POTENTIAL ANTIDEPRESSANTS: SOME N-SUBSTITUTED DERIVATIVES OF (*E*)-11-(3-METHYLAMINOPROPYLIDENE)-6,11-DIHYDRODIBENZO[*b*,*e*]THIEPIN*

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Alkylation reactions of (*E*)-11-(3-methylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*II*) with allyl bromide, propargyl bromide, 2-chloroethanol, 1-chloropropan-2-ol and 3-chloropropanol gave the N-substituted derivatives *III*—*VII*. Acylation of amino alcohols *V*—*VII* with acetyl chloride and decanoyl chloride resulted in the esters *VIII*—*XI*. 6,11-Dihydrodibenzo-[*b*,*e*]thiepin-11-carboxylic acid was transformed *via* the acid chloride to the amide *XIV*. Out of the compounds prepared, only the amino alcohols *V*—*VII* and the ester *VIII* revealed in pharmacological tests the activity similar to that of tricyclic antidepressants; their activity is lower than that of prothiadene (*I*). The decanoates *IX*—*XI* are devoid of antireserpine activity; the attempt at finding long-acting depot antidepressant agents in this way was thus unsuccessful. The amide *XIV* has mild anticonvulsant activity.

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin showed significant antireserpine activity and the substance found extensive use in the treatment of mental depressions[1-3]; it was established that the preparation used in therapy (prothiadene, dosulepin, dothiepin) consists almost exclusively of the (*E*)-isomer *I* (ref.[4]). In the preparation of the (*Z*)-isomer, which was necessary for pharmacological comparison, there was obtained a larger quantity of the demethyl analogue of compound *I*, *i.e.* (*E*)-11-(3-methylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]-thiepin (*II*) (refs[4,5]). This compound (northiadene) was identified as a metabolite of prothiadene (*I*) (ref.[6]) and was found to be likewise a pharmacologically[7], as well as clinically active antidepressant agent[8]. In the present study it has been used as the starting material of synthesis of a series of N-substituted derivatives with the aim at finding further compounds with antidepressant activity.

Compound *II* was alkylated with allyl bromide in dimethylformamide at room temperature in the presence of sodium carbonate and gave in addition to the quaternary salt *XII* the desired N-allyl derivative *III*. In an analogous alkylation with propargyl bromide benzene was used as the medium and the reaction was carried out without a condensing agent; there was obtained the N-propargyl derivative *IV*.

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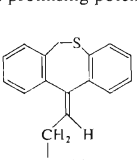
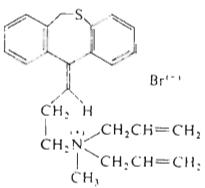
This compound contains in its molecules the N-methylpropargylamine fragment which is typical for a number of compounds having central stimulating and monoamine oxidase inhibiting properties, *cf.* pargyline[9], clorgyline[10], deprenaline[11], compound TZ-650 (ref.[12]) and N-propargyl-1-indanamines[13,14]. For this reason, compound *IV* was considered a promising potential antidepressant agent.



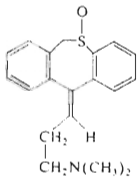
I, R = CH_3
II, R = H
III, R = $CH_2CH{=}CH_2$
IV, R = $CH_2C{\equiv}CH$
V, R = CH_2CH_2OH
VI, R = $CH_2CH(OH)CH_3$
VII, R = $(CH_2)_3OH$
VIII, R = $(CH_2)_3OCOCH_3$
IX, R = $(CH_2)_2OCO(CH_2)_8CH_3$
X, R = $CH_2CHOCO(CH_2)_8CH_3$ (CH_3 branch)
XI, R = $(CH_2)_3OCO(CH_2)_8CH_3$

Reactions of compound *II* with 2-chloroethanol, 1-chloropropan-2-ol and 3-chloropropanol in dimethylformamide at 130–135°C in the presence of sodium carbonate resulted in the amino alcohols *V*–*VII*. Compound *VI* has also been prepared by a reaction of compound *II* with 1,2-epoxypropane in boiling methanol. With the exception of opipramol[15], tricyclic amino alcohols did not find use as antidepressants. Our products *V*–*VII* were used as starting materials of the synthesis of esters, for which the properties of long-acting antidepressants, especially in depot forms for intramuscular administration of solutions of bases in oils, had to be considered. The patent literature[16,17] reports about such properties of the esters of opipramol (1-[3-(dibenz[*b*,*f*]azepin-5-yl)propyl]-4-(2-hydroxyethyl)piperazine) with fatty acids: after intramuscular administration of doses of 50–500 mg in sesame oil once in 1–2 weeks they should be effective as depot antidepressant and anxiolytic agents. It is a unique literature report which never found a confirmation in clinical literature. In our case we acylated in the first line the alcohol *VII* with acetyl chloride in chloroform in the presence of triethylamine and obtained the acetate *VIII*, which was transformed to the rather well water-soluble hydrochloride. The amino alcohols *V*–*VII* were further acylated with decanoyl chloride[18] in chloroform at room temperature; the oily bases *IX*–*XI* obtained were characterized as crystalline oxalates which were used in two cases (*IX*, *X*) for pharmacological evaluation after oral administration. In the third case (*XI*) the oxalate was transformed to the pure base,

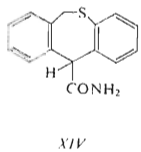
whose identity was confirmed by the ^{1}H NMR spectrum and which was used for preparing the solution in oil for intramuscular adminstration. The ester *XI* has also been prepared by a reaction of the alcohol *VII* with decanoyl chloride in pyridine at room temperature; in this case the base *XI* was purified by chromatography.



XII



XIII



XIV

In the experimental part the preparation of a salt of prothiadene (*I*) (ref.[1,2]) with 4,4'-methylenebis(3-hydroxy-2-naphthoic) acid (pamoic, embonic acid) is described. The salts of pharmaceutically interesting bases with this acid are characterized by a very low solubility in water and they are devoid of the usual and unpleasent bitter taste[19]. The S-oxide *XIII*, derived from prothiadene, which is its metabolite, was described in the form of base and succinate[5]; its hydrochloride is described in the Experimental.

The amides derived from some tricyclic systems, which are typical for the structure of antidepressant agents, were shown to have anticonvulsant activity. The examples are dibenzo[*a*,*d*]cycloheptene-5-carboxamide (cytenamide)[20] and its 10,11-dihydro-derivative (cyheptamide)[20,21]. For this reason we have now prepared the amide *XIV* from 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carboxylic acid[22] *via* the acid chloride in the usual way.

Most of the compounds prepared were pharmacologically evaluated in the form of salts, described in the Experimental, as potential antidepressants using methods, described previously[23]. The results of these tests are assembled in Table I including imipramine[24] and prothiadene[1,2,4,25] as standards. The compounds tested were mostly administered parenterally and the doses (in mg/kg) were calculated for the bases. The acute toxicity was estimated in mice on intravenous administration and the usual medium lethal doses (LD_{50}) are given in the Table I. The discoordinating effect of the substances was determined in the rotarod test in mice likewise on intravenous administration and the medium effective doses in the time of maximum effect (ED_{50}) are reported. As a criterion of a non-specific central depressant effect, the influence of compounds on the duration of the thiopental sleeping time in mice was studied; thiopental (40 mg/kg *i.v.*) was administered 10 min after the *i.v.* administration of the tested compound (in a dose corresponding to 20% of the LD_{50} value). The Table I gives multiples of the control group values (thiopental = 1) and their statistical significance (+, $p = 0{\cdot}05$) in comparison with the control group. As criteria

of a potential antidepressant activity, the antireserpine effects in two tests and the anticataleptic activity were determined. The influence on the reserpine ptosis was examined in mice: the tested compounds were administered in a dose of 40 mg/kg intraperitoneally in the interval of 3 h 45 min after the administration of reserpine (4 mg/kg *i.p.*). The tabulated values represent the medium maximum differences of the scores of ptosis before and after the administration of the tested compound and their statistical significance in comparison with the control group is indicated. The tests of the influence on the ulcerogenic effect of reserpine were carried out in rats. The tested compounds were administered in a dose of 50 mg/kg subcutaneously simultaneously with reserpine (5 mg/kg *i.p.*). The tabulated values are again differences of the medium scores of the appearance of ulcerations between the experimental and the control group; their statistical significance is indicated. The anticataleptic activity was evaluated in rats; the catalepsy was elicited by prochlorperazine in a dose of 20 mg/kg *i.p.* and evaluated for 5 h in 1 h intervals. The tested compounds were administered orally in a dose of 100 mg/kg 1 h before prochlorperazine. The Table I reports the percentage of animals (groups by 10 animals) in which the cataleptic reaction was blocked by this premedication (in the prochlorperazine control group the cataleptic effect appeared in 100% animals).

The results given in Table I lead to the following conclusions: The allyl derivative *III* has properties of a tranquillizer. It has a rather strong activity in the rotarod test and out of all compounds of this group it is most potent in potentiating the thiopental sleep. Its antireserpine effect in the test of ptosis is insignificant and it slightly enhances the ulcerogenic effect of reserpine in rats. It is devoid of anticataleptic action. With compounds *IV*—*VIII* some features of activity profile characteristic for tricyclic antidepressants are apparent; all of them, however, are less active than the standards (imipramine and prothiadene). With the propargyl deriv-

TABLE I

Pharmacological properties of the potential antidepressants *III*—*VIII*

Substance	Acute toxicity LD_{50} mg/kg	Rotarod ED_{50} mg/kg	Thiopental potentiation, multiple values	Antireserpine effects		Anti cataleptic effect, per cent of animals
				ptosis, score differences	gastric ulcers, score differences	
Imipramine	30·0	14·0	1·8	$1·4^+$	$2·0^+$	50
I	27·7	5·0	$1·6^+$	$1·6^+$	$1·1^+$	40
III	29·0	7·6	$8·2^+$	0·6	−0·8	0
IV	86·0	20·5	1·1	$0·6^+$	$-1·0^+$	10
V	34·5	15·8	2·4	$1·0^+$	0·2	30
VI	20·5	7·0	1·7	$0·8^+$	0·2	10
VII	35·0	15·5	1·2	$0·7^+$	0·8	20
VIII	41·0	18·5	$3·3^+$	$0·9^+$	0·8	0

ative *IV* the very low central depressant activity is striking and further the contradiction between the significant antireserpine activity in the test of ptosis and the enhancing the ulcerogenic activity of reserpine. The 2-hydroxyethyl derivative *V* resembles most by some of the properties the standards (toxicity, discoordinating effect, thiopental potentiation, antireserpine effect in the test of ptosis, anticataleptic effect); it is, however, practically inactive towards the ulcerogenic effect of reserpine.

Further pharmacological data: Acute toxicity in mice on oral administration; the dose of 100 mg/kg of compounds *V*–*VIII* is nontoxic; the dose of 500 mg/kg of compound *I* is lethal for 70% animals, with compound *VI* for 60% animals, compound *VII* for 40% animals and compound *VIII* for 50%. Compounds *III* and *IV* were tested also for anticataleptic actions towards perphenazine; the results are identical with values in the Table pertaining to prochlorperazine.

Compounds *V*–*VII*, *IX*, *X* and *XIV* were tested by methods of the general pharmacological screening. With compounds *V*–*VII* some additional effects were found. Compound *V*: In concentrations of 0·5–1% it has local anaesthetic effect in the test of corneal anaesthesia on the rabbit's eye; in a dose of 2·5 mg/kg *i.v.* it has a brief hypertensive effect in normotensive rats; in concentrations of 1–10 μg/ml it has spasmolytic effect towards barium chloride contractions of the isolated rat duodenum; in concentrations of 25–50 μg/ml it shows a negatively inotropic effect on the rabbit's heart atria; in doses above 5 mg/kg *i.v.* and in subcutaneous doses of 2·5–5 mg/kg it brings about central excitation in mice which is in some contradiction with the thiopental potentiation found (the mentioned discoordinating effect may be the result of excitation and likewise the antireserpine and anticataleptic activity may be in the same connection). Compound *VI*: In concentrations of 0·1–0·5% the local anaesthetic effect in the test of corneal anaesthesia; brief rises of the blood pressure in rats after a dose of 2 mg/kg *i.v.*; spasmolytic effect towards barium chloride in concentrations of 1–10 μg/ml; negatively inotropic and positively chronotropic effects in concentrations of 5–10 μg/ml; excitation in mice in a dose of 4 mg/kg *i.v.* Compound *VII*: local anaesthetic effect in the test of corneal anaesthesia in concentrations of 0·5 to 1%; a brief rise of blood pressure after a dose of 1 mg/kg *i.v.*; spasmolytic effect towards barium chloride in a concentration of 10 μg/ml; antihistamine effect in the test of histamine detoxication in guinea-pigs after a dose of 0·5 mg/kg *s.c.* Compound *IX* (hydrogen oxalate): LD_{50} above 2 500 mg/kg *p.o.*; the dose screened, D = 300 mg/kg *p.o.*; antihistamine effect in guinea-pigs after a dose of 100 mg/kg *p.o.*; antiarrhythmic effect towards aconitine in rats at the dose D; indication of anticonvulsant effect towards pentetrazole in mice at the dose D; antireserpine effect was not found. Compound *X* (hydrogen oxalate): LD_{50} above 2 500 mg/kg *p.o.*; the dose screened, D = 300 mg/kg *p.o.*; diuretic effect in mice in a dose of 100 mg/kg *p.o.*; antihistamine effect in doses of 100–300 mg/kg *p.o.*; antiarrhythmic effect at the dose D; antireserpine effect was not found. Compound *XIV*: LD_{50} = 2 000 mg/kg *p.o.*;

the dose screened, D = 300 mg/kg *p.o.*; anticonvulsant effect towards pentetrazole in mice, PD_{50} = 140 mg/kg *p.o.*; towards nicotine convulsions, PD_{50} = 214 mg/kg *i.p.*; in the electroshock test, PD_{50} = 116 mg/kg *p.o.* Compound *XI* was tested as a potential depot antidepressant agent in the form of a solution of the base in sunflower oil(1 ml solution contained 20 mg base). In tests in rats (influencing the ulcerogenic effect of reserpine and influencing the perphenazine catalepsy) the compound in intramuscular doses of 100 mg/kg did not show the properties of a tricyclic antidepressant at intervals of 3–7 days after the administration. It was nontoxic in mice in a dose of 600 mg/kg *s.c.*

The substances were also tested for antimicrobiol activity *in vitro* (Dr J. Turinová, bacteriological department of this institute). The microorganisms used and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Mycobacterium tuberculosis* H37Rv, *IX* 50; *Saccharomyces pasterianus*, *III* 100, *IV* 100, *IX* 100, *X* 100; *Trichophyton mentagrophytes*, *III* 50, *IV* 50, *VIII* 100, *IX* 50, *X* 50; *Candida albicans*, *III* 100, *IV* 100, *IX* 100, *X* 100; *Aspergillus niger*, *III* 100, *IV* 100, *IX* 50, *X* 50. The substances were inactive towards *Streptococcus* β-*haemolyticus*, *Streptococcus faecalis* *Staphylococcus pyogenes aureus*, *Pseudomonas aeruginosa*, *Escherichia coli* and *Proteus vulgaris*.

EXPERIMENTAL

The melting points of analytical preparations were determined in the Kofler's block and are not corrected; the samples were dried *in vacuo* of about 70 Pa over P_2O_5 at room temperature or at 77°C. The IR spectra were recorded with a Unicam SP 200G spectrophotometer and most of the ^{1}H NMR spectra with a ZKR 60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel.

(*E*)-11-[3-(N-Allyl-N-methylamino)propylidene]-6,11-dihydrodibenzo[*b*,*e*]thiepin (*III*)

A stirred mixture of 14·1 g *II* (ref.[4]), 5·3 g Na_2CO_3 and 10 ml dimethylformamide was treated dropwise with 6·6 g allyl bromide. The mixture was stirred for 2 h at room temperature, diluted with water and shaken with benzene; three layers were formed. The benzene layer was separated and the basic product was extracted into excessive 5% hydrochloric acid. The solution of the hydrochloride was made alkaline with NH_4OH and the base was isolated by extraction with benzene. The extract was dried with K_2CO_3 and evaporated; 5·6 g (35%) crude oily *III*. Chromatography on a column of 120 g neutral Al_2O_3 (activity II) with elution with benzene yielded the homogeneous product which was neutralized with HCl in a mixture of ethanol and ether and gave the hydrochloride, m.p. 171–173°C (ethanol–ether). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 11·40 (bs, 1 H, NH^+), 6·90–7·50 (m, 8 H, Ar—H), 5·90 (t, J = 7·0 Hz, 1 H, C=CH of propylidene), *c.* 5·90 (m, 1 H, CH= of allyl), 5·38 and 5·32 (2 d, J = 9·0 and 15·0 Hz, 2 H, $=CH_2$ of allyl), 4·75 and 3·30 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·00–3·80 (m, 4 H, CH_2NCH_2), 2·54 (s, 3 H, NCH_3), *c.* 2·40 (m, 2 H, CH_2 in the middle of propylidene). For $C_{21}H_{24}ClNS$ (357·9) calculated: 70·46% C, 6·76% H, 9·91% Cl, 3·91% N, 8·96% S; found: 70·28% C, 6·81% H, 9·95% Cl, 3·95% N, 9·04% S.

The oily layer, which was insoluble in benzene as well as in water, was separated and crystallized after some time of standing; 3·6 g (16%), m.p. 112–116°C (ethanol–acetone–ether). It was identified as N,N-diallyl-N-[3-(6*H*-dibenzo[*b*,*e*]thiepin-11-ylidene)propyl]-N-methylammonium bromide (*XII*). For $C_{24}H_{28}BrNS$ (442·5) calculated: 18·06% Br, 3·17% N, 7·25% S; found: 18·31% Br, 3·02% N, 7·09% S.

(*E*)-11-[3-(N-Methyl-N-propargylamino)propylidene]-6,11-dihydrodibenzo[*b*,*e*]thiepin (*IV*)

A solution of 14·1 g *II* (ref.[4]) in 40 ml benzene was stirred, cooled to 4°C and treated dropwise over 75 min with a solution of 6·6 g propargyl bromide in 5 ml benzene. The mixture was allowed to stand overnight at room temperature, treated with 100 ml water and 15 ml NH_4OH and stirred for 15 min. The mixture was extracted with benzene, the extract was dried with K_2CO_3 and evaporated under reduced pressure. The residue (11·6 g) was chromatographed on a column of 300 g neutral Al_2O_3 (activity II) and benzene eluted in the first fractions 8·0 g (50%) homogeneous oily product. Neutralization with HCl in a mixture of ethanol and ether yielded 5·7 g hydrochloride, m.p. 150–152°C (ethanol–ether). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 11·80 (bs, 1 H, NH^+), 6·80–7·50 (m, 8 H, Ar–H), 5·90 (t, J = 7·0 Hz, 1 H, C=CH), 4·71 and 3·30 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·00–4·00 (m, 5 H, CH_2NCH_2 and C≡CH), 2·65 (s, 3 H, NCH_3), *c.* 2·40 (m, 2 H, CH_2 in the middle of propylidene). For $C_{21}H_{22}ClNS$ (355·9) calculated: 70·86% C, 6·23% H, 9·96% Cl, 3·94% N, 9·01% S; found: 70·66% C, 6·18% H, 10·14% Cl, 3·99% N, 9·17% S.

(*E*)-11-(3-[N-(2-Hydroxyethyl)-N-methylamino]propylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*V*)

A stirred mixture of 28·1 g *II* (ref.[4]), 20 ml dimethylformamide, 10·4 g 2-chloroethanol and 13·7 g Na_2CO_3 was heated to 130°C for 4 h. After standing overnight it was diluted with water and extracted with chloroform. The extract was washed with water and the base was transferred by shaking with an excess of 1 : 2 dilute hydrochloric acid into the aqueous layer. The solution of the hydrochloride was made alkaline with NH_4OH, the base was extracted with chloroform, the extract was dried with K_2CO_3 and evaporated under reduced pressure; 23·4 g (72%) crude oily *V*. Neutralization with oxalic acid dihydrate in acetone gave the hydrogen oxalate, m.p. 172–173°C with decomposition (80% aqueous ethanol). For $C_{22}H_{25}.NO_5S$ (415·5) calculated: 63·57% C, 6·07% H, 3·37% N, 7·72% S; found: 63·65% C, 6·24% H, 3·41% N, 7·49% S.

(*E*)-11-(3-[N-(2-Hydroxypropyl)-N-methylamino]propylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VI*)

A) A mixture of 14·0 g *II* (ref.[4]), 10 ml dimethylformamide, 7·2 g 1-chloropropan-2-ol and 10·8 g Na_2CO_3 was processed similarly like in the preceding case. There were obtained 13·0 g (77%) crude oily base which was neutralized with HCl in a mixture of ethanol and ether. Hydrochloride, m.p. 148–150°C (ethanol–acetone–ether). IR spectrum (KBr): 726, 742, 761 (4 adjacent Ar–H), 1 000, 1 037, **1 067**, **1 146**, 1 240, 1 315, 1 402 (C–O in CHOH), 1 453, 1 464, 1 482 (Ar), 2 670 (NH^+), 3 290 cm^{-1} (OH). ^1H NMR spectrum ($C_5^2H_5N$): δ 6·80–7·50 (m, 8 H, Ar–H), 5·80 (t, J = 7·0 Hz, 1 H, C=CH), 4·74 and 3·30 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 4·50 (m, 1 H, CH–O), 2·40–3·60 (m, 7 H, $CH_2CH_2NCH_2$ and OH), 2·86 (s, 3 H, NCH_3), 1·16 (d, J = 6·0 Hz, 3 H, C–CH_3). For $C_{21}H_{26}ClNOS$ (376·0) calculated: 67·08% C, 6·97% H, 9·43% Cl, 3·73% N, 8·53% S; found: 66·72% C, 7·13% H, 9·42% Cl, 3·61% N, 8·57% S.

B) A solution of 28·1 g *II* (ref.[4]) in 40 ml methanol was stirred and treated dropwise over 10 min with a solution of 9·5 g 1,2-epoxypropane in 20 ml methanol. The mixture was refluxed for 30 min, allowed to stand overnight at room temperature and evaporated *in vacuo*, the residue (33·8 g) was dissolved in 90 ml ethanol, the solution treated with a slight excess of HCl in ether and finally 220 ml ether were added. After 5 days standing 15·0 g (40%) hydrochloride (m.p. 146–149°C) were obtained. The product proved identical with that obtained under *A*).

(*E*)-11-(3-[N-(3-Hydroxypropyl)-N-methylamino]propylidene)-
-6,11-dihydrodibenzo[*b,e*]thiepin (*VII*)

A mixture of 14·0 g *II* (ref.[4]), 10 ml dimethylformamide, 7·2 g 3-chloropropanol and 10·8 g Na_2CO_3 was stirred and heated to 135°C for 2 h. The mixture was processed like in the two preceding cases. There were obtained 10·1 g (60%) oily *VII*. Neutralization of the base in acetone with hydrochloric acid gave the hydrochloride, m.p. 185—187°C (ethanol). IR spectrum (KBr): 736, 775 (4 adjacent Ar—H), 1 048, **1 066**, 1 079, 1 122, 1 255, 1 429 (C—O in CH_2OH), 1 460, 1 470, 1 476 (Ar), 2 525, 2 610, 2 650 (NH^+), 3 348 cm^{-1} (OH). For $C_{21}H_{26}ClNOS$ (376·0) calculated: 67·08% C, 6·97% H, 9·43% Cl, 3·73% N, 8·53% S; found: 66·29% C, 7·10% H, 9·36% Cl, 3·66% N, 8·56% S.

(*E*)-11-(3-[N-(3-Acetoxypropyl)-N-methylamino]propylidene)-
-6,11-dihydrodibenzo[*b,e*]thiepin (*VIII*)

A solution of 8·5 g *VII* and 5·1 g triethylamine in 20 ml chloroform was stirred and slowly treated dropwise with a solution of 3·9 g acetyl chloride in 10 ml chloroform. After standing overnight the mixture was washed with dilute NH_4OH and with water, the solution was dried with K_2CO_3, filtered with charcoal and evaporated under reduced pressure; 9·3 g (93%) crude oily *VIII*. It was dissolved in 30 ml acetone, the solution treated with a slight excess of HCl in ether and diluted with ether. On standing overnight there crystallized 6·2 g hydrochloride, m.p. 154—156°C (ethanol–ether). IR spectrum (KBr): 752, 774 (4 adjacent Ar—H), 1 038, 1 060, **1 236** (C—O in RCOOR'), 1 425 (C—H in NCH_3), 1 472, 1 587 (Ar), 1 736 (RCOOR'), 2 500, 2 580 cm^{-1} (NH^+). For $C_{23}H_{28}ClNO_2S$ (418·0) calculated: 66·08% C, 6·75% H, 8·48% Cl, 3·35% N, 7·67% S; found: 66·05% C, 6·95% H, 8·63% Cl, 3·27% N, 7·65% S.

(*E*)-11-(3-[N-(2-Decanoyloxyethyl)-N-methylamino]propylidene)-
6,11-dihydrodibenzo[*b,e*]thiepin (*IX*)

A solution of 6·5 g *V* in 10 ml chloroform was stirred and treated dropwise with a solution of 6·6 g decanoyl chloride[18] in 5 ml chloroform and the mixture was allowed to stand overnight. It was then stirred for 3 h with 50 ml 4% NH_4OH, the chloroform solution was separated, washed with water, dried (K_2CO_3) and evaporated *in vacuo*. The oily residue (11·3 g) was neutralized with 3·0 g oxalic acid dihydrate in acetone; 8·6 g (76%) hydrogen oxalate, m.p. 122—124°C (acetone). For $C_{32}H_{43}NO_6S$ (569·7) calculated: 67·45% C, 7·61% H, 2·46% N, 5·63% S; found: 67·18% C, 7·79% H, 2·40% N, 5·68% S.

(*E*)-11-(3-[N-(2-Decanoyloxypropyl)-N-methylamino]propylidene)-
-6,11-dihydrodibenzo[*b,e*]thiepin (*X*)

A solution of 8·8 g *VI* in 16 ml chloroform was treated with 8·6 g decanoyl chloride[18] and the mixture processed like in the preceding case. There were obtained 12·0 g (79%) hydrogen oxalate of *X*, m.p. 146—148°C (acetone). For $C_{33}H_{45}NO_6S$ (583·8) calculated: 67·89% C, 7·77% H, 2·40% N, 5·49% S; found: 67·69% C, 7·82% H, 2·62% N, 5·28% S.

(*E*)-11-(3-[N-(3-Decanoyloxypropyl)-N-methylamino]propylidene)-
6,11-dihydrodibenzo[*b,e*]thiepin (*XI*)

A) A solution of 8·8 g *VII* in 16 ml chloroform was treated with 8·6 g decanoyl chloride[18] and the mixture processed similarly like in the preceding two cases. There were obtained 11·2 g

(74%) hydrogen oxalate, m.p. 142–144 °C (acetone). For $C_{33}H_{45}NO_6S$ (583·8) calculated: 67·89% C, 7·77% H, 2·40% N, 5·49% S; found: 67·79% C, 7·54% H, 2·49% N, 5·39% S.

The pure oxalate was decomposed with dilute NH_4OH and the base was isolated by extraction with ether and was used on the one hand for pharmacological testing and for recording the ^1H NMR spectrum on the other (C^2HCl_3): δ 6·80–7·30 (m, 8 H, Ar–H), 5·89 (t, J = 7·0 Hz, 1 H, C=CH), 4·90 and 3·30 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 4·00 (t, J = 6·0 Hz, 2 H, CH_2O), 2·00–2·50 (m, 8 H, $CH_2CH_2NCH_2$ and $COCH_3$), 2·10 (s, 3 H, NCH_3), 1·68 and 1·25 (m and s, 16 H, remaining 7 CH_2 of decanoyl and CH_2 in the middle of propylidene), 0·88 (def. t, 3 H, terminal CH_3 of decanoyl).

B) A solution of 4·6 g *VII* in 21 ml pyridine was slowly treated with 5·1 g decanoyl chloride[18] and the mixture was allowed to stand overnight at room temperature. It was then diluted with water and extracted with ether. The extract was washed with water, $NaHCO_3$ solution, dried with K_2CO_3 and evaporated. The residue was chromatographed on a column of 160 g neutral Al_2O_3 (activity II). Benzene eluted in the first fractions 5·0 g (75%) homogeneous base *XI*; it gave the hydrogen oxalate melting at 142–144° C (acetone), identical with the product obtained under *A*).

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

A solution of the sodium salt of 4,4′-methylenebis(3-hydroxy-2-naphthoic) acid was prepared by stirring 7·8 acid with 1·6 g NaOH in 120 ml water. It was filtered and the filtrate added under vigorous stirring to a solution of 13·2 g hydrochloride of *I* (ref.[2,4]) in 50 ml water. The precipitated salt of *I* was filtered after 30 min standing, washed with water and dried *in vacuo*; 15·0 g (76%) monohydrate containing per 1 molecule of the acid 2 molecules of *I*, m.p. 170°C (softening starting from 128°C). For $C_{61}H_{58}N_2O_6S_2 \cdot H_2O$ (997·2) calculated: 73·45% C, 6·06% H, 2·81% N, 6·43% S; found: 72·99% C, 6·17% H, 2·76% N, 6·40% S.

(*E*)-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin S-Oxide (*XIII*)

The hydrochloride was prepared by dissolving 70 g base *XIII* (ref.[5]) in 150 ml ethanol and by treatment with an excess of HCl in ethanol. The solution was evaporated *in vacuo*, the residue dissolved in 200 ml boiling ethanol, the solution was filtered and the filtrate treated with 100 ml ether. After standing overnight the product was filtered, washed with ethanol and dried *in vacuo*; 72·1 g (92%), m.p. 211–215°C. Analytical sample, m.p. 216–218°C (ethanol–ether). For $C_{19}H_{22}ClNOS$ (347·9) calculated: 65·59% C, 6·37% H, 10·19% Cl, 4·03% N, 9·22% S; found: 65·33% C, 6·35% H, 10·18% Cl, 4·05% N, 9·29% S.

6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-carboxamide (*XIV*)

A mixture of 3·1 g 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carboxylic acid[22] with 20 ml benzene was treated with 2·9 g $SOCl_2$ and the mixture was refluxed for 5 h. Benzene and excess of $SOCl_2$ were evaporated *in vacuo*, the residue was dissolved in 3 ml acetone and the solution was slowly added to 20 ml stirred NH_4OH. After standing overnight the precipitated product was filtered and the mother liquor was processed by evaporation; 2·4 g (75%), m.p. 177·5–179·5°C. Analytical sample, m.p. 179–180°C (ethanol). IR spectrum (Nujol): 752, 761 (4 adjacent Ar–H), 1 493, 1 596, 3 028 (Ar), 1 665 ($RCONH_2$), 3 140, 3 200, 3 245, 3 422 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·90–7·50 (m, 8 H, Ar–H), 6·75 (bs, 2 H, $CONH_2$), 4·95 (s, 1 H, Ar_2CHCO), 4·78 and 3·78 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$). For $C_{15}H_{13}NOS$ (255·3) calculated: 70·56% C, 5·13% H, 5·49% N, 12·56% S; found: 70·38% C, 5·28% H, 5·50% N, 12·68% S.

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