SYNTHESIS OF THE SEMI-RIGID ANALOGUES OF PROTHIADENE AND DITHIADENE AS POTENTIAL ANTIDEPRESSANT AND ANTIHISTAMINE AGENTS: 11-[2-(DIMETHYLAMINOMETHYL)CYCLOHEXYLIDENE]-6,11-DIHYDRODIBENZO[*b*,*e*]THIEPINS AND 4-[2-(DIMETHYLAMINOMETHYL)-CYCLOHEXYLIDENE]-4,9-DIHYDROTHIENO-[2,3-*c*]-2-BENZOTHIEPINS

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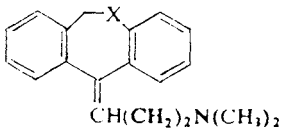
Reaction of dibenzo[*b*,*e*]thiepin-11(6*H*)-one with 2-(dimethylaminomethyl)cyclohexylmagnesium chloride gave a mixture of stereoisomeric amino alcohols *IX* from which four homogeneous bases (*IX-A* to *IX-D*) were separated by chromatography. Dehydration of these compounds with boiling dilute hydrochloric acid afforded mixtures of racemic geometric isomers of the title compound *VII*, which were separated by crystallization. To the prevailing less polar base *VII-A* (*E*)-configuration was assigned on the basis of the IR spectrum. Using a similar procedure, thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one gave mixture of amino alcohols *X* from which three homogeneous stereoisomers *X-A* to *X-C* were isolated. Their dehydration resulted in both expected racemic geometric isomers *VIII-A* and *VIII-B*. Pharmacological testing proved the character of an antidepressant for the semi-rigid analogue of dithiadene *VIII*.

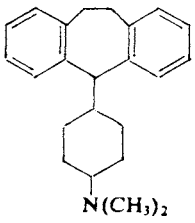
Molecules of the antidepressant agents amitriptyline (*I*) (ref.[1]) and prothiadene (dosulepin, dothiepin) (*II*) (ref.[2]) contain the sterically highly flexible aminopropylidene side chains enabling the localization of the amino group in various distances from the aromatic nuclei. The question about the influence of fixing the position of this amino group on the activity may be solved by synthesis and testing of more or less rigid analogues of compounds *I* and *II*. Literature[3-6] describes the synthesis of several groups of rigid analogues of amitriptyline (*I*) and its 10,11-dehydro congener in which the connection of the amino group to the tricyclic skeleton is realized by an alicyclic ring; out of the described compounds *III* – *VI*, for the first three an important biological activity was claimed[3-5].

In the series of dibenzo[*b*,*e*]thiepin derivatives, *i.e.* in the series of prothiadene (*II*) analogues, aminocycloalkylidene or aminocycloalkyl derivatives have not yet been described. As the first type of such compounds we selected 11-[2-(dimethylaminomethyl)cyclohexylidene] derivatives *VII*; the double bond in these compounds bring about the existence of two geometric isomers and the presence of a chiral centre means that both of the isomers exist as pairs of the optically active enantio-

mers. In the present communication we are describing the synthesis of compounds of formula *VII* and at the same time also the synthesis of similar analogues of 4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (dithiadene[7]) of formula *VIII*. The stereochemical situation with these compounds is similar like with compounds of formula *VII*.

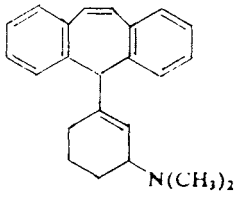


I, X = CH_2
II, X = S

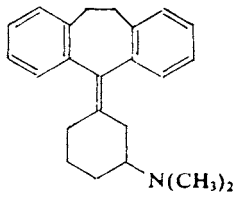


III

IV

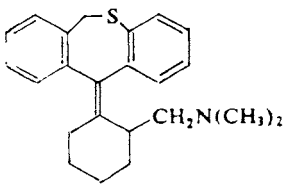


V

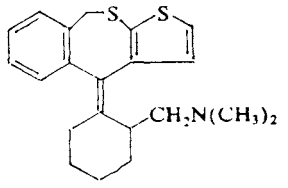


VI

Synthesis of compounds *VII* and *VIII* started from the corresponding tricyclic ketones, *i.e.* dibenzo[*b*,*e*]thiepin-11(6*H*)-one[8] and thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one[9], which were subjected to treatment with 2-(dimethylaminomethyl)-cyclohexylmagnesium chloride. This Grignard reagent was obtained from 2-(dimethylaminomethyl)cyclohexanone[10–12] which was reduced with sodium borohydride[13] or with lithium aluminium hydride[14] to the inhomogeneous 2-(dimethylaminomethyl)cyclohexanol (mixture of *cis*- and *trans*-isomer) (for different reduction procedures and preparation of individual isomers, *cf.*[10,13,15,16]). Reaction with



VII



VIII

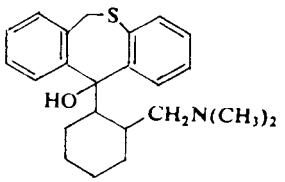
thionyl chloride was used for preparing 2-(dimethylaminomethyl)cyclohexyl chloride[17] (for a different procedure, *cf.*[18]); the product obtained in this way was contaminated with N,N-dimethyl-1-cyclohexenylmethylamine[14] which was mostly removed by fractional distillation. Finally, we used for further work a product containing 98·2–99·8% 2-(dimethylaminomethyl)cyclohexyl chloride according to gas chromatography. This method could not differentiate the *cis*- and *trans*-isomer. With regard to the fact that literature[13,15] indicates the *trans*-isomer as the main component of the inhomogeneous 2-(dimethylaminomethyl)cyclohexanol, and the following step (treatment with thionyl chloride) is apparently connected with the reversal of configuration on C-1, our 2-(dimethylaminomethyl)cyclohexyl chloride consisted probably mostly of the *cis*-isomer.

The Grignard reagent was prepared from 2-(dimethylaminomethyl) cyclohexyl chloride in tetrahydrofuran and its reaction with dibenzo[*b*,*e*]thiepin-11(6*H*)one[8] afforded a mixture of basic and neutral products which were separated by distribution between an aqueous solution of tartaric acid and benzene. The neutral product (approximately 30% of the total product) was a mixture of two compounds which were identified by comparison with standards by means of thin-layer chromatography as 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[8] (the main neutral product formed by reduction of the starting ketone by the Grignard reagent; this reduction is the main side reaction involved) and the minor as di(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl) ether[19,20]. From the basic product, which was obtained by releasing from the solution of the tartrates, the volatile bases were first removed by distillation under reduced pressure. Their quantity made almost 50% of the total basic product and we are dealing here with products of decomposition of the starting 2-(dimethylaminomethyl)-cyclohexyl chloride (dehydrochlorination) and of the Grignard reagent (hydrolysis and oxidation). It has been found by means of gas chromatography that this volatile fraction consists of 44% N,N-dimethyl-1-cyclohexenylmethylamine[14], 42% N,N-dimethylcyclohexylmethylamine[21] and 10% 2-(dimethylaminomethyl)cyclohexanol[13].

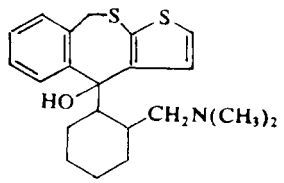
The remaining nonvolatile base is the mixture of the stereoisomeric amino alcohols *IX*. The formula shows the presence of three chiral centers which corresponds to the existence of four racemates. Because the components of this mixture showed some differences in polarity, separation of this mixture by column chromatography on silica gel was carried out and after crystallization of the individual fractions there were obtained four homogeneous isomers $C_{23}H_{29}NOS$ differing by polarity and melting points. Arranged according to the increasing polarity there were designed as *IX-A* (minor product), *IX-B*, *IX-C* (prevailing product) and *IX-D*. On the basis of ^{1}H NMR and IR spectra and conformational analysis an attempt at defining the stereostructure of isomers was made. The models showed that connection of the cyclohexane ring to the tricycle can only be equatorial. This means that hydrogen on $C_{(1)}$ of the cyclohexane ring must be axial in all of the isomers. With regard to the fact that the signal of this proton in the ^{1}H NMR spectra of compounds *IX-A*

and *IX-B* is splitted to a doublet by one further axial proton ($J > 8$ Hz), the dimethylaminomethyl residue in both these compounds must be in axial position. In compounds *IX-C* and *IX-D* the signal of the proton on $C_{(1)}$ of the cyclohexane ring is splitted by two axial protons on carbons $C_{(2)}$ and $C_{(6)}$ to a triplet; this means that the dimethylaminomethyl group must be in these compounds in the equatorial position. These conclusions are confirmed by chemical shifts of one proton of the methylene group of the substituent (dimethylaminomethyl). With compounds *IX-C* and *IX-D* this proton is much more shielded by the hydroxyl group. The differentiation of the pairs *IX-A*; *IX-B* and *IX-C*; *IX-D* is thus based on the chemical shifts of the signal of the proton on $C_{(1)}$ of the cyclohexane ring which is influenced by shielding by two adjacent protons on the aromatic nuclei. With compounds *IX-A* and *IX-C* the value of δ is lower (the proton is in the shielding zone of the aromatic rings); on the other hand with compounds *IX-B* and *IX-D* the value of δ is higher (the proton is not shielded by the aromatic rings).

A similar reaction of thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one[9] with 2-(dimethylaminomethyl)cyclohexylmagnesium chloride resulted likewise in a mixture from whose basic part three crystalline bases were isolated corresponding to the formula *X*; the fourth one is present in a minute amount only (TLC). The isolated compounds arranged according to the increasing polarity, were designated as *X-A* (minor product), *X-B* and *X-C* (main product). Their relative configurations were not investigated.



IX



X

It has been found that dehydration of the individual amino alcohols *IX* with boiling dilute hydrochloric acid leads always to mixtures of two geometric isomers of formula *VII* having approximately the same composition. For this reason this dehydration was preparatively carried out using the mixture of compounds *IX*. In an almost theoretical yield there was obtained a mixture of the olefinic bases *VII*. Isolation of the pure compounds was carried out by crystallization of the enriched fractions (in the case of compound *VII-A* the base was crystallized and *VII-B* was crystallized in the form of the hydrochloride). From a comparison of IR spectra of both bases (*VII-A*, *VII-B*) with the spectra of prothiadene (*II*) and its isomer[22] in the range of extraplanar vibrations of the aromatic C–H bonds ($700-800\ cm^{-1}$) there appears for the isomer *VII-A* the (*E*)-configuration as the most likely one and (*Z*)-configuration for the isomer *VII-B*.

In contradiction to the case just described, the analogous acid catalyzed dehydration of the amino alcohols *X-A*, *X-B* and *X-C* proceeds differently and was, therefore, carried out separately with each of the isomers. Dehydration of the prevailing isomer *X-C* afforded an almost homogeneous olefinic base which was designated as *VIII-A*. IR and UV spectra delivered an indication of evidence that we are dealing here with the (*E*)-isomer[9]. Amino alcohol *X-A* afforded similarly the olefinic base *VIII-B* to which (Z)-configuration was tentatively assigned. Dehydration of compound *X-B* gave an inhomogeneous product which is a mixture of the isomers *VIII-A* and *VIII-B*. ^{1}H NMR spectra of the olefinic bases *VIII-A* and *VIII-B* showed splitted signals of the N-methyl groups protons and characterized these compounds as mixtures of two pairs of different components; it is assumed that they are conformers which are stable at room temperature.

All four olefinic bases (*VII-AB* and *VIII-AB*) were converted to crystalline hydrochlorides which, however, because of the very low water-solubility, were unsuitable for pharmacological testing. For this reason the aqueous solutions of methanesulfonates of compound *VII-B* and of the mixture *VIII-A* + *VIII-B* were used for testing and were prepared by dissolving the bases in aqueous solutions of equivalents of methanesulfonic acid. Pharmacological testing was oriented to the expected thymoleptic (antidepressant) and antihistamine activities; the doses given were calculated for bases. Acute toxicity in mice on oral administration, LD_{50} in mg/kg: *VII*, 325; *VIII*, 302; on intravenous administration: *VII*, 41·4; *VIII*, 42·7. Discoordinating activity in the rotarod test in mice: ataxia is brought about only after the administration of sublethal intravenous doses; approximate values of ED_{50} for both compounds (*VII*, *VIII*) are 30 mg/kg. In the photo-cell method of Dews the compounds in oral doses of 10 mg/kg do not influence the spontaneous locomotor activity in mice. Antireserpine effects: *a*) Inhibition of the hypothermic effect of reserpine in mice; compound *VIII* in intraperitoneal doses of 2 and 4 mg/kg antagonized the reserpine effect with statistical significance. *b*) Inhibition of the ulcerogenic effect of reserpine in rats; in an oral dose of 50 mg/kg compound *VIII* has a mild, but statistically significant antagonistic effect, compound *VII* in the same dose is inactive. Anticataleptic effect: in oral doses of 50 mg/kg both compounds are ineffective as inhibitors towards the perphenazine catalepsy in rats. Antiserotonin effect in the test of serotonin oedema of the rat paws: while compound *VII* in an oral dose of 10 mg/kg shows a slight effect, compound *VIII* in the same dose was without effect. Antihistamine activity in the test of histamine aerosol in guinea pigs: in oral doses of 10 mg/kg both compounds are inactive. Antihistamine activity in the test of histamine detoxication in guinea-pigs: in subcutaneous doses of 10 mg/kg both compounds are inactive. In conclusion it may be stated that only compound *VIII*, which brought about antireserpine effects in two tests, has the character of a potential antidepressant. Compound *VII* showed only some peripheral antiserotonin effect. Both compounds were devoid of antihistamine activity. With only one excep-

tion all results related to administration of a single dose. The possibility cannot be excluded that activities could be found in higher doses which, however, would be unimportant from the standpoint of practical usefulness.

Compounds *VII* and *VIII* were also tested for antimicrobial activity *in vitro*; they showed some inhibiting activity exclusively towards cocci (minimum inhibitory concentrations in μg/ml given): *Streptococcus β-haemolyticus*, *VII* 25, *VIII* 25; *Streptococcus faecalis*, *VII* 25; *VIII* 25; *Staphylococcus pyogenes aureus*, *VII* 12·5, *VIII* 12·5.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and they are not corrected; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in cyclohexane) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Perkin Elmer 298 spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer, and mass spectra with MCH 1320 and Varian MAT 44S spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

2-(Dimethylaminomethyl)cyclohexyl Chloride

Reduction of 46·6 g 2-(dimethylaminomethyl)cyclohexanone[12] (b.p. 69—70°C/67 Pa) with 5·9 g $NaBH_4$ in 750 ml ethanol gave 38·2 g (81%) mixture of *cis*- and *trans*-2-(dimethylaminomethyl)-cyclohexanol, b.p. 98—130°C/2·1 kPa (lit.[13], b.p. 97—120°C/2·27—2·40 kPa). Reduction of 217 g 2-(dimethylaminomethyl)cyclohexanone[12] with 26·8 g $LiAlH_4$ in 1·6 l ether gave 212 g (96%) similar *cis*- and *trans*-mixture, b.p. 64—79°C/133 Pa (lit.[14], b.p. 87—92°C/1·33 kPa). Reaction of this mixture (117 g) with 111 g $SOCl_2$ in 850 ml benzene gave 141·5 g crude 2-(dimethylaminomethyl)cyclohexyl chloride hydrochloride, m.p. 220—223°C. Its decomposition with 100 g Na_2CO_3 in 400 ml water, extraction with ether and distillation afforded 118·5 g crude base, b.p. 70—105°C/2·7 kPa. According to gas chromatography this base contained about 30% N,N-dimethyl-1-cyclohexenylmethylamine[14]. Careful and repeated fractional distillation of this crude base with using an efficient column gave finally 84·2 g (64%) homogeneous base, b.p. 88°C/1·6 kPa (lit.[17], b.p. 83—84°C/2·13 kPa, yield 56%). ^{1}H NMR spectrum: δ 4·49 (bm, 1 H, equatorial 1-H), 2·20 (s, 6 H, CH_3NCH_3), 1·30—2·50 (m, remaining CH and 5 CH_2).

(±)-11-[2-(Dimethylaminomethyl)cyclohexyl]-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ols (*IX*)

Mg (4·7 g) was activated by boiling for 2 min with chloroform, dried and heated with a few crystals of iodine. After cooling 10 ml tetrahydrofuran and about a quarter of the solution of 28·5 g 2-(dimethylaminomethyl)cyclohexyl chloride in 50 ml tetrahydrofuran were added. The mixture was treated with some further crystals of iodine and 2 drops of 1,2-dibromoethane and was warmed by a bath of 50°C. The reaction started after 15 min stirring, the heating was discontinued and the rest of the chloride solution was added over 20 min. The mixture was then stirred and refluxed for 1 h. The solution of the Grignard reagent was transferred by nitrogen pressure into a dropping funnel and under cooling with ice and water it was dropped into a stirred solution of 20·3 g dibenzo[*b*,*e*]thiepin-11(6*H*)-one in 75 ml tetrahydrofuran. The temperature was maintained by cooling at 10—15°C. The mixture was stirred at this temperature for 1·5 h, it was then decomposed by treatment with a solution of 67·5g tartaric acid in 325 ml water

under external cooling. The neutral components of the mixture were extracted with benzene. the extract was dried with $Na_2SO_4/MgSO_4$ and evaporated. The residue (14·7 g) was chromatographed on a column of 250 g silica gel. Benzene eluted first 0·3 g of the least polar component and then 8·0 g mixture which was identical by TLC (comparison with authentic substances) to consist of prevailing quantity of 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol[8] and a minor part of di(6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl) ether[19,20].

The aqueous solution was made alkaline with aqueous ammonia and the released bases were extracted with dichloromethane. The extract was washed with 50 ml water, dried with K_2CO_3 and evaporated under reduced pressure. From the residue (25·2 g) the volatile bases were distilled off *in vacuo*; 10·1 g fraction, b.p. 40–65°C/0·13 kPa. This fraction was characterized by gas chromatography and by comparison with authentic standards; it was found that it consisted of 44% N,N-dimethyl-1-cyclohexenylmethylamine[14], 42% N,N-dimethylcyclohexylmethylamine[21] and 10% 2-(dimethylaminomethyl)cyclohexanol[13]. The nonvolatile residue (14·7 g, 42%) is the crude mixture of stereoisomeric *IX* (oil solidifying by cooling to a glassy mass). This mixture can directly be used for the next step.

In order to separate this mixture, 10·7 g were chromatographed on a column of 170 g silica gel using chloroform as the eluent. The first to be eluted were 0·4 g base *IX-A*, m.p. 197–200°C (ethanol). UV spectrum: λ_{max} 262·5 nm (log ε 3·82), inflexes at 286 nm (3·21), 296·5 nm (3·00). IR spectrum: 750 (4 adjacent Ar—H), 1 050 (C—OH in the ring), 1 590, 1 655, 3 050 (Ar), 2 640, 2 715, 2 780 (N...H—O, N—CH_3), infl. 3 140 cm^{-1} (OH). ^{1}H NMR spectrum: δ 7·85 (m, 2 H, 1,10-H_2), 8·61 (s, 1 H, OH), 6·80–7·30 (m, 6 H, remaining ArH), 3·81 and 4·71 (ABq, J = 13·0 Hz, 1 + 1 H, ArCH_2S), 3·80 (bd, J = 11·0 Hz, 1 H, 1-H of cyclohexane), 3·10 (bt, 1 H, of CH_2N), 1·88 (bs, 6 H, CH_3NCH_3), 1·10–2·00 (m, remaining CH and CH_2 groups). For $C_{23}H_{29}NOS$ (367·5) calculated: 75·17% C, 7·95% H, 3·81% N, 8·72% S; found: 75·38% C, 7·92% H, 3·93% N, 8·79% S.

The preceding product was followed by 1·6 g base *IX-B*, m.p. 208–210°C (ethanol). UV spectrum: λ_{max} 237 nm (log ε 4·12), 268 nm (3·76), infl. 286 nm (3·37) and 286·5 nm (3·00). IR spectrum: 754 (4 adjacent Ar—H), 1 040 (C—OH in the ring), 1 159 (C—O, C—N), 1 584, 3 000, 3 045, 3 080 (Ar), 2 600, 2 700 (N...H—O, N—CH_3), 3 000–3 300 cm^{-1} (OH). ^{1}H NMR spectrum: δ 7·95 and 7·70 (2 m, 1 + 1 H, 1,10-H_2), 9·12 (s, 1 H, OH), 6·90–7·30 (m, 6 H, remaining ArH), 3·98 and 4·62 (ABq, J = 13·0 Hz, 1 + 1 H, ArCH_2S), 4·21 (bd, J = 11·0 Hz, 1 H, 1-H of cyclohexane), 3·10 (bt, 1 H of CH_2N), 2·12 (bs, 6 H, CH_3NCH_3), 1·20–2·00 (m, remaining CH and CH_2 groups). For $C_{23}H_{29}NOS$ (367·5) calculated: 75·17% C, 7·95% H, 3·81% N, 8·72% S; found: 75·56% C, 7·86% H, 3·91% N, 8·88% S.

Further to be eluted were 4·3 g base *IX-C*, m.p. 161–163°C (ethanol). UV spectrum: λ_{max} 266 nm (log ε 3·75), inflexes at 235 nm (4·08), 285 nm (3·35) and 295 nm (3·00). IR spectrum: 750 (4 adjacent Ar—H), 1 034 (C—OH in the ring), 1 562, 1 590, 3 020, 3 050, 3 070 (Ar), 2 765, 2 795, 2 820 (N...H—O, N—CH_3), infl. 3 200 cm^{-1} (OH). ^{1}H NMR spectrum: δ 7·78 (m, 2 H, 1,10-H_2), *c.* 7·20 (bs, 1 H, OH), 6·80–7·30 (m, 6 H, remaining ArH), 4·00 and 4·98 (ABq, J = = 13·0 Hz, 1 + 1 H, ArCH_2S), 3·28 (bt, J = 9·0 Hz, 1 H, 1-H of cyclohexane), 2·15 (dd, 1 H, of CH_2N), 1·84 (s, 6 H, CH_3NCH_3), 1·20–2·00 (m, remaining CH and CH_2 groups). For $C_{23}H_{29}NOS$ (367·5) calculated: 75·17% C, 7·95% H, 3·81% N, 8·72% S; found: 75·40% C, 7·87% H, 3·91% N, 8·90% S.

As the most polar fraction there were eluted 1·1 g base *IX-D*, m.p. 139–141°C (ethanol–hexane). UV spectrum: λ_{max} 240 nm (log ε 4·12), 270 nm (3·71), inflexes at 289 nm (3·34) and 297 nm (3·03). IR spectrum: 744, 755 (4 adjacent Ar—H), 1 045 (C—OH in the ring), 1 165 (C—O, C—N), 1 560, 1 578, 1 590, 1 600, 3 000, 3 060 (N...H—O), infl. 3 200 cm^{-1} (OH). ^{1}H NMR spectrum: δ 7·79 (m, 2 H, 1,10-H_2), *c.* 6·90 (bs, 1 H, OH), 6·80–7·30 (m, 6 H, remaining ArH), 3·90 and 4·40 (ABq, J = 13·0 Hz, 1 + 1 H, ArCH_2S), 3·74 (bt, J = 9·0 Hz, 1 H, 1-H of cyclo-

hexane), 2·08 (dd, 1 H of CH_2N), 1·90 (s, 6 H, CH_3NCH_3), 1·20—2·00 (m, remaining CH and CH_2 groups).

(±)-4-[2-(Dimethylaminomethyl)cyclohexyl]-4,9-dihydrothieno[2,3-*c*]-
-2-benzothiepin-4-ols (*X*)

Grignard reagent was prepared from 35·1 g 2-(dimethylaminomethyl)cyclohexyl chloride and 5·85 g Mg in 75 ml tetrahydrofuran similarly like in the preceding case. Under stirring and cooling to 0—5°C the reagent was added dropwise over 30 min to a solution of 23·2 g thieno[2,3-*c*]-
-2-benzothiepin-4(9*H*)-one[9] in 90 ml tetrahydrofuran. The mixture was stirred for 2 h without cooling and allowed to stand overnight at room temperature. Under cooling to 5—10°C, the stirred mixture was decomposed by a slow addition of a solution of 73·5 g tartaric acid in 400 ml water. Neutral products were removed by extraction with benzene and the aqueous layer was made alkaline with aqueous ammonia. The bases were extracted with dichloromethane, the extract was washed with 50 ml water, dried with K_2CO_3 and evaporated under reduced pressure. From the residue the volatile bases were distilled off *in vacuo*; 16·0 g, b.p. 35—60°C/70 Pa. The residue (23·5 g, 63%) is the oily mixture of stereoisomeric *X*. It may be used in this form for the next step or separated by chromatography on a column of 500 g silica gel. Some fractions obtained were almost homogeneous, other fractions were mixtures of two compounds which had to be separated by rechromatography and purified by crystallization. The yields of the individual isomers given are amounts which resulted from the balance of the whole separation process.

A mixture of chloroform and benzene 1 : 1 eluted as the least polar component 1·7 g amino alcohol *X-A* which was crystallized from a mixture of ethanol and dichloromethane and melted then at 190—192°C. UV spectrum: λ_{max} 240 nm (log ε 3·97), inflexes at 233·5 nm (4·01) and 287·5 nm (3·65). IR spectrum: 725, 764, 846 (4 and 2 adjacent Ar—H), 1 025, 1 040 (C—OH in the ring), 2 600, 2 710 (N...H—O), 3 050, 3 090, 3 100 cm^{-1} (Ar); in CS_2: 709, 720, 759, 829, 841 (4 and 2 adjacent Ar—H), 1 030, 1 040 (C—OH in the ring), infl. 2 710, 2 770, 2 820 (N—CH_3), infl. 2 630 and 3 150 (N...H—O), 3 010, 3 050 cm^{-1} (Ar). ^1H NMR spectrum: δ 9·10 (s, 1 H, OH), 7·90 (m, 1 H, 5-H), *c.* 7·10 (m, 4 H, 2,6,7,8-H_4), 6·84 (d, J = 5·0 Hz, 1 H, 3-H), 4·50 and 3·92 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·70 (bd, J = 12·0 Hz, 1 H, equatorial 1-H of cyclohexane), 2·13 (s, 6 H, CH_3NCH_3). For $C_{21}H_{27}NOS_2$ (373·6) calculated: 67·52% C, 7·29% H, 3·75% N, 17·17% S; found: 67·54% C, 7·34% H, 3·79% N, 16·90% S.

A 6 : 4 mixture of chloroform and benzene eluted then 4·6 g of a somewhat more polar amino alcohol *X-B* which crystallized from a mixture of ethanol and dichloromethane and melted at 181—183°C. UV spectrum: λ_{max} 274·5 nm (log ε 3·77), infl. 243 nm (3·86). IR spectrum: 749, 765, 825, 845 (4 and 2 adjacent Ar—H), 1 061 (C—OH in the ring), 2 600, 2 640, 2 715 (N...H—O, N—CH_3), 3 000, 3 010, 3 055, 3 080 cm^{-1} (Ar); in CS_2: 697, 714, 750, 763, 825, 842 (4 and 2 adjacent Ar—H), 1 039, 1 049, 1 060 (C—OH in the ring), infl. 2 650 and 3 150 (N...H—O), 2 760, 2 815 (N—CH_3), 3 020, 3 055, 3 090 cm^{-1} (Ar). ^1H NMR spectrum: δ 8·10 (bs, 1 H, OH), 7·72 (m, 1 H, 5-H), 7·23 (d, J = 5·0 Hz, 1 H, 2-H), 7·15 (m, 3 H, 6,7,8-H_3), 6·85 (d, J = 5·0 Hz, 1 H, 3-H), 4·80 and 3·60 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 2·10 (s, 6 H, CH_3NCH_3). For $C_{21}H_{27}NOS_2$ (373·6) calculated: 67·52% C, 7·29% H, 3·75% N, 17·17% S; found: 67·16% C 7·30% H, 3·68% N, 17·05% S.

Chloroform alone, finally, eluted 6·0 g of the most polar amino alcohol *X-C* crystallizing from a mixture of ethanol and dichloromethane and melting at 156—158°C. UV spectrum: λ_{max} 236 nm (log ε 3·96), 242 nm (3·96), 289·5 nm (3·63). IR spectrum: 765, 829, 849 (4 and 2 adjacent Ar—H), 1 040, 1 050 (C—OH in the ring), infl. 2 680 and 3 200 (N...H—O), 2 790, 2 820 (N—CH_3), 3 060, 3 090 cm^{-1} (Ar); in CS_2: 710, 719, 759, 824, 841, 859, 881 (4 and 2 adjacent Ar—H), 1 037, 1 049 (C—OH in the ring), 2 770, 2 790, 2 820 (N—CH_3), 3 013, 3 058, 3 088

(Ar), infl. 3 200 cm^{-1} (OH). ^1H NMR spectrum: δ 7·73 (m, 1 H, 5-H), 7·31 (bs, 1 H, OH), *c.* 7·00 (m, 3 H, 6,7,8-H_3), 7·08 (d, 1 H, 2-H), 6·80 (d, J = 5·0 Hz, 1 H, 3-H), 4·30 and 3·88 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·21 (bt, J = 9·0 Hz, 1 H, axial 1-H of cyclohexane), 2·05 (s, 6 H, CH_3NCH_3). For $C_{21}H_{27}NOS_2$ (373·6) calculated: 67·52% C, 7·29% H, 3·75% N, 17·17% S; found: 67·62% C, 7·30% H, 3·82% N, 17·02% S.

(±)-(*E*,*Z*)-11-[2-(Dimethylaminomethyl)cyclohexylidene]-6,11-dihydrodibenzo[*b*,*e*]thiepins (*VII*)

A mixture of stereoisomeric *IX* (4·6 g) was refluxed for 6·5 h with 100 ml 1 : 1 dilute hydrochloric acid with stirring. After cooling it was made alkaline with NH_4OH and extracted with chloroform. The extract was washed with 50 ml water, dried with K_2CO_3 and evaporated under reduced pressure; the residue (4·2 g, 96%) is a mixture of (±)-(*E*)-*VII* and (±)-(*Z*)-*VII*. This mixture was chromatographed on a column of 280 g silica gel using a mixture of 50% benzene, 45% chloroform a 5% chloroform saturated with NH_3 as the eluent. The chromatography resulted only in a partial concentration of the less polar component in the first fractions and of the more polar one in the last fractions. The mixture from the first fractions (1·7 g) was repeatedly crystallized from ethanol; 0·70 g *VII-A*, m.p. 145–147°C, to which the structure of (±)-(*E*)-*VII* was assigned. UV spectrum: λ_{max} 229 nm (log ε 4·40), 265 nm (3·95), 301 nm (3·35), infl. 308 nm (3·30). IR spectrum (CS_2): 730, 747, 759 (4 adjacent Ar—H), 2 760, 2 810 (N—CH_3), 3 010, 3 053 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·80–7·30 (m, 8 H, ArH), 5·20 and 3·32 (ABq, J = = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 1·80 (s, 6 H, CH_3NCH_3), 1·30–2·80 (m, remaining CH + + 5 CH_2). For $C_{23}H_{27}NS$ (349·5) calculated: 79·03% C, 7·79% H, 4·01% N, 9·17% S; found: 78·97% C, 7·88% H, 3·87% N, 9·32% S.

Hydrochloride, solvate 2 : 1 with ethanol, m.p. 256–259°C with decomposition (ethanol–ether). For $C_{23}H_{28}ClNS + 0{\cdot}5\ C_2H_6O$ (409·0) calculated: 70·47% C, 7·64% H, 8·67% Cl, 3·43% N, 7·84% S; found: 70·69% C, 7·40% H, 9·40% Cl, 3·55% N, 8·26% S.

The remaining chromatographic fractions (2·5 g) were dissolved in ethanol and converted by treatment with excessive HCl in ether to the crude hydrochloride which was crystallized repeatedly from a mixture of 98% ethanol and ether; 0·75 g homogeneous hydrochloride of *VII-B*, m.p. 258–261°C with decomposition, to which the structure of (±)-(*Z*)-*VII* was ascribed. Mass spectrum, *m*/*z* (composition and %): 349 (M^+ corresponding to $C_{23}H_{27}NS$, 0·5%), 258 ($C_{20}H_{18}$, 0·6), 215 ($C_{17}H_{11}$, 0·3), 202 ($C_{16}H_{10}$, 0·3), 58 (C_3H_8N, 100). For $C_{23}H_{28}ClNS$ (386·0) calculated: 71·57% C, 7·31% H, 9·19% Cl, 3·63% N, 8·31% S; found: 71·27% C, 7·20% H, 9·32% Cl, 3·74% N, 8·48% S.

This hydrochloride was decomposed with NH_4OH, the base was isolated by extraction with dichloromethane and purified by crystallization from ethanol; base *VII-B*, m.p. 103–106°C. UV spectrum: λ_{max} 265 nm (log ε 3·94), 300 nm (3·31), infl. 227 nm (4·38), infl. 308 nm (3·25). IR spectrum (CS_2): 730, 756, infl. 770 (4 adjacent Ar—H), 2 760, 2 810 (N—CH_3), 3 010, 3 053 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·80–7·30 (m, 8 H, ArH), 5·10 and 3·33 (ABq, J = 13·0 Hz, 1 + 1 H, $ArCH_2S$), 3·02 (bm, 1 H, 2-H of cyclohexane), 2·00 (s, 6 H, CH_3NCH_3). For C_{23}. . $H_{27}NS$ (349·5) calculated: 79·03% C, 7·79% H, 4·01% N, 9·17% S; found: 79·11% C, 7·90% H, 3·93% N, 8·70% S.

(±)-(*E*,*Z*)-4-[2-(Dimethylaminomethyl)cyclohexylidene]-4,9-dihydrothieno[2,3-*c*]-2-benzothiepins (*VIII*)

A) X-C (3·3 g) was stirred and refluxed for 30 min with 50 ml 1 : 1 dilute hydrochloric acid, the mixture was cooled, treated with NH_4OH and extracted with dichloromethane. The extract

was dried, filtered through a column of 30 g silica gel and evaporated *in vacuo*. There crystallized 3·1 g almost homogeneous olefinic base which is completely pure after three recrystallizations from ethanol; 1·1 g (35%) *VIII-A*, m.p. 146–150°C. (*E*)-Configuration was assigned with some reservation. UV spectrum: λ_{max} 288·5 nm (log ε 3·83), inflexes at 220 nm (4·37) and 230 nm (4·34) IR spectrum (CS_2): 711, **734**, 760, 830, 839 (4 and 2 adjacent Ar—H), 2 760, 2 810 (N—CH_3), 3 010, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 2·21 and 2·02 (2 s, 6 H, CH_3NCH_3). For $C_{21}H_{25}NS_2$ (355·6) calculated: 70·94% C, 7·09% H, 3·94% N, 18·04% S; found: 70·83% C, 7·19% H, 3·93% N, 17·89% S.

Hydrochloride, solvate 2 : 1 with ethanol, m.p. 218–224°C with decomposition (ethanol–ether). Mass spectrum, *m/z* (%): 355 (M^+ corresponding to $C_{21}H_{25}NS_2$, 0·2%), 221 ($C_{15}H_9S$, 0·4), 84 (0·5), 58 (100), 44 (8). For $C_{21}H_{26}ClNS_2 + 0{\cdot}5\ C_2H_6O$ (415·1) calculated: 63·66% C, 7·04% H, 8·54% Cl, 3·38% N, 15·45% S; found: 63·64% C, 6·72% H, 8·90% Cl, 3·92% N, 15·80% S.

B) *X-A* (1·1 g) was similarly dehydrated with 16 ml refluxing 1 : 1 dilute hydrochloric acid. Similar processing gave 1·0 g almost homogeneous *VIII-B*, which crystallized from a mixture of ethanol and hexane and melted at 135–138°C. The (*Z*)-configuration was assigned on the basis of the UV and IR spectra. UV spectrum: λ_{max} 287·5 nm (log ε 3·81), inflexes at 230 nm (4·36) and 228 nm (4·33). IR spectrum (CS_2): 711, 730, 760, 830, 840 (4 and 2 adjacent Ar—H), 2 760, 2 810 (N—CH_3), 3 010, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 6·60 and 6·70 (2 d, 1 H, 3-H), 5·13; 3·38 and 4·94; 3·48 (2 ABq, 2 H, $ArCH_2S$), 2·10 and 1·78 (2 s, 6 H, CH_3NCH_3). For $C_{21}H_{25}NS_2$ (355·6) calculated: 70·94% C, 7·09% H, 3·94% N, 18·04% S; found: 71·00% C, 7·20% H, 3·95% N, 18·10% S.

Hydrochloride, solvate 2 : 1 with ethanol, m.p. 245–249°C with decomposition (ethanol–ether). Mass spectrum was practically identical with that of *VIII-A* hydrochloride. For $C_{21}H_{26}ClNS_2 \cdot 0{\cdot}5\ C_2H_6O$ (415·1) calculated: 63·66% C, 7·04% H, 8·54% Cl, 3·38% N, 15·45% S; found: 63·58% C, 6·83% H, 9·00% Cl, 3·61% N, 15·63% S.

C) Similar dehydration of *X-B* gave a mixture of *VIII-A* and *VIII-B*, m.p. 129–149°C, which was repeatedly crystallized from ethanol to give a small quantity of *VIII-A*, m.p. 144–149°C.

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