maleate, m.p. 108–110°C (acetone-ether). For $C_{23}H_{27}NO_6S$ (445·5) calculated: 62·00% C, 6·11% H, 3·14% N, 7·20% S; found: 62·32% C, 6·25% H, 3·21% N, 7·21% S.

2-(2-Ethylphenylthio)benzoic Acid (*XIV*)

2-Ethylthiophenol[9] (23·8 g) was added at 50°C to a stirred solution of 33 g KOH in 340 ml water and after 10 min stirring 42·0 g 2-iodobenzoic acid and 1·8 g Cu were added. The mixture was refluxed for 9 h. After cooling to 50°C it was filtered with active carbon and the filtrate was acidified with hydrochloric acid. After standing overnight the separated product was filtered, washed with water, dried in vacuo, and crystallized from 100 ml benzene; 47·3 g (85%) of *XIV*, m.p. 153–159°C. Analytical sample, m.p. 158–160°C (benzene). UV spectrum: 254·4 (3·95), 315·2 (3·64). IR spectrum: 750 (4 adjacent Ar—H); 910, 1 040, 1 255, 1 670, 2 550, 2 640, infl. 3 150 (COOH); 1 555, 1 582, 1 600 (Ar). ^{1}H NMR spectrum (60°C): 1·20 t, 3 H (CH_3 of ethyl

J = 7·0); 2·80 q, 2 H (CH_2 of ethyl, J = 7·0); 6·50—7·70 m, 7 H (H-3, 4, 5 and 4 ArH of ethylphenylthio); 8·15 m, 1 H (H-6); 12·15 s, 1 H (COOH). For $C_{15}H_{14}O_2S$ (258·3) calculated: 69·74% C, 5·46% H, 12·41% S; found: 69·85% C, 5·41% H, 12·27% S.

2-(2-Ethylphenylthio)benzyl Alcohol (*XV*)

A stirred suspension of 29·2 g *XIV* in 200 ml benzene was treated dropwise over 45 min with 85 ml 50% solution of sodium dihydrobis(2-methoxyethoxy)aluminate in toluene at 15—20°C. The mixture was stirred for 3 h at 10—20°C, allowed to stand overnight, decomposed by a slow addition of 150 ml 10% NaOH at 10—15°C, after 20 min stirring the organic layer was separated and the aqueous one was extracted with benzene. The combined organic solutions were washed with 10% NaOH and water, dried, and evaporated; 24·1 g (87%) of crude *XV* which was distilled in vacuo, b.p. 186—194°C/1·5 kPa. The distillate crystallized on standing, m.p. 46—48°C (hexane). IR spectrum: 742, 760 (4 adjacent Ar—H); 1 025, 1 035 (CH_2OH); 1 568, 1 585, 3 050 (Ar); 3 200, 3 270 (OH). ^{1}H NMR spectrum: 1·21 t, 3 H (CH_3 of ethyl, J = 7·0); 2·20 bs, 1 H (OH); 2·78 q, 2 H (CH_2 of ethyl, J = 7·0); 4·70 bs, 2 H ($ArCH_2O$); 6·80—7·60 m, 8 H (ArH). For $C_{15}H_{16}OS$ (244·4) calculated: 73·73% C, 6·60% H, 13·12% S; found: 73·81% C, 6·45% H, 13·06% S.

2-(2-Ethylphenylthio)benzyl Chloride (*XVI*)

A stirred mixture of 20·2 g *XV* and 8·3 ml pyridine was treated at 10—20°C with 8·1 ml $SOCl_2$, added dropwise. The mixture was stirred for 2 h at room temperature, then warmed for 1 h to 30—40°C, cooled, and decomposed with 33 ml water. The product was isolated by extraction with benzene. Processing of the extract gave 13·6 g (63%) of *XVI*, b.p. 174°C/1·5 kPa. For C_{15}·$H_{15}ClS$ (262·8) calculated: 68·55% C, 5·75% H, 13·49% Cl, 12·20% S; found: 68·80% C, 5·74% H, 13·19% Cl, 11·98% S.

2-(2-(2-Ethylphenylthio)phenyl)acetonitrile (*XVII*)

A solution of 13·6 g *XVI* in 15 ml ethanol was treated with a solution of 3·8 g NaCN in 6 ml water and the stirred mixture was refluxed for 13 h. Ethanol was evaporated, the residue was diluted with water and extracted with benzene. Processing of the extract and distillation of the residue gave 11·3 g (63%) of crude product which was shown to contain 73% of *XVII*. The GC-MS spectrometer separated three main components of this product and their mass spectra were recorded. The main component is the desired *XVII*: 253 (M^+, $C_{16}H_{15}NS$, 70), 238 (8), 236 (5), 235(6), 221 (25), 197 (45), 165 (13), 147 (25), 131 (10), 105 (100). The second component is evidently identical with *XV*: 244 (M^+, $C_{15}H_{16}OS$), 226, 211, 197, 193, 178, 137, 135, 105. For the third component the structure of 2-(2-ethylphenylthio)benzyl ethyl ether was suggested: 272 (M^+, $C_{17}H_{20}OS$), 243, 242, 226, 211, 197, 193, 178, 137, 135, 105. IR spectrum of the crude product (film): 750 (4 adjacent Ar–H); 1 568, 1 585, 3 005, 3 050 (Ar); 2 248 (R—CN); 3 500 (OH). ^{1}H NMR spectrum showed that the crude product contains 73% of *XVII*; the spectrum belonging to *XVII*: 1·28 t, 3 H (CH_3 of ethyl, J = 7·0); 2·80 q, 2 H (CH_2 of ethyl, J = 7·0); 3·81 s, 2 H ($ArCH_2CN$); 6·90—7·70 m, 8 H (ArH). For $C_{16}H_{15}NS$ (253·4) calculated: 75·84% C, 5·97% H, 12·66% S; found: 75·36% C, 6·10% H, 12·47% S. The nitrogen content is much lower than the theoretical one due to the presence of nitrogen-free impurities.

2-(2-(2-Ethylphenylthio)phenyl)acetic Acid (*XVIII*)

A solution of 8·8 g 73% *XVII* in 35 ml ethanol was treated with a solution of 8·6 g KOH in 20 ml water and the mixture was refluxed for 7 h. The solvents were evaporated in vacuo, the residue

was dissolved in 110 ml water, the solution was washed with benzene and acidified with hydrochloric acid. The separated oily product was isolated by extraction with benzene. Processing of the extract and crystallization of the residue from a mixture of benzene and light petroleum gave 6·8 g (100%) of *XVIII*, m.p. 56–58·5°C. Ref.[8], m.p. 56–58°C.

The authors wish to thank their colleagues at the Research Institute for Pharmacy and Biochemistry for their contributions to the present study: Drs I. Koruna, J. Schlanger, O. Matoušová, Mrs A. Hrádková, and Mrs Z. Janová (spectral data); Mrs J. Komancová, Mrs V. Šmídová, Mrs J. Kropáčová, and Mrs A. Svatošová (elemental analyses); Drs J. Metyš, S. Wildt, V. Holá, Mrs J. Horáková, and Mrs E. Šulcová (pharmacological and microbiological screening).

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Translated by the author (M.P.).