HETEROCYCLIC ETHERS DERIVED FROM 6,11-DIHYDRODIBENZO-[*b*,*e*]THIEPIN-11-OLS AND 4,9-DIHYDROTHIENO[2,3-*c*]-2--BENZOTHIEPIN-4-OL; A NEW SERIES OF POTENTIAL ANTIDEPRESSANTS AND ANTIHISTAMINE AGENTS

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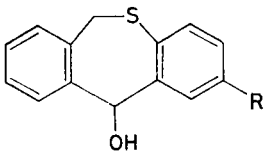
Reactions of 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin and methanesulfonates of 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*I*), its 2-methyl derivative *II* and 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol (*III*) with 1-methylpiperidin-4-ol, 1-methylperhydroazepin-4-ol (*XIX*), and tropine gave the ethers *V*—*X*. Their methanesulfonates were pharmacologically tested and showed antireserpine, anticataleptic, and antihistamine activities of various degree. The most active compounds were the ethers *V* and *VI*.

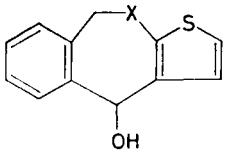
Several 2-(tert.amino)alkyl ethers, derived from 6,11-dihydrodibenzo[*b*,*e*]thiepin--11-ol (*I*) and of its 2-substituted derivatives, were described in previous papers[1-3] and patents[4-6] of our team; they were found to possess important antihistamine effects, only negligible antireserpine activity, and to lack completely the neuroleptic action. Quaternary salts of these compounds[7] were found to be parasympatholytics with a slight peripheral antiserotonin activity. The research of Sandoz[8-11] investigated analogous tropine ethers and one of the quaternaly salts of this series("AA 28—263") was described as an anticholinergic antiasthmatic[12,13]. 2-Dimethylaminoethyl ether derived from 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol (*III*) (ref.[14]) has also properties of an antihistamine agent whereas similar ethers derived from 9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-ol (*IV*) were described as having antitetrabenazine and anticholinergic activities[15,16]. It was clear that basic ethers of the tricyclic alcohols *I*, *III*, and *IV*, in general, are potential neurotropic and psychotropic substances and, therefore, it has been decided to investigate further ethers of this type with heterocyclic basic residues, *viz.* 1-methyl-4-piperidyl, 1--methylperhydro-4-azepinyl, and 3α-tropanyl. Their synthesis and results of a preliminary pharmacological screening are being described in the present communication.

Preparation of the starting tricyclic alcohols *I*—*IV* was described in the literature by the following methods: *I* from dibenzo[*b*,*e*]thiepin-11(6*H*)-one[17] by reduction with sodium borohydride in methanol[17] or with lithium aluminium hydride in ether[18]; *II* from 2-methyldibenzo[*b*,*e*]thiepin-11(6*H*)-one[19] by reduction with

sodium borohydride in ethanol[20]; *III* from thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one[14] by the same method[14]; *IV* from 9,10-dihydrobenzo[4,5]cyclohepta[1,2-*b*]-thiophen-4-one[21] by reduction with zinc and sodium hydroxide in aqueous ethanol[15].



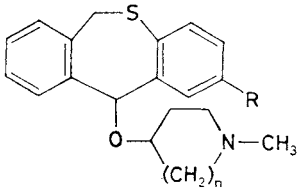
I, R = H
II, R = CH_3



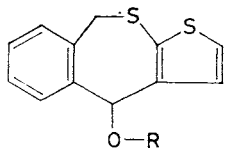
III, X = S
IV, X = CH_2

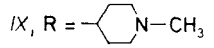
The alcohols *I*, *III*, and *IV* have now been prepared by reduction of the mentioned ketones with sodium dihydridobis(2-methoxyethoxo)aluminate (method[22,23]). In the case of the alcohol *IV*, the reduction of the ketone with sodium borohydride proved most favourable. 11-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin[24], obtained now from the alcohol *I* by treatment with thionyl chloride, was reacted with 1-methylpiperidin-4-ol in the presence of potassium carbonate in boiling xylene and gave the base *V*. A similar reaction using 1-methylperhydroazepin-4-ol (*XIX*) (refs[25,26]) and a similar processing including chromatography of the crude product gave a poor yield on the oily ether *VI* (mixture of two racemates). The ether bond in these products is evidently very weak and is cleaved already by aqueous solutions of organic acids. The synthetic procedure was, therefore, modified in the following way: the alcohols *I*–*IV* were first transformed by treatment with methanesulfonyl chloride in pyridine to methanesulfonates which were subjected in pyridine to treatment with the corresponding heterocyclic amino alcohol at 80°C. The isolation of the crude base by extraction into aqueous tartaric acid was omitted and the mixture of products was separated by chromatography on silica gel. The oily bases were transformed to hydrogen maleates. In the case of the alcohols *I* + *XIX*, the ether *VI* was obtained in a yield of 35%. Treatment of this base with methyl iodide in warm ethanol afforded the crystalline methiodide. Similar reactions of the alcohol *II* (*via* mesylate) with 1-methylpiperidin-4-ol and the homologue *XIX* gave 71%, and 28%, respectively, of the ethers *VII* and *VIII* (mixture of two racemates). After the reaction of *III* methanesulfonate with 1-methylpiperidin-4-ol, the basic product could be extracted with aqueous tartaric acid without complications and the homogeneous oily base *IX* was obtained in a yield of 72%. On the other hand, the reaction of *III* methanesulfonate with the amino alcohol *XIX* afforded a complex mixture from which only 9% of a quasi-homogeneous base (mixture of two racemates) could be obtained by chromatography; neutralization with maleic acid in ethanol was accompanied by cleavage and crystalline maleate was not obtained. A similar

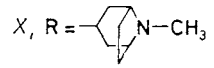
reaction of *III* methanesulfonate with tropine and similar processing gave 26% of the homogeneous oily base *X*. Attempts to prepare similarly the corresponding ethers by reactions of the *IV* methanesulfonate with 1-methylpiperidin-4-ol and 1-methylperhydroazepin-4-ol (*XIX*) gave 45%, and 9%, respectively, of the bases which were cleaved during the neutralization reactions with maleic acid in ethanol and none crystalline maleate could be isolated. The experiments with no crystalline maleates were considered unsuccessful and were discontinued.



V, R = H; *n* = 2
VI, R = H; *n* = 3
VII, R = CH_3; *n* = 2
VIII, R = CH_3; *n* = 3



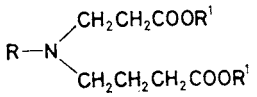
IX, R = 

X, R = 

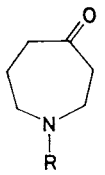
1-Methylperhydroazepin-4-ol (*XIX*) is accessible by reduction of the ketone *XIV* with lithium aluminium hydride in ether[25]. The preparation of the starting ketone *XIV* was described by ring enlargement of 1-methyl-4-piperidone with diazomethane, prepared *in situ* by decomposition of N-nitrosomethylurethane (24%) (ref.[27]) or with free diazomethane in methanol (25%) (ref.[28]). We have now attempted to prepare this ketone by a similar method with diazomethane, generated *in situ* by decomposition of 4-toluenesulfonylmethylnitrosamide[29] (analogy of the synthesis of cycloheptanone from cyclohexanone[30]). The crude ketone *XIV* was obtained in the yield of only 6% and characterized by gas chromatography as containing 70% of the desired substance (20% of the starting 1-methyl-4-piperidone and 10% of higher boiling components). From the neutral by-product, bis(4-tolyl) sulfone[31] was isolated; the mode of its formation is not clear. Anyway, the method is not suitable for preparing the ketone *XIV*. A further attempt started from the reaction of ethyl 3-methylaminopropionate[32] with ethyl 4-iodobutyrate[33] in boiling chloroform in the presence of potassium carbonate. Ethyl 4-(N-(2-ethoxycarbonylethyl)-N-methyl)-aminobutyrate (*XI*) was obtained and we attempted to transform this ester to the ketone *XIV* by the Dieckmann cyclization[34] (with sodium hydride in boiling benzene) and by the following refluxing with 20% hydrochloric acid. There was no product which could be extracted from the alkaline aqueous solution by organic solvent; the cyclization, evidently, did not take place.

A new method for preparing 1-methylperhydroazepin-4-ol (*XIX*) proceeding *via* 1-benzyl-1,2,3,5,6,7-hexahydroazepin-4-one (*XV*) has now been elaborated. Methyl

4-(N-benzyl-N-(2-methoxycarbonylethyl))aminobutyrate (*XII*) was obtained by reaction of methyl 3-(benzylamino)propionate[35,36] with methyl 4-iodobutyrate[37,38] in boiling chloroform in the presence of potassium carbonate. A similar reaction of ethyl 3-(benzylamino)propionate[39] with ethyl 4-iodobutyrate[33] represents a modified procedure for preparing the known[40–42] ethyl 4-(N-benzyl-N-(2-ethoxycarbonylethyl))aminobutyrate (*XIII*); this diester was hard to distill and was used for further



XI, R = CH_3; R^1 = C_2H_5
XII, R = $CH_2C_6H_5$; R^1 = CH_3
XIII, R = $CH_2C_6H_5$; R^1 = C_2H_5

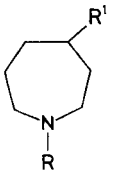


XIV, R = CH_3
XV, R = $CH_2C_6H_5$

step as the crude product (thin-layer chromatography proved the almost complete homogeneity). Both diesters *XII* and *XIII* were subjected to Dieckmann cyclization with potassium ethoxide in boiling xylene or toluene; the resulting keto esters were immediately hydrolyzed and decarboxylated with boiling dilute hydrochloric acid. 1-Benzyl-1,2,3,5,6,7-hexahydroazepin-4-one (*XV*) was isolated as the hydrochloride and was obtained in yields of 23%, and 37%, respectively. The literature[42–44] described the preparation of *XV* by ring enlargement of 1-benzyl-4-piperidone with diazomethane; in one case[45] the Dieckmann cyclization of the diester *XIII* with sodium ethoxide was mentioned. The ketone *XV* was reduced with sodium dihydridobis(2-methoxyethoxo)aluminate (method[22,23]) to 1-benzylperhydroazepin-4-ol (*XVI*) (ref.[43]) which was characterized by the picrate. An attempt to carry out the reduction of the oxo group together with the N-debenzylation by hydrogenation on the Adams catalyst in ethanol at normal pressure and room temperature led only to the first step and the reaction stopped in the stage of 1-benzylperhydroazepin-4-ol (*XVI*). Treatment of this amino alcohol with ethyl chloroformate in boiling benzene led simultaneously to esterification and N-debenzylation and the oily compound *XVII* was obtained in a yield of 77%; its structure was corroborated by spectra. There were two by-products: the lower boiling benzyl chloride and the more hydrophilic hydroxy carbamate *XVIII*. Compound *XVIII* was reduced with lithium aluminium hydride in a mixture of ether and tetrahydrofuran to give in a high yield 1-methylperhydroazepine-4-ol (*XIX*) (*cf.*[25]).

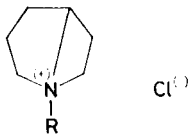
Literature[25] reported that reaction of the amino alcohol *XIX* with thionyl chloride affords 4-chloro-1-methylperhydroazepine (*XX*) hydrochloride. The free base *XX* is unstable an on heating over 70°C is quickly transformed to the quaternary salt *XXII*. This salt when heated over 200°C regenerates the chloro compound *XX*

which is formed together with 2-(2-chloroethyl)-1-methylpyrrolidine. We have carried out reaction of the amino alcohol *XIX* with thionyl chloride in benzene and obtained the hydrochloride of *XX* in agreement with the published statement[25]. We have found that the base *XX* can be distilled *in vacuo* (with prevailing isomerization to *XXII*) and we have prepared the picrate from the distillate which differs by its melting point from the literature[25] value; heating of the base *XX* over 50°C results in a quick formation of a solid which is evidently the quaternary salt *XXII*.



XVI, R = $CH_2C_6H_5$; R^1 = OH
XVII, R = $COOC_2H_5$; R^1 = $OCOOC_2H_5$
XVIII, R = $COOC_2H_5$; R^1 = OH
XIX, R = CH_3 ; R^1 = OH
XX, R = CH_3 ; R^1 = Cl
XXI, R = $CH_2C_6H_5$; R^1 = Cl

The amino alcohol *XVI*, likewise, affords by treatment with thionyl chloride the corresponding chloro compound *XXI* for which the boiling point value was given[43]. As the primary product we have prepared and characterized the hydrochloride of *XXI*. Its decomposition by the aqueous solution of potassium carbonate gave the free base *XXI* which could be distilled *in vacuo* (with partial isomerization to *XXIII*). The distillate solidified on standing at room temperature quickly to the crystalline 1-benzyl-1-azoniabicyclo[3·2·0]heptane chloride (*XXIII*). We are dealing here with a quaternary salt because its IR spectrum lacks bands in the area of 2 250 to 2 700 cm^{-1} (NH^+). The mass spectrum characterized the compound erroneously as the base *XXI*, evidently due to the thermic isomerization of compound *XXIII* like described[25] for the N-methyl analogue.



XXII, R = CH_3
XXIII, R = $CH_2C_6H_5$

Compounds *V*–*X* were pharmacologically tested in the form of hydrogen maleates; they were administered orally and the doses given (in mg/kg) were calculated per bases. Acute toxicity in female mice, LD_{50}: *V* (VÚFB-15 600), 221; *VI*, 188; *VII*, 375; *VIII*, 260; *IX*, 216; *X*, 412. In sublethal doses the compounds have central depressant and convulsant activity. Incoordinating activity in the rotarod test

in mice, ED_{50}: *V*, 64·5; *VI*, 33; *VII*, 54·2; *VIII*, 66; *IX*, 38·8; *X*, >50 (maximum at 30–45 min after the administration). Influence on the locomotor activity of male mice in the test of Dews: *V*, 10 mg/kg increases the activity, 50 mg/kg brings about intensive inhibition of the activity. Inhibition of the ulcerogenic effect of reserpine in rats: *V*, doses of 20 and 50 mg/kg antagonize the effect with statistical significance; *VI*, the same doses have significant effect, the dose of 5 mg/kg is inactive; *VII*, the dose of 20 mg/kg has a slight effect; *VIII*, *IX*, and *X*, in doses of 50 mg/kg only slight effects. Inhibition of the reserpine ptosis in mice: *V*, significant effect only in the dose of 100 mg/kg. The reserpine hypothermia in mice is decreased by doses of 10–50 mg/kg of compound *V* to 72–82% of the control value. Antagonization of perphenazine catalepsy in rats: *V*, doses of 40–50 mg/kg act anticataleptically in most of the animals, the dose of 20 mg/kg has still a significant effect; *VI*, 50 mg/kg is anticataleptic in all rats in the experiment, the dose of 20 mg/kg is practically without effect; *VII* and *VIII*, inactive in doses of 50 mg/kg; *IX*, the dose of 50 mg/kg was anticataleptic in 20% animals; *X*, the dose of 50 mg/kg was anticataleptic in 30–40% of the animals. Inhibition of the lethal effect of yohimbine in mice: *V*, ED_{50} = 62 mg/kg. The effect of serotonin in the test of rat paw oedema is not influenced by doses of 10 mg/kg of compounds *V*–*X*. Receptor binding studies *in vitro*: Compounds *V*–*X* in concentration of 100 nmol l^{-1} do not influence the binding of [^{3}H]imipramine in rat hypothalamus; compound *V* does not influence the binding of [^{3}H]desipramine in rat hypothalamus at the same concentration. Antihistamine activity in the test of histamine aerosol in guinea-pigs, PD_{50}: *V*, 0·47; *VI*, 0·34; *VII*, 0·32; *VIII*, 0·41; *IX*, 0·40; *X* 1·30. Antihistamine activity in the test of histamine detoxication in guinea-pigs: *V*, doses of 2 and 10 mg/kg protect more than 50% of the animals; *VI*, the dose of 2 mg/kg protects 50% and the dose of 10 mg/kg 75% of the animals; *VII*, the dose of 2 mg/kg protects 50% of the animals; *VIII*, the dose of 10 mg/kg protects four animals out of the group of seven, the dose of 2 mg/kg is inactive; *IX*, 10 mg/kg 50%, 2 mg/kg 25%; *X*, 10 mg/kg 25%. Potentiation of the thiopental sleeping time in mice: *VII* in the dose of 150 mg/kg prolongs the sleeping time to 200% of the control value. Analgesic action (chemical stimulation by intraperitoneal administration of acetic acid) in mice: *VII*, ED_{50} = 50 mg/kg. Antitussic action in guinea-pigs (the cough was elicited by the aerosol of citric acid): *IX*, the dose of 100 mg/kg reduced the number of cough attacks to 68% in comparison with the control (100%). In conclusion, compounds *V* (VÚFB-15 600) and *VI* (VÚFB-16 529) are potential antidepressants of an almost classical profile of activity (antireserpine and anticataleptic activity, mild discoordinating effects, and in low doses increase and in higher dose strong decrease of locomotor activity), and medium active antihistamine agents. Surprising was the inactivity in the test of influencing the binding of [^{3}H]imipramine and [^{3}H]desipramine in rat hypothalamus.

Antimicrobial tests *in vitro* (microorganism and the minimum inhibitory concentration in μg/ml given unless it exceeds 100 μg/ml): *Staphylococcus pyogenes*

aureus, *VI*, 100; *VII*, 100; *VIII*, 100; *X*, 50; *Streptococcus faecalis*, *X*, 100; *Trichophyton mentagrophytes*, *VI*, 50; *VII*, 50; *VIII*, 50; *X*, 50.

EXPERIMENTAL

The melting points of analytical preparations 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. IR spectra (mostly in Nujol) were recorded with a Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra with Varian MAT 44S and MCH-1320 spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with $MgSO_4$, Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotating evaporator.

6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ol (*I*)

A solution of 113 g dibenzo[*b*,*e*]thiepin-11(6*H*)-one[17] in 480 ml benzene was stirred and treated at 40–45°C over 1 h with 242 ml 50% solution of sodium dihydridobis(2-methoxyethoxo)-aluminate in toluene. The stirring was continued for 3 h at room temperature, the mixture was then slowly treated with 260 ml 10% NaOH under external cooling with ice-cold water, the organic layer was separated, the aqueous one was extracted with 100 ml benzene and the organic layers were combined, washed with water, dried, and evaporated. The residue was crystallized from a mixture of 130 ml benzene and 170 ml hexane; 98·7 g (87%) *I*, m.p. 108–109°C. Ref.[17], m.p. 107–108°C.

4,9-Dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol (*III*)

Thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one[14] (109 g) in 470 ml benzene was similarly reduced with 226 ml 50% solution of sodium dihydridobis(2-methoxyethoxo)aluminate in toluene. The mixture was decomposed with 245 ml 10% NaOH and the final residue was crystallized from a mixture of 120 ml benzene and 80 ml hexane; 78·0 g (71%) *III*, m.p. 118–120°C. Ref.[14], m.p. 119–122°C.

9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophen-4-ol (*IV*)

A) 9,10-Dihydrobenzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one[21] (21·4 g) in 90 ml benzene was reduced similarly with 48 ml 50% sodium dihydridobis(2-methoxyethoxo)aluminate in toluene. The mixture was decomposed with 105 ml 10% NaOH. The crude product (14·0 g, m.p. 104–105°C) was crystallized from a mixture of 12 ml benzene and 5 ml hexane; 9·7 g (45%), m.p. 111–112°C. Ref.[15], m.p. 111–112°C.

B) A solution of 32·1 g 9,10-dihydrobenzo[4,5]cyclohepta[1,2-*b*]thiophen-4-one[21] in 200 ml ethanol was stirred and treated at 35–38°C over 15 min with 5·7 g $NaBH_4$. The mixture was stirred for 1 h at 60°C, cooled to 25°C and slowly treated with 50 ml water. Ethanol was distilled off, the residue was diluted with 50 ml water and extracted with dichloromethane. The dried extract was filtered through a layer of silica gel and evaporated. The residue was crystallized from a mixture of 30 ml benzene and 50 ml hexane; 29·5 g (91%) *IV*, m.p. 108–111°C.

11-Chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin

I (8·6 g) was dissolved in 30 ml dichloromethane and the stirred solution was treated over 15 min with 8·9 g $SOCl_2$, added dropwise. The mixture was stirred and refluxed for 4·5 h, evaporated *in vacuo*, the residue was diluted with 25 ml benzene which was evaporated again. This procedure was repeated once more and the residue was crystallized from a mixture of 15 ml cyclohexane and 5 ml hexane; 8·6 g (93%), m.p. 80–84°C. Ref.[24], m.p. 81–82°C.

Ethyl 4-(N-(2-Ethoxycarbonylethyl)-N-methyl)aminobutyrate (*XI*)

A mixture of 100 ml chloroform, 10·0 g ethyl 3-methylaminopropionate[32], 17·5 g ethyl 4-iodobutyrate[33], and 15 g K_2CO_3 was stirred and refluxed for 12 h. After standing overnight the mixture was filtered, the solid washed with chloroform and the filtrate was distilled; 11·5 g (62%) *XI*, b.p. 120°C/130 Pa. ^{1}H NMR spectrum: δ 4·10 (q, J = 7·0 Hz, 4 H, 2 $COOCH_2$), 2·20–2·80 (m, 8 H, CH_2NCH_2 and 2 CH_2CO), 2·20 (s, 3 H, NCH_3), 1·80 (m, 2 H, CH_2 in the middle of the propane chain), 1·25 (t, J = 7·0 Hz, 6 H, 2 CH_3 in ethyls). For $C_{12}H_{23}NO_4$ (245·4) calculated: 58·74% C, 9·47% H, 5·71% N; found: 59·37% C, 9·73% H, 6·32% N.

1-Methyl-1,2,3,5,6,7-hexahydroazepin-4-one (*XIV*)

A suspension of 69·5 g 4-toluenesulfonylmethylnitrosamide[29] in 90 ml 90% ethanol was treated with 30·6 g 1-methyl-4-piperidone, the mixture was cooled to 5°C and at this temperature treated under stirring with a solution of 8·3 g KOH in 28 ml 90% ethanol, added dropwise over 2 h. The mixture was stirred at 5–10°C for 1 h, was made alkaline with 15 g KOH and distilled with steam. The distillate (1·5 l) was acidified with hydrochloric acid and evaporated *in vacuo*, the base was released with a solution of K_2CO_3, and extracted with chloroform. The extract was dried, evaporated and distilled; 2·1 g (6%) crude *XIV*, b.p. 65–72°C/70 Pa. Gas chromatography showed that the product contained in addition to 70% of *XIV*, 20% of the starting 1-methyl-4-piperidone and 10% of higher boiling components. The product, when neutralized with HCl in ether, afforded the hydrochloride melting at 160°C with decomposition. Refs[27,28], b.p. 97–100°C/2·4 kPa and 67–71°C/0·9 kPa; hydrochloride, m.p. 166·5–167·5°C.

The solution, remaining after the steam distillation, was made alkaline with excessive KOH and extracted with ether. The extract was dried and evaporated; 15·0 g oily mixture of two components which was chromatographed on a column of 50 g silica gel (Fluka 60). Benzene eluted 10·4 g substance boiling at 142–145°C/65 Pa, a mixture of two components which did not separate on chromatography. The distillation residue (0·7 g) crystallized and was identical with one component of the distillate. It was identified as bis(4-tolyl) sulfone, m.p. 161–164°C (ethanol). Mass spectrum (*m*/*z*, composition, %): 246 (M^+ corresponding to $C_{14}H_{14}O_2S$, 37%), 165 ($C_{13}H_9$, 6), 139 (C_7H_7OS, 100), 91 (C_7H_7, 26), 65 (24). UV spectrum (methanol): λ_{max} 245 nm (log ε 4·30). IR spectrum: 820 (2 adjacent Ar—H), 1 153, 1 290, 1 300, 1 318 ($ArSO_2Ar$), 1 490, 1 596, 3 030, 3 060 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·90 and 7·25 (2 d, J = 8·5 Hz, 8 H, ArH), 2·35 (s, 6 H, 2 $ArCH_3$). For $C_{14}H_{14}O_2S$ (246·3) calculated: 68·26% C, 5·73% H; found: 68·04% C, 5·75% H. Ref.[31], m.p. 158°C.

Methyl 4-(N-Benzyl-N-(2-methoxycarbonylethyl))aminobutyrate (*XII*)

A mixture of 760 ml chloroform, 522 g methyl 3-(benzylamino)propionate[35,36], 678 g methyl 4-iodobutyrate[37], and 392 g K_2CO_3 was stirred and refluxed for 4·5 h. Methyl 4-iodobutyrate (62 g) was added and the refluxing was continued for 3 h. After standing overnight the solid was filtered off and washed with chloroform. The filtrate was evaporated *in vacuo*. The residue was

diluted with 1·8 l ether, 500 g ice were added and the stirred mixture was neutralized with a solution of 280 g methanesulfonic acid in 750 ml water. The aqueous layer was separated, the organic one was washed with 300 ml 10% methanesulfonic acid, the aqueous solutions were combined, washed with 500 ml ether, cooled to 5°C, 1·2 l benzene and 0·25 kg ice were added, and the mixture was made alkaline with 340 g Na_2CO_3 under stirring. The benzene layer was separated, the aqueous one was extracted three times with 150 ml benzene, the combined extracts were washed with water, dried and evaporated *in vacuo*. The residue (779 g, 98%), being almost homogeneous according to TLC, was distilled *in vacuo* in three portions; 723 g (91%), b.p. 178—180°C/0·3 kPa. ^{1}H NMR spectrum: δ 7·22 (s, 5 H, C_6H_5), 3·64 and 3·59 (2 s, 3 + 3 H, 2 OCH_3), 3·52 (s, 2 H, $ArCH_2N$), 2·10—2·90 (m, 8 H, $COCH_2CH_2NCH_2$ and CH_2CO), 1·80 (m, 2 H, remaining CH_2). For $C_{16}H_{23}NO_4$ (293·4) calculated: 65·51% C, 7·90% H, 4·78% N; found: 66·02% C, 8·16% H, 4·99% N.

Ethyl 4-(N-Benzyl-N-(2-ethoxycarbonylethyl))aminobutyrate (*XIII*)

Similarly like in the preceding case, 223 g ethyl 3-(benzylamino)propionate[39], 312 g ethyl 4-iodobutyrate[33], and 156 g K_2CO_3 were reacted in 300 ml boiling chloroform. Ethyl 4-iodobutyrate was added in two further portions (27 and 13 g) and the total time of refluxing was 7 h. The product was also isolated *via* aqueous solution of methanesulfonate. Final extraction with benzene gave 327 g (94%) homogeneous (TLC) *XIII*. Refs[40,41], b.p. 171—173°C/13 Pa.

In our hands, attempt at distillation of this product *in vacuo* led to decomposition to 1-benzyl-2-pyrrolidone[46], b.p. 117—118°C/13 Pa. ^{1}H NMR spectrum: δ 7·20 (s, 5 H, C_6H_5), 4·40 (s, 2 H, $ArCH_2N$), 3·20 (t, 2 H, CH_2N in the ring), 2·40 (t, 2 H, CH_2CO), 1·95 (m, 2 H, remaining CH_2). Ref.[47], b.p. 112—113°C/11 Pa.

1-Benzyl-1,2,3,5,6,7-hexahydroazepine-4-one (*XV*)

A) K (36·7 g) was melted in 250 ml xylene at 90°C (nitrogen atmosphere) and under stirring, 45·4 g ethanol were added dropwise over 25 min. The mixture was stirred and refluxed for 1 h and 150 ml xylene were distilled off. The residue was cooled to 80°C, diluted with 4 l xylene, heated to reflux and treated over 16 h with a solution of 250 g *XII* in 400 ml xylene. During this time, 400 ml mixture of xylene with ethanol and methanol were distilled off. After cooling, the reaction mixture was extracted three times with 240 ml water and three times with 250 ml 3M-HCl, the extracts were combined and refluxed for 6 h. It was filtered with charcoal while hot, cooled, neutral products were removed by extraction with ether, and the aqueous solution was evaporated *in vacuo*. The residue was dissolved in 600 ml water, the solution was made alkaline with NH_4OH and extracted with dichloromethane. The extract was washed with water, dried with K_2CO_3 and evaporated *in vacuo*. The residue was dissolved in 500 ml benzene and the solution was filtered through a column of 500 g neutral Al_2O_3 (activity II). The column was washed with 500 ml benzene and the filtrate was evaporated. The residue (94·8 g) was dissolved in 200 ml ethanol, the solution was acidified with a solution of HCl in ethanol and evaporated *in vacuo*. The residue was crystallized from a mixture of 65 ml methanol and 150 ml ether giving 47·0 g (23%) hydrochloride of *XV*, m.p. 192—194°C with decomposition (ethanol). IR spectrum: 697, 750 (5 adjacent Ar—H), 1 495, 3 030, 3 040, 3 065 (Ar), 1 712 (C=O), 2 380, 2 475, 2 540, 2 660 cm^{-1} (NH^+). For $C_{13}H_{18}ClNO$ (239·8) calculated: 65·13% C, 7·57% H, 14·79% Cl, 5·84% N; found: 65·19% C, 7·64% H, 14·94% Cl, 5·83% N. Refs[43,45], m.p. 186—187°C.

B) *XIII* (221 g) was similarly cyclized with potassium ethoxide (prepared from 29·7 g K) in 2·7 l xylene. After cooling, the mixture was extracted with water and then with 350 ml 2M-HCl (in three parts). The extracts were mixed with 1·68 l hydrochloric acid and the mixture was

stirred and refluxed for 6 h. The hot solution was filtered with 15 g charcoal and after cooling, the filtrate was washed with 250 ml benzene. The aqueous layer was evaporated *in vacuo*, the residue was dissolved in 1·0 l water, the solution was made alkaline with NH_4OH under cooling and the base was extracted with benzene. The extract was washed with water, dried, filtered through 200 g neutral Al_2O_3 (washed with 200 ml benzene), and the filtrate was evaporated *in vacuo*. The residue was dissolved in an excess of ethanolic HCl solution and the solution obtained was evaporated *in vacuo* again. The residue gave by crystallization from a mixture of methanol and ether 61·1 g (37%) hydrochloride of *XV*, m.p. 192—194°C with decomposition (ethanol).

1-Benzylperhydroazepin-4-ol (*XVI*)

A) A solution of 89 g *XV* hydrochloride in 80 ml water was made alkaline with 52 g K_2CO_3 in 55 ml water and the released base was isolated by extraction with benzene (350 ml). The extract was dried with K_2CO_3, the mixture was filtered and the solid washed with 20 ml benzene. The filtrate was stirred and treated over 45 min with 190 g 50% solution of sodium dihydridobis-(2-methoxyethoxo)aluminate in toluene, added dropwise at 20—25°C. It was stirred for 2 h and allowed to stand overnight at room temperature. Under stirring, the solution was decomposed by a slow addition of 200 ml 10% NaOH. After separation, the aqueous layer was extracted with benzene, the benzene layers were combined, dried, and evaporated. The residue was distilled; 70·0 g (92%) *XVI*, b.p. 140—142°C/0·13 kPa. Ref.[43], b.p. 129°C/67 Pa.

Picrate, m.p. 136—138°C (ethanol–benzene). For $C_{19}H_{22}N_4O_8$ (434·4) calculated: 52·53% C, 5·10% H, 12·90% N; found: 52·74% C, 5·22% H, 12·87% N.

B) A solution of 95 g *XV* hydrochloride in a mixture of 35 ml water and 725 ml ethanol was treated with 3·3 g $PtO_2 . H_2O$ and the mixture was hydrogenated under shaking at normal conditions (pressure, temperature) until cessation of hydrogen consumption (18 h). The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was treated with a solution of 69 g K_2CO_3 in 65 ml water and the product was isolated by extraction with chloroform. Distillation gave 35·8 g (44%) *XVI*, b.p. 115—118°C/0·3 kPa. IR spectrum (film): 700, 730, 750 (5 adjacent Ar—H), 1 029, 1 036 (CHOH in the ring), 1 491, 1 572, 1 598, 3 020, 3 055, 3 080 (Ar), 2 770, 2 810 (CH_2—N), 3 350 cm^{-1} (OH). ^1H NMR spectrum: δ 7·20 (s, 5 H, C_6H_5), 4·55 (s, 2 H, $ArCH_2N$), 4·45 (bs, 1 H, OH), 4·00 (bm, 1 H, CH—O), 1·50—3·00 (m, 5 CH_2 of perhydroazepine). For $C_{13}H_{19}NO$ (205·3) calculated: 76·05% C, 9·33% H, 6·82% N; found: 75·77% C, 9·62% H, 7·06% N.

1-(Ethoxycarbonyl)-4-(ethoxycarbonyloxy)perhydroazepine (*XVII*)

A solution of 79·0 g *XVI* in 300 ml benzene was stirred and treated over 15 min with a solution of 83·6 g ethyl chloroformate in 100 ml benzene. The temperature of the mixture rose spontaneously to 60°C and a viscous oil separated (probably the hydrochloride of the mixed carbonate). The mixture was stirred and refluxed for 1 h, cooled and treated with a solution of 40 g K_2CO_3 in 250 ml water. The benzene layer was separated, the aqueous one extracted with benzene. The combined benzene solutions were dried and under stirring slowly treated with a second portion of 83·6 g ethyl chloroformate. The mixture was refluxed for 1 h, was cooled and washed twice with 30 ml 5% tartaric acid, twice with saturated $NaHCO_3$, and with water, it was dried and distilled through a short column. The first fraction (42·3 g, b.p. 69—71°C/4 kPa) consisted mainly of benzyl chloride. The product *XVII* distilled at 155—157°C/0·5 kPa and was obtained in the yield of 76·8 g (77%). Mass spectrum, *m/z* (formula, %): 259 (M^+ corresponding to

$C_{12}H_{21}NO_5$, 3%), 214 ($C_{10}H_{16}NO_4$, 1·5), 187 ($C_9H_{17}NO_3$, 5), 169 ($C_9H_{15}NO_2$, 43), 141 ($C_7H_{11}NO_2$, 60), 140 ($C_7H_{10}NO_2$, 71), 96 ($C_6H_{10}N$, 53), 56 (44), 44 (57), 43 (86), 42 (100), 41 (76). IR spectrum (film): 1 250 (C—O in COOR), 1 690 (NCOOR), 1 739 (ROCOOR'). ^{1}H NMR spectrum: δ 4·70 (bm, 1 H, CH—O), 4·11 and 4·07 (2 q, J = 7·0 Hz, 2 + 2 H, 2 $COOCH_2$), 3·40 (bm, 4 H, CH_2NCH_2), 1·80 (m, 6 H, remaining 3 CH_2 of perhydroazepine), 1·25 and 1·21 (2 t, J = 7·0 Hz, 3 + 3 H, 2 CH_3). For $C_{12}H_{21}NO_5$ (259·3) calculated: 55·58% C, 8·16% H, 5·40% N; found: 56·54% C, 8·39% H, 5·54% N.

The washings were combined, saturated with K_2CO_3 and extracted with chloroform. The extract was dried and distilled; 3·6 g (5%), b.p. 143—144°C/0·5 kPa. This more hydrophilic product was identified as 1-(ethoxycarbonyl)perhydroazepin-4-ol (*XVIII*). IR spectrum (film): 1 030, 1 094 (CHOH), 1 230, 1 262 (C—O in COOR), 1 670 (NCOOR), 3 420 cm^{-1} (OH). ^{1}H NMR spectrum: δ 4·08 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 3·80 (bm, 1 H, CH—O), 3·38 (bm, 4 H, CH_2NCH_2), 2·42 (bs, 1 H, OH), 1·70 (bm, 6 H, remaining 3 CH_2 of perhydroazepine), 1·25 (t, J = 7·0 Hz, 3 H, CH_3). For $C_9H_{17}NO_3$ (187·2) calculated: 57·73% C, 9·15% H, 7·48% N; found: 57·79% C, 9·24% H, 7·28% N.

1-Methylperhydroazepin-4-ol (*XIX*)

A solution of 81·5 g *XVII* in a mixture of 400 ml tetrahydrofuran and 250 ml ether was added dropwise over 30 min to a stirred suspension of 38·1 g $LiAlH_4$ in 400 ml ether. The mixture was stirred and refluxed for 6 h. After standing overnight it was decomposed under external cooling by a slow addition of 38 ml water, 38 ml 15% NaOH, and 115 ml water, stirred for 1 h, filtered with suction, and the solid on the filter washed with 250 ml ether. The filtrate was dried and distilled; 47·4 g (86%) *XIX*, b.p. 105—107°C/2 kPa. IR spectrum (film): 1 045 (CHOH in the ring), 2 800 (N—CH_3), 3 320 cm^{-1} (OH). For $C_7H_{15}NO$ (129·2) calculated: 65·25% C, 11·73% H, 10·84% N; found: 65·22% C, 11·73% H, 10·01% N. Ref.[25], b.p. 96°C/1·5 kPa.

4-Chloro-1-methylperhydroazepine (*XX*)

A solution of 8·8 g *XIX* in 40 ml benzene was stirred and treated over 30 min with 8·9 g $SOCl_2$, added dropwise. The mixture was refluxed for 30 min, cooled, the solvent was decanted from the syrupy hydrochloride which was washed with boiling benzene, dried *in vacuo* (10·4 g, 83%), and crystallized from a mixture of 2-propanol and ether, m.p. 124—126°C. Ref.[25], m.p. 126—127°C.

A solution of 10·0 g crude hydrochloride in 50 ml water was treated with NH_4OH and the base was isolated by extraction with dichloromethane. Processing of the extract gave 7·0 g crude base whose distillation gave only 0·7 g base *XX*, b.p. 30—35°C/2 kPa. The distillation residue solidified and is evidently the described *XXII* (ref.[25]).

The distillate (0·5 g) was neutralized with 0·8 g picric acid in 7 ml boiling ethanol; the picrate of *XX*, m.p. 138—139°C (ethanol). For $C_{13}H_{17}ClN_4O_7$ (376·8) calculated: 41·44% C, 4·55% H, 9·41% Cl, 14·87% N; found: 41·42% C, 4·66% H, 9·60% Cl, 15·06% N. Ref.[25], m.p. 173—174°C with decomposition.

1-Benzyl-4-chloroperhydroazepine (*XXI*)

A solution of 7·2 g *XVI* in 70 ml benzene was stirred and treated at 10°C with a solution of 8·9 g $SOCl_2$ in 10 ml benzene, added dropwise over 30 min. The mixture was stirred for 1 h at room temperature and evaporated *in vacuo*. The crystalline residue (9·7 g, 99%) is the hydrochloride of *XXI* and was purified by crystallization from a mixture of 2-propanol and ether, m.p. 134—137°C. ^{1}H NMR spectrum ($C^2H_3O^2H$): δ 7·35 (m, 5 H, C_6H_5), 4·28 (s, 2 H,

$ArCH_2N$), 3·30 (m, 5 H, CH_2NCH_2 and CH—Cl), 1·70—2·50 (m, 6 H, remaining 3 CH_2 of perhydroazepine). For $C_{13}H_{19}Cl_2N$ (260·2) calculated: 60·00% C, 7·36% H, 27·25% Cl, 5·38% N; found: 59·76% C, 7·23% H, 27·32% Cl, 5·35% N.

1-Benzyl-1-azoniabicyclo[3·2·0]heptane Chloride (*XXIII*)

A solution of 35·9 g *XVI* in 190 ml benzene was treated under stirring at 50°C with 27·1 g $SOCl_2$, added dropwise over 30 min. The temperature was maintained between 50 and 60°C. The mixture was then refluxed for 2 h with stirring, cooled to 10°C, the precipitated *XXI* hydrochloride was filtered and washed with benzene. It was then treated with a solution of 50 g K_2CO_3 in 100 ml water and the base *XXI* was isolated by extraction with benzene. The extract was dried with K_2CO_3 and evaporated at max. 35°C. The residue (23·4 g) gave by distillation only 5·1 g liquid *XXI*, b.p. 105—108°C/70 Pa (ref.[43], b.p. 104—105°C/67 Pa). On standing at room temperature for 3 h, the distillate solidified completely to a substance insoluble in benzene, which was identified as the monohydrate of *XXIII*. Mass spectrum, *m*/*z* (formula, %): 233 (M^+ corresponding to $C_{13}H_{18}ClN$ formed by thermic isomerization of *XXIII*, 2·5%), 188 ($C_{13}H_{18}N$, 17), 160 ($C_{11}H_{14}N$, 58), 146 ($C_7H_{13}ClN$, 5), 91 (C_7H_7, 100). IR spectrum: 705, 765 (5 adjacent Ar—H), *1* 500, 1 587, 3 010, 3 040, 3 060, 3 090 (Ar), 3 390 cm^{-1} (H_2O). ^1H NMR spectrum: δ 7·70 and 7·35 (2 m, 5 H, C_6H_5), 5·30 (m, 1 H, CHN^+), 5·15 (s, 2 H, $ArCH_2N^+$), 4·75, 4·00, and 1·70—3·80 (3 m, 1 + 1 + 8 H, 5 CH_2 in the rings). For $C_{13}H_{18}ClN + H_2O$ (241·8) calculated: 64·58% C, 8·35% H, 14·66% Cl, 5·79% N; found: 65·54% C, 7·82% H, 14·62% Cl, 6·35% N.

11-(1-Methyl-4-piperidyloxy)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*V*)

A solution of 2·1 g 1-methylpiperidin-4-ol in 10 ml xylene was treated with 1·8 g K_2CO_3 and with a solution of 4·1 g 11-chloro-6,11-dihydrodibenzo[*b*,*e*]thiepin in 25 ml xylene, and the mixture was stirred and refluxed for 7 h. After standing overnight it was washed with 50 ml water and from the organic layer the bases were extracted into a solution of 3·5 g (+)-tartaric acid in 50 ml water. The aqueous solution was made alkaline with NH_4OH and the released bases were isolated by extraction with dichloromethane. The extract was washed with water, dried and evaporated. The residue was dissolved in chloroform containing 5% methanol and the solution was chromatographed on a column of 10 g silica gel. The column was washed with 350 ml of the mentioned mixture of solvents. Evaporation of the filtrate gave 3·95 g (73%) homogeneous oily base *V*. ^1H NMR spectrum: δ 6·40—7·60 (m, 8 H, ArH), 5·75 (bs, 1 H, Ar_2CH—O), 2·25 (s, 3 H, NCH_3), 1·60—3·80 (m, 11 H, CH_2S, 4 CH_2 and CH of piperidyl).

Hydrogen maleate, m.p. 180—182°C (ethanol–ether). For $C_{24}H_{27}NO_5S$ (441·6) calculated: 65·28% C, 6·16% H, 3·17% N, 7·26% S; found: 64·70% C, 6·16% H, 3·20% N, 7·27% S.

11-(1-Methylperhydroazepin-4-yloxy)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VI*)

A) A mixture of 6·2 g 11-chloro-6,11-dihydrodibenzo[*b*, *e*]thiepin, 50 ml xylene, 3·88 g *XIX* and 2·76 g K_2CO_3 was stirred and refluxed for 10 h. After cooling the mixture was washed with 120 ml water and from the xylene layer the bases were extracted into a solution of 10 g (+)-tartaric acid in 150 ml water. The aqueous extract was made alkaline with NH_4OH and the bases were extracted with dichloromethane. Processing of the extract gave a crude product which was dissolved in benzene and chromatographed on a column of 25 g silica gel (Merck). Elution with benzene separated first 0·7 g of little polar impurities and elution with a mixture of 90% chloroform, 5% chloroform saturated with NH_3 (by shaking with NH_4OH) and 5% methanol gave 1·5 g (18%) quasi homogeneous base *VI* (mixture of two racemates).

Hydrogen maleate, m.p. 129—132°C (ethanol–ether). For $C_{25}H_{29}NO_5S$ (455·6) calculated: 65·91% C, 6·42% H, 3·07% N, 7·04% S; found: 66·02% C, 6·50% H, 3·11% N, 7·20% S.

Methiodide (2·2 g) was obtained by treatment of a solution of 1·7 g base *VI* in 10 ml ethanol with 1·4 g methyl iodide, standing for 1 h at room temperature and refluxing for 10 min; m.p. 210—214°C (ethanol–ether). For $C_{22}H_{28}INOS$ (481·4) calculated: 54·89% C, 5·86% H, 26·36% I, 2·91% N, 6·66% S; found: 54·21% C, 5·86% H, 26·34% I, 2·76% N, 6·78% S.

B) A solution of 8·0 g *I* in 25 ml pyridine was stirred and treated over 10 min with 4·6 g methanesulfonyl chloride, added dropwise. The temperature rose spontaneously to 50°C. The mixture was stirred for 4 h and allowed to stand overnight. Under stirring it was treated with 6·8 g *XIX* and heated for 6 h to 75—80°C. After standing overnight it was distributed between 100 ml dichloromethane and 100 ml water. The aqueous layer was extracted with dichloromethane, the organic layers were combined, washed with 50 ml saturated NaCl solution, dried and evaporated. Similar chromatography like under *A* on 70 g silica gel afforded 5·5 g (35%) oily *VI*. Its hydrogen maleate (m.p. 128—131°C) was identical with the salt obtained under *A*.

2-Methyl-11-(1-methyl-4-piperidyloxy)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VII*)

A solution of 11·7 g *II* (ref.[20]) in 30 ml pyridine was treated under stirring over 10 min with 6·3 g methanesulfonyl chloride, the mixture was stirred for 4 h without heating and allowed to stand overnight. 1-Methylpiperidin-4-ol (11·5 g) was added, the mixture was heated to 75—80°C and stirred at this temperature for 6 h. After standing overnight it was distributed by shaking between 100 ml dichloromethane and 100 ml water and the aqueous layer was extracted with dichloromethane, the combined organic layers were washed with 50 ml saturated NaCl solution, dried and evaporated *in vacuo*. The residue was dissolved in benzene and chromatographed on a column of 110 g silica gel (Merck). Elution with benzene removed 2·2 g impurities and the product was eluted with chloroform containing 3% of methanol; 12·1 g (71%) oily *VII*. IR spectrum (film): 752, 765, 809, 875, 879 (4 and 2 adjacent and solitary Ar—H), 1 062, 1 105 (R—O—R'), 1 480, 1 600 (Ar), 2 670, 2 730, 2 775 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 6·70 to 7·50 (m, 7 H, ArH), 5·65 (bs, 1 H, Ar_2CH—O), 2·20 (s, 6 H, $ArCH_3$ and NCH_3).

Hydrogen maleate, m.p. 184—186°C (ethanol–ether). Mass spectrum, *m/z* (formula, %): 339 (M^+ corresponding to $C_{21}H_{25}NOS$, 3%), 224 ($C_{15}H_{12}S$, 84), 192 ($C_{15}H_{12}$, 34), 114 ($C_6H_{12}NO$, 34), 99 (89), 98 ($C_6H_{12}N$, 100), 70 (53), 54 (88). For $C_{25}H_{29}NO_5S$ (455·6) calculated: 65·91% C, 6·42% H, 3·07% N, 7·04% S; found: 65·93% C, 6·57% H, 3·00% N, 7·16% S.

2-Methyl-11-(1-methylperhydroazepine-4-yloxy)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*VIII*)

A solution of 8·5 g *II* (ref.[20]) in 25 ml pyridine was stirred and treated over 15 min with 4·6 g methanesulfonyl chloride, the mixture was stirred for 4 h, allowed to stand overnight, treated with 6·8 g *XIX*, and heated under stirring for 6 h to 80°C. The mixture was processed similarly like in the preceding cases. The crude product was chromatographed on 70 g silica gel (Merck) and elution with a mixture of 90% chloroform, 2% methanol, and 5% chloroform saturated with NH_3 gave 3·5 g (28%) oily *VIII* (mixture of two racemates). ^1H NMR spectrum: δ 6·70—7·40 (m, 7 H, ArH), 5·60 (bs, 1 H, Ar_2CH—O), 2·24 and 2·18 (2 s, 3 + 3 H, $ArCH_3$ and NCH_3).

Hydrogen maleate, m.p. 158—161°C (ethanol–ether). For $C_{26}H_{31}NO_5S$ (469·6) calculated: 66·50% C, 6·65% H, 2·98% N, 6·83% S; found: 66·52% C, 6·74% H, 2·93% N, 6·91% S.

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

A solution of 11·7 g *III* in 35 ml pyridine was stirred and cooled, and treated over 15 min with 6·6 g methanesulfonyl chloride, added dropwise. The mixture was stirred for 4 h and allowed to stand overnight. 1 Methylpiperidin-4-ol (11·5 g) was added, the mixture was heated to 80°C until the solid was dissolved, cooled to 60° and stirred at this temperature for 3 h. After standing overnight at room temperature, the mixture was decomposed with 300 ml water and extracted with chloroform. The extract was washed with water, dried, and evaporated *in vacuo*. The remaining pyridine was removed by evaporation with 50 ml xylene which was repeated once more. From the chloroform solution the bases were extracted by shaking into a solution of 35 g (+)-tartaric acid in 200 ml water, divided in three parts. The aqueous extract was made alkaline with NH_4OH and the bases were isolated by extraction with dichloromethane. The extract was washed with water, dried and evaporated. The residue was chromatographed on 70 g silica gel. Fractions eluted with benzene and chloroform were discarded, and elution of the desired product proceeded with a mixture of 92% chloroform, 3% methanol and 5% chloroform saturated with NH_3; 11·9 g (72%) homogeneous oily base *IX*. IR spectrum: 766 (4 adjacent Ar—H), 838 (2 adjacent thiophene C—H), 1 039, 1 070 cm^{-1} (R—O—R').

Hydrogen maleate, m.p. 147—150°C (ethanol–ether). For $C_{22}H_{25}NO_5S_2$ (447·6) calculated: 59·04% C, 5·63% H, 3·13% N, 14·33% S; found: 58·79% C, 5·84% H, 3·15% N, 14·19% S.

4-(3α-Tropanyloxy)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*X*)

A solution of 11·7 g *III* in 35 ml pyridine was stirred and treated over 15 min with 6·3 g methanesulfonyl chloride at max. 30°C (external cooling). The mixture was stirred for 1·5 h and allowed to stand overnight. Tropine (14·1 g) was added to the semi-solid substance, the mixture was heated to 80°C and the solution formed was stirred at this temperature for 5·5 h. After cooling it was treated with 200 ml water and extracted with dichloromethane. The extract was dried and evaporated *in vacuo*. The residue was dissolved in benzene and chromatographed on 70 g silica gel. Elution with benzene and chloroform removed the less polar contaminants. Elution with a mixture of 92% chloroform, 5% chloroform saturated with NH_3, and 3% methanol afforded 4·7 g (26%) of the homogeneous oily *X*. IR spectrum (film): 759 (4 adjacent Ar—H), 840 (2 adjacent thiophene C—H), 1 113 (R.O.R'), 1 490, 1 515, 1 590, 1 600, 3 015, 3 030, 3 060, 3 070 (Ar), 2 790 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 7·20 (m, 4 H, ArH of *o*-phenylene), 6·98 (d, J = 5·0 Hz, 1 H, 2-H), 6·89 (d, J = 5·0 Hz, 1 H, 3-H), 5·40 (s, 1 H, Ar_2CH—O), 5·11 and 3·75 (ABq, J = 13·0 Hz, 1 + 1 H, CH_2S), 3·58 (bm, 1 H, tropine CH—O), 3·00 (bm, 2 H, CHNCH), 2·20 (s, 3 H, CH_3N), 1·80 (m, 8 H, remaining 4 CH_2 of tropane).

Hydrogen maleate, m.p. 187—189°C (ethanol–ether). For $C_{24}H_{27}NO_5S_2$ (473·6) calculated: 60·87% C, 5·75% H, 2·96% N, 13·54% S; found: 61·06% C, 5·79% H, 2·95% N, 13·34% S.

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