6,11-DIHYDRODIBENZO[*b,e*]THIEPIN-11-THIOL AND -11-ACETIC ACID DERIVATIVES; SOME 2-METHYL-6,11-DIHYDRODIBENZO[*b,e*]THIEPINS; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

Vladimír VALENTA, František KVIS**, Jiří NĚMEC*** and Miroslav PROTIVA

Research Institute for Pharmacy and Biochemistry, 130 00 Prague 3

Received January 23th, 1979

11-Chloro-6,11-dihydrodibenzo[*b,e*]thiepin was transformed *via* the isothiourea *V* to the thiol *IV* which was used for the synthesis of aminoalkyl sulfides *VII* and *VIII* and of the methylpiperazide *X*. The same starting compound was used for alkylating diethyl malonate and *via* the intermediates *XIV* and *XV*, 6,11-dihydrodibenzo[*b,e*]thiepin-11-acetic acid (*XVI*) was obtained, which was converted to the methylpiperazide *XVIII*. Oxime *XIX* and 2-diethylaminoethylimine *XX* were prepared from 2-methyldibenzo[*b,e*]thiepin-11(6*H*)-one (*II*). Reduction of the ketone *II* afforded 2-methyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XII*) giving by treatment with sodium amide and 3-dimethylaminopropyl chloride the amine *XXIII*. In the reaction of 6,11-dihydrodibenzo[*b,e*]-thiepin-11-ol with sodium amide and 3-dimethylaminopropyl chloride, C-alkylation took place in addition to the expected etherification resulting in the diamine *XXII*. Reaction of phthalide with 4-aminothiophenol gave the acid *XXIV* which was transformed to the 3-dimethylaminopropyl ester *XXV* and N-acetyl derivative *XXVI*. Compound *XXVI* was cyclized with zinc chloride to the ketone *III*. Some of the compounds prepared exhibit structurally less specific peripheral and vegetative neurotropic effects (local anaesthetic, spasmolytic) and cardiovascular activity (antiarrhythmic).

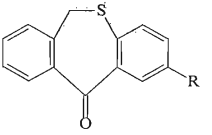
In the present paper, dibenzo[*b,e*]thiepin-11(6*H*)-one (*I*) (ref.[1-5]) and its 2-methyl derivative *II* (ref.[2,4-7]) were used for preparing some new amines of the dibenzo[*b,e*]-thiepin series, for which some types of neurotropic activity could be expected.

Aminoalkyl ethers derived from 6,11-dihydrodibenzo[*b,e*]thiepin-11-ol[8] exhibited a considerable degree of antihistaminic activity[9] inducing the interest in analogous thioethers. 11-Chloro-6,11-dihydrodibenzo[*b,e*]thiepin[10], accessible in two steps from the ketone *I* (ref.[3]), was used as the starting compound of their synthesis. Thiourea was alkylated with this compound which resulted in the hydrochloride of the isothiourea *V*, giving by alkaline hydrolysis 6,11-dihydrodibenzo[*b,e*]thiepin-11-thiol (*IV*). This compound could not be obtained pure and was used for further

* Part CXXXII in the series Neurotropic and Psychotropic Agents; Part CXXXI: This Journal *44*, 2677 (1979).

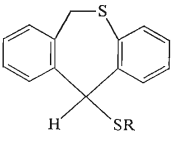
** Department of Technical Development, Léčiva, Prague 10.

*** Affiliated unit at Rosice n/L.



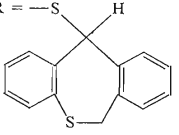
I, R = H
II, R = CH_3
III, R = $NHCOCH_3$

work crude. It is easily oxidized with air oxygen to the crystalline and high-melting disulfide *VI* and attempt at its distillation led to decomposition yielding 6,11-dihydrodibenzo[*b*,*e*]thiepin (*XI*) (ref.[10]) as a crystalline product. Treatment of the crude thiol *IV* with a solution of sodium ethoxide in ethanol gave the sodium salt which reacted with 2-dimethylaminoethyl chloride and 3-dimethylaminopropyl chloride under the formation of the sulfides *VII* and *VIII*. After the termination of our experiments, a paper[11] was published describing similar sulfides and including our



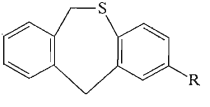
IV, R = H
V, R = C(=NH)NH$_2$

VI, R = —S— (H, S)

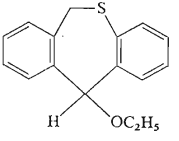


VII, R = $(CH_2)_2N(CH_3)_2$
VIII, R = $(CH_2)_3N(CH_3)_2$
IX, R = $CH_2COOC_2H_5$

X, R = CH_2CON (piperazine) NCH_3



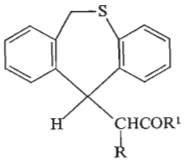
XI, R = H
XII, R = CH_3



XIII

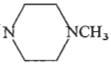
compound *VII*. In the synthesis, however, a different method was used, consisting in the case of compound *VII* in the reaction of 11-chloro-6,11-dihydrodibenzo[*b*,*e*]-thiepin with 2-dimethylaminoethanethiol. Reaction of the sodium salt of *IV* with ethyl bromoacetate yielded the ester *IX* which was heated with 1-methylpiperazine to give the 4-methylpiperazide *X*, isolated as the crystalline maleate.

An attempt to alkylate diethyl malonate with 11-chloro-6,11-dihydrodibenzo[*b*,*e*]-thiepin[10] in ethanol in the presence of sodium ethoxide led only to ethanolysis under the formation of the ethyl ether *XIII*. For enabling the desired reaction, it was necessary to use sodium hydride in an aprotic medium (benzene); in this way the malonic ester *XIV* was obtained. Its alkaline hydrolysis afforded the corresponding malonic acid *XV*. Longer heating in boiling xylene or 1-butanol effects partial decarboxylation; even heating of the acid *XV* to 150°C without any solvent does not result in the complete decarboxylation. This proceeds quantitatively by heating in pyridine in the presence of piperidine and affords 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-acetic acid (*XVI*). This acid was mentioned in patents[12,13] but the synthesis has not been described. Additional compounds described in these patents indicate that the synthesis was different from our procedure. *Via* the acid chloride *XVII*, the 4-methylpiperazide *XVIII* was prepared.



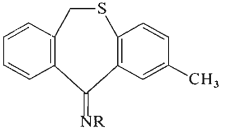
XIV, R = $COOC_2H_5$, $R^1 = OC_2H_5$
XV, R = COOH, R^1 = OH
XVI, R = H, R^1 = OH

XVII, R = H, R^1 = Cl

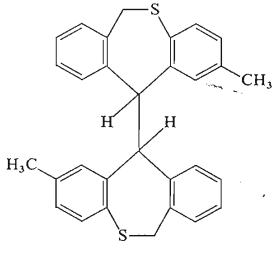
XVIII, R = H, R^1 = 

Heating of the ketone *II* with hydroxylamine hydrochloride in pyridine yielded the oxime *XIX*. Heating of the same ketone with 2-diethylaminoethylamine and titanium tetrachloride in benzene gave the basic imine *XX*. Similar imines were described in patents[14] and claimed to have antidepressant, anticonvulsant and antiparkinsonic activity. The ketone *II* was reduced with zinc in boiling acetic acid to 2-methyl-6,11--dihydrodibenzo[*b*,*e*]thiepin (*XII*) (analogy[10]). The same compound was formed by treatment of 2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[7] with an ethanolic hydrogen chloride solution; we are probably dealing here with a disproportionation reaction (the ketone *II* as the second product was detected chromatographically).

On the other hand, reduction of the just mentioned alcohol with zinc in a heterogeneous boiling system of toluene, ethanol and hydrochloric acid, resulted in a mixture of two oxygen-free substances which was easily separated on the basis of different solubilities in toluene. The minor and toluene-soluble product was identified as compound *XII*. The insoluble and main product, having high melting point, is considered to be compound *XXI* with a doubled molecule (in agreement with the analysis). In an attempt at transforming 2-methyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[7] to the 3-dimethylaminopropyl ether by treatment with a mild excess of sodium amide and 3-dimethylaminopropyl chloride in benzene, an oily base was obtained in a low yield affording a dihydrochloride. The analysis of this salt and the ^{1}H-NMR spectrum of the base indicated that in addition to the desired ether formation, a C-alkylation must have taken place. Carbon atoms 6 and 11 of the skeleton are to be considered; on the basis of the ^{1}H-NMR spectrum, the structure *XXII* was assigned. Alkylation of compound *XII* with sodium amide and 3-dimethylaminopropyl chloride in toluene gave also a basic product, isolated as hydrochloride. In this case too, alkylation in position 6 or 11 is possible; the ^{1}H-NMR spectrum does not represent an unequivocal solution. Only on the basis of analogy with the preceding case and with some cases described earlier[15], structure *XXIII* is prefered for the product.

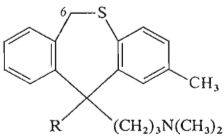


XIX, R = OH
XX, R = $(CH_2)_2N(C_2H_5)_2$

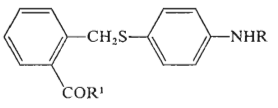


XXI

Heating the sodium salt of 4-aminothiophenol with phthalide[16] in ethanol gave 2-(4-aminophenylthiomethyl)benzoic acid (*XXIV*). The IR spectrum and the course of further reactions of this product excluded the isomeric structure of 2-hydroxymethyl-4'-mercaptobenzanilide. The potassium salt of the acid *XXIV* was treated with 3-dimethylaminopropyl chloride in ethanol resulting in the basic ester *XXV*. Acetylation of the amino acid *XXIV* gave the acetamido acid *XXVI* which was treated with zinc chloride in a mixture of acetic anhydride and acetic acid at 100°C. Cyclization to the ketone *III* took place, the structure of the product having been corroborated by spectra.



XXII, R = $O(CH_2)_3N(CH_3)_2$
XXIII, R = H



XXIV, R = H, R^1 = OH
XXV, R = H, R^1 = $O(CH_2)_3N(CH_3)_2$
XXVI, R = $COCH_3$, R^1 = OH

Some of the compounds prepared were pharmacologically evaluated using methods of the general screening. The results are summarized in Table I. The little soluble substances (*V* and *XVI*), which were administered orally, have low toxicity. Out of the soluble compounds, mostly administered intravenously, *XX* and *XXV* are considerably toxic. The central neurotropic effects are not too significant. High doses exhibit mostly mild excitation (*V*, *VII*, *VIII*) or a two-phase effect, *i.e.* first excitation followed by depression (*X*). A rather significant depressant effect was shown only by the basic ester *XXV* having also incoordinating activity. Most of the compounds potentiate the thiopental sleep; the basic sulfide *VII* is most active in this line being almost equipotent with chlorpromazine. The anticonvulsant effect was shown only by the isothiuronium salt *V* exhibiting towards pentetrazole, as well as towards electroshock approximately 50% of the phenytoine activity.

Most of the compounds exhibit the structurally unspecific local anaesthetic effect, especially in the test of corneal anaesthesia. Compounds *XX* and *XXV* surpass the activity of trimecaine in this test; they also exhibit a high degree of antiarrhythmic activity (against aconitine). The majority of the products elicit spasmolytic action on the isolated rat duodenum. The more structurally specific parasympatholytic effect is most important with the basic sulfide *VII* (about 50% of the atropine activity). The same compound was also the most active one in the test for musculotropic spasmolytic activity and surpassed papaverine in this line; it exhibited also milder but still significant mydriatic and antihistamine actions. From the other effects, the clear antiinflammatory activity of the acid *XVI* is worth mentioning.

The compounds prepared were also tested in the form of the salts described for antimicrobial activity *in vitro* (Dr A. Čapek and Dr J. Turinová, Bacteriological department of this institute). The microorganisms used, numbers of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus* β-*haemolyticus*, *VII* 50, *VIII* 50; *Staphylococcus pyogenes aureus*, *VII* 50, *VIII* 50; *Mycobacterium tuberculosis* H37RV, *VII* 25, *VIII* 25, *X* 50, *XXV* 50; *Saccharomyces pasterianus*, *XXV* 100; *Trichophyton mentagrophytes*, *XXV* 100; *Candida albicans*, *XXV* 100; *Aspergillus niger*, *XXV* 100. Compounds *V*, *XVIII* and *XX* were inactive towards all of the microorganisms tested.

TABLE I

Pharmacological Properties of the Compounds Synthesized (doses in mg/kg unless stated otherwise in the notes)

Compound[a] Code number	Acute toxicity LD_{50}	Dose D[b] Administration	CNS effects ED	Local anaesthesia ED	Spasmolytic effects ED	Cardiovascular and other effects, ED
V VÚFB-10 068	1 250	200 oral	150[c] 200[d,e]	—	—	75[f,g]
VII VÚFB-8 066	50	10 *i.v.*	>10[c] 0·75[h]	1%[i]	0·1[j] 1[k]	25—50[l,m] 7·5[n]; 5·0[o]
VIII VÚFB-10 116	50	10 *i.v.*	>10[c]	1%[i]	1[j]; 5[k]	—
X VÚFB-10 113	62	12 *i.v.*	>12[p] 7·5[h]	>1%[i]	10[j,k]	50[l,m] >12[q]
XVI VÚFB-10 112	>2 500	300 oral	200[h]	—	—	300[r]
XVIII VÚFB-10 114	62	12 *i.v.*	4[h]	—	10[j,k]	10—25[l,m]
XX VÚFB-10 022	15	3 *i.v.*	2[h]	0·25—0·5%[t]	0·5[j] 5[k]	5—10[l,r]; 1[s] 0·75[q]; 15[t]
XXV VÚFB-10 667	12	3 *i.v.*	2[u] 2[v]	0·5%[w] 0·2%[i]	5[j] 10[k]	1—2·5[l,m] 0·2—2·0[g]

[a] The compounds were tested in the form of salts described in the Experimental. [b] Dose used in most of the tests in the general screening programme. [c] CNS effects; a dose eliciting excitation in mice. [d] Anticonvulsant effect; a dose inhibiting significantly convulsions in mice elicited by pentetrazole (for phenytoine as a standard, ED = 100 mg/kg orally). [e] Anticonvulsant effect; a dose protecting 50% mice against the tonic-extensor convulsions of the hind extremities brought about by electroshock (for phenytoine as a standard, ED = 100 mg/kg orally). [f] Hypotensive effect; a dose decreasing the blood pressure of normotensive rats by 10%. [g] Antiarrhythmic effect; a dose prolonging significantly the latency of ventricular extrasystoles in rats, elicited by the infusion of aconitine (for quinidine as a standard, ED = 17·5 mg/kg orally or 7·5 mg/kg *i.v.*). [h] Thiopental potentiation; a dose prolonging the duration of the thiopental sleeping time in mice to 200% of the control value (for chlorpromazine as a standard, ED = 0·5 mg/kg). [i] Corneal anaesthesia; a concentration bringing about in 50% rabbits a complete anaesthesia of the eye cornea (for trimecaine as a standard, ED = 1%). [j] Spasmolytic (parasympatholytic) effect; a concentration in μg/ml exhibiting a reduction of the acetylcholine contractions of the isolated rat duodenum by 50% (for atropine as a standard, ED = 0·05 μg/ml). [k] Spasmolytic (musculotropic) effect; a concentration in μg/ml exhibiting a reduction of barium chloride contractions of the isolated rat duodenum by 50% (for papaverine as a standard, ED = 5 μg/ml). [l] Heart inotropy; a concentration in μg/ml eliciting a decrease of inotropy of the isolated rabbit heart atrium by 25%. [m] Heart frequency; a concentration in μg/ml decreasing the frequency of the

EXPERIMENTAL

The melting points of analytical preparations were determined in the Kofler block and are not corrected; the samples were dried *in vacuo* at 70 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (in KBr unless stated otherwise) with a Unicam SP 200G spectrophotometer and ^{1}H-NMR spectra in $CDCl_3$ with a ZKR-60 (Zeiss, Jena) spectrometer (unless stated otherwise). The homogeneity of the compounds was checked by chromatography on thin layers of alumina or silica gel.

S-(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)isothiourea (*V*)

A mixture of 19·7 g 11-chloro-6,11-dihydrodibenzo[*b,e*]thiepin[10], 6·8 g thiourea and 150 ml ethanol was refluxed for 11 h. It was then diluted with 100 ml ether and allowed to stand for 48 h. The precipitated hydrochloride was filtered, washed with ether and dried *in vacuo*; 18·1 g (70%), m.p. 167—171°C. Analytical sample, m.p. 169—174°C (ethanol–ether). IR spectrum: 745 (4 adjacent Ar—H), 1660 (C=N), 3020 (NH_3^+), 3180 (NH), 3325 cm^{-1} (NH_2). For $C_{15}H_{15}ClN_2S_2$ (322·9) calculated: 55·79% C, 4·68% H, 10·98% Cl, 8·68% N, 19·87% S; found: 55·23% C, 4·63% H, 10·88% Cl, 8·73% N, 19·61% S.

6,11-Dihydrodibenzo[*b,e*]thiepin-11-thiol (*IV*)

A mixture of 26·5 g hydrochloride of *V*, 22·5 g KOH and 30 ml ethanol was refluxed for 90 min. Ethanol was evaporated *in vacuo*, the residue diluted with H_2O, the solution washed with benzene, overlayered with 200 ml ether and acidified under cooling with hydrochloric acid. The product was extracted with ether, the extract was dried with $MgSO_4$ and evaporated. The residue (15·8 g, 79%) is the crude oily *IV* which was used for further work in this form.

The aqueous layer containing a solid substance was filtered and the by-product (2·5 g) was purified by crystallization from benzene, m.p. 198°C with decomposition. The analysis identified the product as bis(6,11-dihydrodibenzo[*b,e*]thiepin-11-yl) disulfide (*VI*). For $C_{28}H_{22}S_4$ (486·7) calculated: 69·09% C, 4·56% H, 26·35% S; found: 69·43% C, 4·65% H, 26·37% S.

◄

isolated rabbit heart atrium by 25%. [n] Mydriatic effect; an *i.p.* dose exhibiting the increase of mice eye pupil diameter by 100% (for atropine as a standard, ED = 0·17 mg/kg *i.p.*) — [o] Antihistamine effect; an *s.c.* dose protecting 50% guinea-pigs from the lethal effect of histamine in a dose of 5 mg/kg (for mebrophenhydramine as a standard, ED = 0·25 mg/kg *s.c.*). [p] CNS effect; the dose given exhibited first excitation in mice followed by depression. [q] Anticoagulant action; a dose prolonging the bleeding time in mice to 200% of the control value (for heparine as a standard, ED = 1 mg/kg *i.v.*). [r] Antiinflammatory effect; a dose inhibiting significantly over 24 h the development of the rat hind limb oedema elicited by subplantar administration of 0·1 ml 10% kaolin suspension (for phenylbutazone as a standard, ED = 75 mg/kg). [s] Hypertensive effect; a dose elevating the blood pressure of normotensive rats by 20% for at least 30 s. [t] Antiarrhythmic effect; an *i.p.* dose protecting 50% mice from the occurrence of ventricular fibrillations elicited by inhalation of chloroform. [u] CNS effect; the dose given has a depressant action in mice, higher doses, on the contrary, increase the activity and reactivity. [v] Incoordinating effect in the rota-rod test in mice; a dose exhibiting ataxia in 50% animals. [w] Local anaesthetic effect; a concentration bringing about a complete anaesthesia in 50% guinea-pigs in the test of infiltration anaesthesia.

An attempt at distillation of 4·5 g crude thiol *IV in vacuo* gave 1·75 g distillate (b.p. 144°C/70 Pa) which solidified on cooling and was recrystallized from a mixture of cyclohexane and light petroleum, m.p. 102·5—103·5°C. Analysis, the ^{1}H-NMR spectrum and comparison with the authentic product[10] enabled the identification as 6,11-dihydrodibenzo[*b,e*]thiepin (*XI*). ^{1}H-NMR spectrum: δ 7·14 and 6·96 (2 s, 8 H, Ar—H), 4·19 and 4·05 (2 s, 4 H, $ArCH_2S$ and $ArCH_2Ar$). For $C_{14}H_{12}S$ (212·3) calculated: 79·19% C, 5·71% H, 15·10% S; found: 79·02% C, 5·76% H, 14·94% S. The authentic sample of *XI* (ref.[10]) melted at 103—104°C; the mixed melting point of both samples did not show depression.

11-(2-Dimethylaminoethylthio)-6,11-dihydrodibenzo[*b,e*]thiepin (*VII*)

A solution of 8·7 g crude *IV* in 30 ml ether was added to a solution of sodium ethoxide (0·83 g Na, 30 ml ethanol), the mixture was stirred for 15 min and treated with a solution of 7·8 g 2-dimethylaminoethyl chloride in 30 ml ether. The mixture was refluxed for 6 h, diluted with 150 ml benzene and washed with H_2O. The basic product was extracted from the organic layer into dilute hydrochloric acid, the solution of the hydrochloride was made alkaline with 5M-NaOH and the base extracted with benzene. Processing of the extract gave 8·1 g (72%) oil which was dissolved in 30 ml ethanol and the solution neutralized with a solution of HCl in ether; 8·1 g hydrochloride, m.p. 194—200°C. Analytical sample, m.p. 201—202°C (ethanol–ether). For $C_{18}H_{22}ClNS_2$ (352·0) calculated: 61·42% C, 6·30% H, 10·07% Cl, 3·98% N, 18·23% S; found: 61·58% C, 6·46% H, 10·19% Cl, 4·06% N, 18·37% S. The literature[11] described the preparation of *VII* by a different method; the product was characterized as a maleate only.

11-(3-Dimethylaminopropylthio)-6,11-dihydrodibenzo[*b,e*]thiepin (*VIII*)

A reaction of 3·0 g crude *IV*, 1·8 g 3-dimethylaminopropyl chloride and sodium ethoxide (from 0·28 g Na) in a mixture of 10 ml ethanol and 22 ml ether was carried out similarly like in the preceding case. There were obtained 3·3 g (82%) oily base, transformed into 2·8 g hydrochloride, m.p. 208—208·5°C (ethanol–ether). For $C_{19}H_{24}ClNS_2$ (366·0) calculated: 62·35% C, 6·61% H, 9·69% Cl, 2·83% N, 17·52% S; found: 62·34% C, 6·68% H, 9·75% Cl, 3·98% N, 17·15% S.

11-(Ethoxycarbonylmethylthio)-6,11-dihydrodibenzo[*b,e*]thiepin (*IX*)

Crude *IV* (15·8 g) was transformed to the sodium salt by treatment with sodium ethoxide (from 1·5 g Na) in a mixture of 75 ml ethanol and 40 ml ether. A solution of 11·0 g ethyl bromoacetate in 10 ml ethanol was added dropwise under stirring and the mixture refluxed for 3 h. The solvents were evaporated *in vacuo*, the residue decomposed with H_2O and extracted with benzene. The extract was washed with 5% NaOH and H_2O, dried with $MgSO_4$ and evaporated *in vacuo*; 14·4 g (67%), m.p. 56—59°C. Analytical sample, m.p. 61—62°C (cyclohexane–light petroleum). IR spectrum: 742, 766 (4 adjacent Ar—H), 1160, 1297, 1742 (COOR), 1485, 3030 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 6·85—7·30 (m, 8 H, Ar—H), 5·44 and 3·57 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 5·38 (s, 1 H, ArCHAr), 4·06 (q, J = 7·0 Hz, 2 H, OCH_2), 2·99 (s, 2 H, SCH_2CO), 1·25 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{18}H_{18}O_2S_2$ (330·5) calculated: 65·42% C, 5·49% H, 19·41% S; found: 65·46% C, 5·68% H, 19·51% S.

11-(4-Methylpiperazinocarbonylmethylthio)-6,11-dihydrodibenzo[*b,e*]thiepin (*X*)

A mixture of 14·4 g *IX* and 14·0 g 1-methylpiperazine was heated for 13 h in a bath of 140°C, dissolved in 100 ml chloroform, the solution washed with H_2O and the basic product transferred

by shaking with an excess of dilute hydrochloric acid into the aqueous phase. The obtained solution of the hydrochloride was made alkaline with 5M-NaOH and extracted with chloroform. Processing of the extract afforded 5·0 g (30%) oily base giving by treatment with 1·65 g maleic acid in a mixture of ethanol and ether 4·4 g hydrogen maleate, m.p. 147—150°C. Analytical sample, m.p. 150—151·5°C (ethanol–ether). For $C_{25}H_{28}N_2O_5S_2$ (500·6) calculated: 59·97% C, 5·64% H, 5·60% N, 12·81% S; found: 59·84% C, 5·76% H, 5·59% N, 12·78% S.

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

A mixture of sodium ethoxide (0·6 g Na and 12 ml ethanol), 4·5 g diethyl malonate, 6·4 g 11-chloro-6,11-dihydrodibenzo[*b,e*]thiepin[10] and 20 ml benzene was stirred and heated to 60—70°C for 3 h. The solvents were evaporated *in vacuo*, the residue decomposed with H_2O and extracted with benzene. The extract was washed with dilute NaOH and H_2O, dried ($MgSO_4$) and distilled; 2·4 g (36%), b.p. 149—150°C/53 Pa. IR spectrum (film): 755 (4 adjacent Ar—H), 1 088 (R—O—R), 1 470, 1 575, 1 595 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 8 H, Ar—H), 5·51 (s, 1 H, Ar_2CHO), 4·70 and 4·00 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 3·52 (q, J = 7·0 Hz, 2 H, OCH_2), 1·26 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{16}H_{16}OS$ (256·3) calculated: 74·98% C, 6·29% H, 12·48% S; found: 74·46% C, 6·79% H, 11·95% S.

Diethyl (6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)malonate (*XIV*)

A solution of 37 g diethyl malonate in 100 ml benzene was added dropwise to a stirred suspension of 5·5 g NaH in 600 ml benzene. The mixture was stirred for 30 min at 50°C and then treated dropwise with a solution of 44 g 11-chloro-6,11-dihydrodibenzo[*b,e*]thiepin[10] in 250 ml benzene. The mixture was refluxed for 5 h, allowed to stand overnight, washed with H_2O, dried with $MgSO_4$, evaporated *in vacuo* and the residue crystallized from a mixture of 25 ml cyclohexane and 10 ml ethanol; 40·0 g (60%), m.p. 93—99°C. Analytical sample, m.p. 100—101°C (cyclohexane–ethanol). IR spectrum: 749, 762 (4 adjacent Ar—H), 1 155, 1 207 (C—O—C), 1 500 (Ar), 1 745 cm^{-1} (COOR). ^{1}H-NMR spectrum: δ 6·80—7·40 (m, 8 H, Ar—H), 4·50—5·60 (m, 4 H, $ArCH_2S$ and Ar_2CH—CH), *c.* 4·00 (m, 4 H, 2 OCH_2), 1·10 (def. t, 6 H, 2 CH_3). For $C_{21}H_{22}O_4S$ (370·5) calculated: 68·08% C, 5·98% H, 8·66% S; found: 68·25% C, 5·94% H, 8·72% S.

(6,11-Dihydrodibenzo[*b,e*]thiepin-11-yl)malonic Acid (*XV*)

A solution of 37·9 g *XIV* in 300 ml ethanol was mixed with a solution of 145 g KOH in 145 ml H_2O and the mixture was refluxed for 3·5 h. Ethanol was distilled off, the residue diluted with 500 ml H_2O and the solution washed with benzene. The aqueous layer was filtered with charcoal while hot and the filtrate acidified with 185 ml hydrochloric acid. After standing overnight, the product was filtered, washed with water and dried *in vacuo*; 31·6 g (93%) monohydrate of *XV*, m.p. 165—167°C. Purification by repeating the precipitation from the solution of sodium salt with hydrochloric acid did not raise the melting point. IR spectrum (Nujol): 750, 761 (4 adjacent Ar-H), 895, 910, 1 218, 1 648, 1 693, 1 731, 2 530 cm^{-1} (COOH). ^{1}H-NMR spectrum (Tesla BS 487C, 80 MHz, CD_3SOCD_3): δ 10·45 (bs, COOH and H_2O), 6·80—7·30 (m, 8 H, Ar—H), 4·99 and 4·13 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 4·59 (d, J = 5·0 Hz, 1 H, Ar_2CH), 4·41 (d, J = 5·0 Hz, 1 H, COCHCO). For $C_{17}H_{16}O_5S$ (332·4) calculated: 61·42% C, 4·85% H, 9·65% S; found: 61·09% C, 4·17% H, 9·28% S.

Crystallization from ethanol gave a solvate with ethanol, m.p. 112—115°C. ^{1}H-NMR spectrum (CD_3SOCD_3) exhibits signals at 3·40 (q) and 1·05 (t) ppm corresponding to CH_2 and CH_3 of ethanol. For $C_{19}H_{20}O_5S$ (360·4) calculated: 63·31% C, 5·59% H, 8·89% S; found: 63·15% C, 5·24% H, 9·44% S.

6,11-Dihydrodibenzo[*b,e*]thiepin-11-acetic Acid (*XVI*)

A mixture of 8·2 g monohydrate of *XV*, 15 ml pyridine and 1 ml piperidine was refluxed for 2·5 h and the hot solution was poured into 80 ml 5M-HCl at 90°C under stirring. After standing overnight, the precipitated product was filtered, washed with H_2O and dried *in vacuo*; 6·8 g (100%), m.p. 209·5—212°C. Analytical sample m.p. 209·5—212·5°C (methanol). IR spectrum: 730, 743, 757 (4 adjacent Ar—H), 942 (COOH), 1265 (C—O), 1715, 2580 cm^{-1} (COOH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 6·85—7·50 (m, 8 H, Ar—H), 4·94 (t, J = 7·0 Hz, 1 H, Ar_2CH), 4·77 and 3·92 (ABq), J = 16·0 Hz, 2 H, $ArCH_2S$), 3·25 (d, J = 7·0 Hz, 2 H, CH_2CO). For $C_{16}H_{14}O_2S$ (270·4) calculated: 71·08% C, 5·22% H, 11·86% S; found: 70·76% C, 5·29% H, 12·09% S. The literature[12,13] mentioned the acid *XVI* without describing its synthesis; a m.p. of 208—209°C was reported.

6,11-Dihydrodibenzo[*b,e*]thiepin-11-acetic Acid Chloride (*XVII*)

A suspension of 3·0 g *XVI* in 20 ml benzene was stirred and treated dropwise with a solution of 3·15 g $SOCl_2$ in 5 ml benzene and the mixture was stirred for 2 h at 60—70°C. Volatile components were evaporated *in vacuo* and the residue was crystallized from a mixture of cyclohexane and light petroleum; 2·9 g (88%), m.p. 108—114°C. Analytical sample, m.p. 112—115°C (cyclohexane–light petroleum). IR spectrum: 740, 749, 774 (4 adjacent Ar—H), 1800 cm^{-1} (COCl). ^{1}H-NMR spectrum: δ 6·80—7·20 (m, 8 H, Ar—H), 4·92 (t, J = 8·0 Hz, 1 H, Ar_2CH), 4·51 and 3·80 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·80 (*d*, J = 8·0 Hz, 2 H, CH_2COCl). For $C_{16}H_{13}$·ClOS (288·8) calculated: 66·54% C, 4·53% H, 12·28% Cl, 11·11% S; found: 66·84% C, 4·76% H, 11·93% Cl, 11·02% S.

11-(4-Methylpiperazinocarbonylmethyl)-6,11-dihydrodibenzo[*b,e*]thiepin (*XVIII*)

A suspension of 8·7 g *XVII* in 50 ml benzene was stirred and treated over 20 min with a solution of 6·0 g 1-methylpiperazine in 15 ml benzene, added dropwise. The mixture was stirred for 3·5 h at 50°C and allowed to stand overnight. It was then washed with H_2O and the basic product extracted into dilute hydrochloric acid. The solution of the hydrochloride was made alkaline with 10% NaOH and the base extracted with benzene. Processing of the extract gave 8·4 g (80%) oily *XVIII*. Hydrogen maleate, m.p. 174—174·5°C (ethanol–ether). For $C_{25}H_{28}N_2O_5S$ (468·6) calculated: 64·08% C, 6·02% H, 5·98% N, 6·85% S; found: 63·82% C, 6·45% H, 5·78% N, 7·19% S.

11-Hydroximino-2-methyl-6,11-dihydrodibenzo[*b,e*]thiepin (*XIX*)

A mixture of 12·0 g *II* (ref.[6]), 35 g NH_2OH.HCl and 100 ml pyridine was refluxed for 24 h. After cooling, it was diluted with 100 ml ethanol and then with H_2O. After standing overnight, the precipitated product was filtered, washed with water and dried *in vacuo*; 9·6 g (76%), m.p. 208—214°C. Analytical sample, m.p. 226—231°C (ethanol). UV spectrum: λ_{max} 232 nm (log ε 4·30), 261 nm (4·00), 320 nm (3·41). IR spectrum: 770, 812 (Ar—H), 1477, 1605 (Ar), 1645 (C=N), 3200 cm^{-1} (OH). For $C_{15}H_{13}NOS$ (255·3) calculated: 70·58% C, 5·13% H, 5·48% N, 12·55% S; found: 70·54% C, 5·25% H, 5·39% N, 12·61% S.

11-(2-Diethylaminoethylimino)-2-methyl-6*H*-dibenzo[*b,e*]thiepin (*XX*)

A stirred mixture of 24 g *II* (ref.[6]), 58 g 2-diethylaminoethylamine and 250 ml benzene was treated dropwise with a solution of 12·4 g $TiCl_4$ in 50 ml benzene and the mixture was refluxed for 8 h. After cooling, the mixture was decomposed with dilute NH_4OH and the solid was filtered

off. The benzene layer of the filtrate was separated, washed with water and the basic product was extracted into dilute hydrochloric acid. The aqueous solution was made alkaline with NH_4OH and the base extracted with benzene. The extract was dried with Na_2SO_4, evaporated, the residue was dissolved in 50 ml ethanol and the solution acidified with an ethanolic HCl solution. Addition of ether precipitated the dihydrochloride; 23·7 g (74%), m.p. 166—180°C. Analytical sample, m.p. 186°C (ethanol). For $C_{21}H_{28}Cl_2N_2S$ (410·4) calculated: 61·42% C, 6·88% H, 17·27% Cl, 6·82% N, 7·81% S; found: 61·28% C, 7·15% H, 17·85% Cl, 6·82% N, 7·89% S.

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

A. A mixture of 2·4 g *II* (ref.[6]), 2·4 g Zn and 40 ml acetic acid was refluxed for 1 h. It was filtered while hot and the filtrate was diluted with water and acidified with hydrochloric acid. The crude product was filtered, washed with H_2O and dried *in vacuo*; 1·9 g (84%), m.p. 102—105°C. Analytical sample, m.p. 105·5—106°C (ethanol). ^{1}H-NMR spectrum: δ 6·50—7·20 (m, 7 H, Ar—H), 4·05 and 3·94 (2 s, 4 H, $ArCH_2S$ and $ArCH_2Ar$), 2·12 (s, 3 H, CH_3). For $C_{15}H_{14}S$ (226·3) calculated: 79·65% C, 6·19% H, 14·15% S; found: 79·68% C, 6·48% H, 14·06% S.

B. A solution of 20·0 g 2-methyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol[7] in 50 ml 20% ethanolic HCl solution was stirred for 2 h at room temperature. Ethanol was evaporated and the residue slightly diluted with acetone. There crystallized 5·5 g substance which proved identical with *XII*, m.p. 104—106°C (acetone). TLC of a sample of the mother liquor proved the presence of the ketone *II*.

Bis(2-methyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-yl) (*XXI*)

A stirred and refluxing mixture of 24·1 g 2-methyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol[7], 100 ml toluene, 50 ml ethanol and 50 ml hydrochloric acid was slowly treated with 25 g amalgamated Zn and the mixture was refluxed for 2 h. After cooling, the separated solid was filtered and the organic product isolated from it by extraction with pyridine. Evaporation gave 14·2 g (63%) crude *XXI* which was recrystallized from a mixture of pyridine, ethanol and water; m.p. 294 to 296°C. For $C_{30}H_{26}S_2$ (450·5) calculated: 79·95% C, 5·82% H, 14·23% S; found: 79·97% C, 6·01% H, 14·17% S. The toluene layer of the filtrate was separated, washed with H_2O, dried (Na_2SO_4) and evaporated. The residue represented 5·2 g needles melting at 105—106°C, identified by comparison with the authentic product as *XII*.

2-Methyl-11-(3-dimethylaminopropoxy)-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo-[*b,e*]thiepin (*XXII*)

2-Methyl-6,11-dihydrodibenzo[*b,e*]thiepin-11-ol[7] (24·1 g) was added to a suspension of 4·7 g powdered $NaNH_2$ in 100 ml benzene and the mixture was refluxed for 2 h. The red solution was treated with 18 g 3-dimethylaminopropyl chloride, refluxed for 5 h, allowed to stand overnight and decomposed with H_2O. The benzene layer was separated and the basic product extracted into diluted hydrochloric acid. The aqueous solution was made alkaline with NH_4OH and the base isolated by extraction with ether. Processing of the extract gave an oily base which was transformed by treatment with hydrogen chloride in ethanol to the dihydrochloride; 4·2 g (9%), m.p. 230—235°C. Analytical sample, m.p. 255°C (ethanol–ether). For $C_{25}H_{38}Cl_2N_2OS$ (485·5) calculated: 61·84% C, 7·89% H, 14·61% Cl, 5·77% N, 6·60% S; found: 62·39% C, 7·90% H, 14·58% Cl, 5·77% N, 6·31% S.

A sample of the salt was decomposed with NH_4OH and the pure base isolated by extraction with ether (oil). ^{1}H-NMR spectrum: δ 8·60—9·00, 8·00—8·40 and 7·30—7·65 (3 m, 7 H, Ar—H),

4·16 (t, J = 6·0 Hz, 2 H, OCH_2), 2·74 (ABq, J = 15·0 Hz, 2 H, $ArCH_2S$), 2·26 and 2·06 (2 s, 12 H, 2 CH_3NCH_3), 2·51 (s, 3 H, Ar—CH_3), 1·64 (m, 2 H, CH_2 in the middle of the 3-dimethylaminopropyl chain), 2·00—2·50 (m, 8 H, remaining 4 CH_2).

2-Methyl-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XXIII*)

A mixture of 4·0 g *XII*, 2·5 g $NaNH_2$ and 50 ml toluene was refluxed for 6 h. The red solution was treated with 5·5 g 3-dimethylaminopropyl chloride and refluxed for 1 h. After standing overnight, it was decomposed with H_2O, the organic layer was separated and the basic product extracted into dilute hydrochloric acid. The aqueous solution of the hydrochloride was made alkaline with NH_4OH and the base extracted with ether. Processing of the extract gave the oily base which was transformed by treatment with ethanolic HCl and by addition of ether to the hydrochloride. It crystallized from a mixture of ethanol and ether as a hemihydrate; 1·5 g (24%), m.p. 211—214°C. ^{1}H-NMR spectrum (CD_3SOCD_3): δ 6·70—7·40 (m, 7 H, Ar—H), *c.* 4·20 (m, 3 H, $ArCH_2S$ and Ar_2CH), 3·15 (t, 2 H, CH_2N), 2·66 (s, 6 H, CH_3NCH_3), 2·20 (s, 3 H, Ar—CH_3), *c.* 1·75 (m, 4 H, remaining 2 CH_2 in the side chain). For $C_{20}H_{26}ClNS + 0{\cdot}5\ H_2O$ (356·9) calculated: 67·30% C, 7·63% H, 9·93% Cl, 3·92% N, 8·98% S; found: 67·91% C, 7·83% H, 10·22% Cl, 3·96% N, 9·38% S.

2-(4-Aminophenylthiomethyl)benzoic Acid (*XXIV*)

A solution of sodium ethoxide was prepared from 200 ml ethanol and 11·1 g Na, 60 g 4-aminothiophenol were added and the refluxing solution was treated with 64·3 g phthalide[16]. The mixture was refluxed for 8 h and poured into 2 l H_2O. The solution was filtered with charcoal and the filtrate acidified with acetic acid. The separated solid was filtered, washed with water and dried *in vacuo*; 93 g (72%), m.p. 130—145°C. Analytical sample, m.p. 152—156°C (ethanol). IR spectrum: 720 and 828 (4 and 2 adjacent Ar—H), 970, 1260 (COOH), 1505, 1608 (Ar), 1705 (ArCOOH), 3335 and 3405 cm^{-1} (NH_2). For $C_{14}H_{13}NO_2S$ (259·3) calculated: 64·86% C, 5·05% H, 5·40% N, 12·35% S; found: 64·88% C, 5·20% H, 5·39% N, 12·95% S.

3-Dimethylaminopropyl 2-(4-Aminophenylthiomethyl)benzoate (*XXV*)

XXIV (2·6 g) was added to a solution of 0·6 g KOH in 30 ml ethanol and the suspension of the potassium salt was treated with 2·0 g 3-dimethylaminopropyl chloride. The mixture was refluxed for 8 h and evaporated. The residue was treated with dilute NH_4OH and the base isolated by extraction with ether. The extract was washed with H_2O, dried and evaporated. The remaining oil was dissolved in ethanol and the solution acidified with ethanolic HCl giving the dihydrochloride which proved to be a monohydrate; 3·3 g (76%), m.p. 150—155°C. Analytical sample, m.p. 170°C (ethanol). IR spectrum (Nujol): 768, 811 (4 and 2 adjacent Ar—H), 1257 (C—O—C), 1495, 1576, 1600 (Ar), 1712 (ArCOOR), 2600, 2740 (NH^+), 3410 cm^{-1} (H_2O). For $C_{19}H_{26}\cdot Cl_2N_2O_2S + H_2O$ (435·4) calculated: 52·41% C, 6·48% H, 16·29% Cl, 6·44% N, 7·36% S; found: 52·40% C, 6·24% H, 16·74% Cl, 6·32% N, 7·39% S.

2-(4-Acetamidophenylthiomethyl)benzoic Acid (*XXVI*)

A mixture of 2·6 g *XXIV*, 30 ml acetic acid and 2·6 g acetic anhydride was stirred for 30 min at 70°C and then diluted with H_2O. After standing overnight, the separated product was filtered, washed with water and dried *in vacuo*; 2·7 g (90%), m.p. 177—181°C. Analytical sample, m.p. 182°C (acetone). The product proved to be a hemihydrate. IR spectrum: 760, 823 (4 and 2 adjacent Ar—H), 920, 1273 (COOH), 1490, 1595 (Ar), 1520, 1534, 1572 (CONH), 1670 (ArCOOH,

CONH), 2520, 2645 (COOH), 3000 (COOH and H_2O), 3300 cm^{-1} (NH). ^{1}H-NMR spectrum (C_5D_5N): δ 10·65 (bs, 1 H, COOH), 10·54 (bs, 1 H, NHCO), 8·15 (m, 1 H, 6-H), 7·00—7·80 (m, 7 H, remaining Ar—H), 4·70 (s, 2 H, $ArCH_2S$), 1·98 (s, 3 H, $COCH_3$). For $C_{16}H_{15}NO_3S$ + + 0·5 H_2O (310·4) calculated: 61·92% C, 5·20% H, 4·51% N, 10·33% S; found: 61·62% C, 4·94% H, 4·38% N, 10·51% S.

2-Acetamidodibenzo[*b*,*e*]thiepin-11(6*H*)-one (*III*)

A mixture of 3·0 g *XXVI*, 5·0 ml acetic acid, 5·0 ml acetic anhydride and 3·0 g anhydrous $ZnCl_2$ was stirred and heated for 2 h to 100°C. It was then poured into 100 ml water and extracted with benzene. The extract was washed with dilute NaOH and H_2O, dried and evaporated; 0·45 g (17%), m.p. 198—199°C. Analytical sample, m.p. 199—201°C (ethanol). UV spectrum: λ_{max} 262 nm (log ε 4·48), 362 nm (3·48). IR spectrum: 733, 767, 833, 856 (4 and 2 adjacent and solitary Ar—H), 1525, 1652 (ArNHCO), 1575, 1592, 1602 (Ar), 1636 (ArCOAr), 3248 cm^{-1} (NH). For $C_{16}H_{13}NO_2S$ (283·3) calculated: 67·84% C, 4·63% H, 4·95% N; found: 67·71% C, 4·75% H, 4·95% N.

The authors are indebted to Drs E. Svátek and J. Holubek, Department of physical chemistry of this institute, for recording and interpretations of the spectra, to Mrs M. Vlková for the technical assistance with the syntheses, and finally to Mrs J. Komancová, Mrs V. Šmídová, Mrs J Kropáčová, Mrs A. Slavíková, Mrs E. Volková, Mr M. Čech and Mr. K. Havel, Department of analytical chemistry of this institute, for carrying out the analyses.

REFERENCES

1. Stach K., Spingler H.: Angew. Chem. *74*, 31 (1962).
2. Protiva M., Rajšner M., Seidlová V., Adlerová E., Vejdělek Z. J.: Experientia *18*, 326 (1962).
3. Rajšner M., Protiva M.: Česk. Farm. *11*, 404 (1962).
4. Stach K., Spingler H.: Monatsch. Chem. *93*, 889 (1962).
5. Gadient F., Jucker E., Lindenmann A., Taeschler M.: Helv. Chim. Acta *45*, 1860 (1962).
6. Rajšner M., Seidlová V., Protiva M.: Česk. Farm. *11*, 451 (1962).
7. Rajšner M., Metyš J., Svátek E., Protiva M.: This Journal *34*, 1015 (1969).
8. Protiva M., Rajšner M., Adlerová E., Seidlová V., Vejdělek Z. J.: This Journal *29*, 2161 (1964).
9. Metyšová J., Metyš J., Votava Z.: Arzneim.-Forsch. *15*, 524 (1965).
10. Seidlová V., Rajšner M., Adlerová E., Protiva M.: Monatsh. Chem. *96*, 650 (1965).
11. Dostert P., Jalfre M.: Eur. J. Med. Chem.-Chim. Ther. *9*, 259 (1974).
12. Winter W., Thiel M., Stach K., Schaumann W., Ribbentrop A. (C. F. Boehringer & Soehne): Fr. 1,547.207 (Ger. Appl. 16.12. 66); Swiss 493 470; Neth. Appl. 67/17.154.
13. Winter W., Fauland E., Stach K., Schmidt F. H., Aumueller W. (C. F. Boehringer & Soehne): S. African 68/1636 (Ger. Appl. 15.03.67); Neth. Appl. 68/3656; Ger. 1,618.112; Chem. Abstr. *70*, 68 204 (1969); *84*, 180 092 (1976).
14. Dostert P., Kyburz E. (F. Hoffmann-La Roche & Co.): Ger. Offen. 2,150.079 (Swiss Appl. 09.10.70); Chem. Abstr. *77*, 19 451 (1972); Belg. 773.649; Derwent C. P. I. No 25 458T; Swiss 545.771 (Appl. 31.08.71); Derwent C. P. I. No 21 143V; Japan. 4 9011—869 (Appl. 24. 03.72); Derwent C. P. I. No 25 831V; U.S. 3,985.895 (Appl. 20.03.74); Derwent C. P. I. No 81 118X.
15. Rajšner M., Svátek E., Seidlová V., Adlerová E., Protiva M.: This Journal *34*, 1278 (1969).
16. Gardner J. H., Naylor C. A. jr: Org. Syn., Coll. Vol. *2*, 526 (1946).

Translated by the author (M. P.).