BENZOCYCLOHEPTENES AND HETEROCYCLIC ANALOGUES AS POTENTIAL DRUGS. III.*

FURTHER SYNTHETIC EXPERIMENTS IN THE SERIES OF 1-BENZOTHIEPIN DERIVATIVES

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Attempts at C-alkylation of 2,3-dihydro-4*H*-1-benzothiepin-5-one (*I*) reached their goal only if the starting compound was activated by a form of 4-ethoxycarbonyl derivative (*II*) or pyrrolidine enamine (*V*); compounds *III* and *IV* were obtained in low yields. Using 8 steps, compound *XVI* was synthesized from ketone *I*. C-Alkylation of 5-phenyl-2,3,4,5-tetrahydro-1-benzothiepin (*XVIII*) led to a low yield of 5-(3-dimethylaminopropyl) derivative *XIX*. Attempts at cyclization of acids *XXVIII* and *XXIX* with the aid of polyphosphoric acid in toluene did not result in 2-aryl-2,3-dihydro-4*H*-1-benzothiepin-5-ones *XXX* but unexpectedly in tetralone derivatives *XXXI* and *XXXII*. Compounds *VII*, *XXIII* and *XXVIII* display signs of hypotensive activity while the expected β-adrenolytic activity (*XVI*) and psychotropic activity (*XIX*) were not found.

The present paper proceeds from a previous study of 1-benzothiepin derivatives[1] and represents a continuation of attempts at finding neurotropically or cardiovascularly active compounds. The starting compound of the work was 2,3-dihydro-4*H*-1-benzothiepin-5-one (*I*) (*ref.*[2]). With the aim of preparing derivatives of ketone *I* with a dialkylaminoalkyl substituent in position 4 we tried to alkylate ketone *I* with 2-dimethylaminoethyl chloride but we did not succeed in reaching the C-alkylated product. The reaction proceeds apparently at the oxygen so that after acid hydrolysis of the reaction mixture only the regenerated ketone *I* is isolated. The tendency of ketone *I* to enolization was observed already before[3]. Activation of position 4 was attempted by introducing the ethoxycarbonyl group; reaction of ketone *I* with diethyl carbonate in the presence of sodium hydride led to the sodium salt of keto ester *II* which was alkylated *in situ* with 2-dimethylaminoethyl chloride. A total of 50% basic product was obtained which was hydrolyzed with dilute hydrochloric acid for the most part to the ketone *I*. The C-alkylated product *III* was obtained only in a 5% yield. We tested C-alkylation of the corresponding enamine (methods in[4-6]). The enamine *V* was alkylated with benzyl chloride and, after hydrolysis, a mixture of ketone *I* and C-benzylated product *IV* was obtained in a 2 : 1 ratio.

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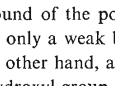
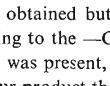
In attempts at alkylation of enamine *V* with 2-dimethylaminoethyl chloride no C-alkyl derivative was detected. We attempted further to O-alkylate the ketone *I* oxime[7] with 2-dimethylaminoethyl chloride and to obtain compound *VI*. A low yield of a compound of the postulated empirical formula was obtained but its IR spectrum showed only a weak band at 1675 cm^{-1}, corresponding to the —C=N— fragment. On the other hand, a very strong band at 3390 cm^{-1} was present, corresponding to the hydroxyl group. For this reason, we prefer for our product the structure *VII*. The compound in the form of hydrochloride is unstable and is split in solution slowly to the starting oxime (all the way to ketone *I*).

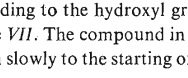


I, R = H
II, R = $COOC_2H_5$

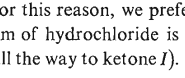


III, R = $CH_2CH_2N(CH_3)_2$
IV, R = $CH_2C_6H_5$

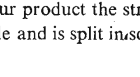
V



VI



VII



VIII

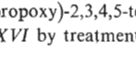
IX, R = H
X, R = $COCH_3$
XI, R = $C(=NOH)CH_3$
XII, R = $NHCOCH_3$

XIII, R = NH_2
XIV, R = OH
XV, R = OCH_2CHCH_2 (O)
XVI, R = $OCH_2CH(OH)CH_2NHCH(CH_3)_2$

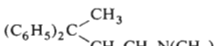
Reaction of the keto ester *II* with phenylhydrazine gives rise readily to a crystalline product of composition $C_{17}H_{14}N_2OS$ which, on the basis of analogous course of a similar reaction of 2-ethoxycarbonyl-1-tetralone[8], is assumed to have the structure

of 2-phenyl-2,3a,4,5-tetrahydropyrazolo(4,3-*d*)-1-benzothiepin-3-one (*VIII*). We took up further the preparation of compound *XVI* which is a 2,3,4,5-tetrahydro-1-benzothiepin analogue of the β-adrenolytic agent "propranolol"[9]. Ketone *I* was converted to 2,3,4,5-tetrahydro-1-benzothiepin (*IX*) (*ref.*[10]) and its 7-acetyl derivative (*X*) (ref.[10,11]). The oxime *XI* prepared in the usual way underwent Beckmann's rearrangement in polyphosphoric acid to yield the 7-acetamido derivative *XII*. Hydrolysis led to amine *XIII* which was converted to phenol *XIV via* the diazonium salt. Reaction with epichlorohydrin resulted in 7-(2,3-epoxypropoxy)-2,3,4,5-tetrahydro-1-benzothiepin (*XV*) which yielded the desired product *XVI* by treatment with isopropylamine.

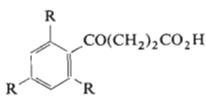
XVII, R = OH
XVIII, R = H
XIX, R = $(CH_2)_3N(CH_3)_2$



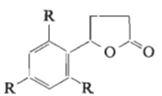
XX, $R^1 = R^2 = H$
XXI, $R^1 = Br$, $R^2 = H$
XXII, $R^1 = R^2 = Br$



XXIII



XXIV, R = H
XXV, R = CH_3

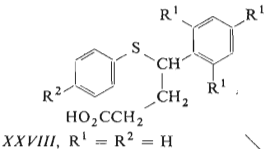


XXVI, R = H
XXVII, R = CH_3

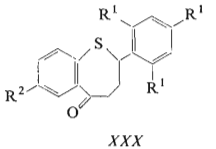
Reaction of ketone *I* with phenyllithium gives rise to a fine yield of the tertiary alcohol *XVII* which does not crystallize even after chromatography and which can be redistilled in high vacuum without decomposition. Under acid catalysis, it is readily dehydrated to 5-phenyl-2,3-dihydro-1-benzothiepin (*XX*). The tertiary alcohol *XVII* was reduced by treatment with red phosphorus and iodine in acetic acid to 5-phenyl-2,3,4,5-tetrahydro-1-benzothiepin (*XVIII*) which was used for aminoalkylation with 3-dimethylaminopropyl chloride. For the formation of the required carbanion we used in this case a reagent composed of sodium and naphthalene in tetrahydrofuran[12]. This reaction resulted in a mixture of products, from which the desired compound *XIX* was isolated in a low yield. The course of the model alkylation of 1,1-diphenylethane[13] with 2-dimethylaminoethyl chloride was much more homogeneous and led to a relatively fine yield of N-(3,3-diphenylbutyl)dimethylamine (*XXII*).

In an attempt to approach the unknown 5-phenyl-1-benzothiepin we tried to brominate the olefinic compound *XX* with N-bromosuccinimide and to dehydrobrominate the product; a mixture resulted from which small amounts of the monobromo and dibromo derivatives of the starting substance were obtained by chromatography. The derivatives are assumed to have structures *XXI* and *XXII*.

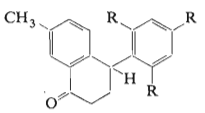
Compounds with the skeleton of 2-aryl-2,3,4,5-tetrahydro-1-benzothiepin (*XXX*) would be the nearest bicyclic analogues of psychotropically effective derivatives of dibenzo(*b*,*e*)thiepin[14]. Our first attempt led to a compound which was not substituted in the benzene rings (*XXX*, $R^1 = R^2 = H$). 3-Benzoylpropionic acid (*XXIV*) (ref.[15]) was converted in the usual way to 4-phenylbutyrolactone (*XXVI*) (ref.[16]). Reaction of *XXVI* with sodium thiophenolate in ethanol led to 4-phenyl-4-(phenylthio)butyric acid (*XXVIII*). In attempting a cyclization of this compound when the formation of ketone *XXX* was assumed ($R^1 = R^2 = H$) or even of 4-(phenylthio)-1-tetralone and when polyphosphoric acid and toluene were used as reagent and solvent we obtained a neutral product from which a small amount of a ketonic fraction in the form of semicarbazone was obtained. The analysis of this compound proved that we were dealing here with a sulfur-free substance. Hydrolysis with oxalic acid resulted in 4-phenyl-7-methyl-1-tetralone (*XXXI*), the structure of which was solved by the NMR spectrum.



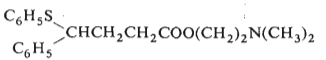
XXVIII, $R^1 = R^2 = H$
XXIX, $R^1 = CH_3$, $R^2 = Cl$



XXX



XXXI, R = H
XXXII, R = CH_3



XXXIII

Polyphosphoric acid apparently causes a splitting of the labile benzyl-S-bond in the molecule of acid *XXVIII* and the formed carbonium cation then attacks the *para*-posi-

tion of the toluene present, giving rise to a C—C bond. The reaction sequence is terminated by the cyclization of the transiently formed acid. Acid *XXVIII* was transformed to the 2-dimethylaminoethyl ester (*XXXIII*) as described in the experimental section. An analogous attempt proceeded from 3-(2,4,6-trimethylbenzoyl)propionic acid (*XXV*) (ref.[17]) where in the terminal phase a 4-(arylthio)-1-tetralone type of compound cannot be formed. As before, a 4-(2,4,6-trimethylphenyl)butyrolactone (*XXVII*) was prepared which reacted with the sodium salt of 4-chlorothiophenol to the acid *XXIX*. The course of cyclization with the aid of polyphosphoric acid in the presence of toluene was analogous to the preceding case. From a complex mixture of neutral compounds a ketone was isolated which, according to its analyses and spectra, is 4-(2,4,6-trimethylphenyl)-7-methyl-1-tetralone (*XXXII*).

The following compounds were tested pharmacologically in a wider spectrum of tests by the methods of general screening (type of application, acute toxicity for mice LD_{50} in mg/kg and finally the dose in mg/kg used in most *in vivo* tests are shown): *VII*-HCl (*i.v.*, 40, 8), *VIII* (*p.o.*, > 2500, 300), *XXIII*-hydrogen maleate (*i.v.*, 50, 10), *XXVIII*-sodium salt (*i.v.*, 250, 50), *XXIX* (*p o*., 2000, 300), *XXXIII*-hydrogen maleate (*i.v.*, 100, 20).

Derivative of oxime *VII* at a dose of 4 mg/kg brought about protracted decrease of blood pressure in rats. More detailed experiments carried out in rats with experimental hypertension (DOCA) did not support the applicable antihypertension activity. The pyrazolone derivative *VIII* showed indications of anticonvulsant activity in the test of antagonization of pentetrazol in mice. On the other hand, the expected analgesic activity could not be demonstrated. Compound *XXIII* decreases blood pressure of normotensive rats and, in agreement with expectation, has an anticholinergic activity (spasmolytic toward acetylcholine in an *in vitro* test and a weaker mydriatic effect). At a concentration of 50 μg/ml it inhibits growth of *Streptococcus β-haemolyticus*. Acid *XXVIII* brings about brief and deep drops of blood pressure in rats, has a pronounced adrenolytic and vasodilatory effect and is toxic for the rat heart. The homologous acid *XXIX* lacks these effects (but there the method of application was different). The basic ester *XXXIII* brings about in rats a brief drop of blood pressure which is followed by a flat hypertension phase. A spasmolytic effect in *in vitro* tests, both against barium chloride and against acetylcholine spasms, was only indicated. More detailed evaluation was carried out with *XVI*-HCl (LD_{50} for mice, *i.v.*, was 40 mg/kg) and *XIX*-hydrogen sulfate (LD_{50}, *i.v.*, 49 mg/kg). The first of these was evaluated as a potential β-adrenolytic[9]. It did not display, however, any antiarrhythmic effect in the adrenaline arrhytmia in rats and it was ineffective in the specific test for β-adrenolytic effect in guinea pigs. Compound *XIX* which is to a certain extent an analogue of bicyclic thymoleptics of the thiophthalane series[18], was tested as a potential psychotropic compound. It showed only a slight potentiation effect on thiopental sleep in mice (threshold dose 5 mg/kg on *i.v.* application). On the other hand, it does not show an inhibitory effect in the rotating-rod test in mice even at high doses, it is inactive in the catalepsy test in rats, it does not affect reserpine ptosis of mice and, at an intraperitoneal dose of 5 mg/kg it is inactive in the histamine aerosol test in guinea-pigs and does not antagonize the effect of serotonin in rats.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block. The samples were dried in the usual way. The UV spectra (in methanol) were recorded on a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol, unless stated otherwise) on a Unicam SP 200 G spectrophotometer and the NMR spectra (in deuteriochloroform) on a ZKR60 spectrometer (Zeiss, Jena).

4-Ethoxycarbonyl-2,3-dihydro-4*H*-1-benzothiepin-5-one (*II*)
and 4-(2-Dimethylaminoethyl)-2,3-dihydro-4*H*-1-benzothiepin-5-one (*III*)

17·8 g ketone *I* in 20 ml diethyl carbonate was added dropwise over an hour under stirring to 5·3 g 50% oil suspension of sodium hydride in 80 ml diethyl carbonate (at 100—120° bath temperature). The mixture was heated for 1·5 h at 140°C, the volatile components being thus distilled away. After cooling, the mixture was treated with 60 ml toluene and 11·8 g 2-dimethylaminoethyl chloride and the mixture was refluxed for 5 h. After standing overnight, it was decomposed with 50 ml water, the organic layer was washed with further 50 ml water and then extracted with 200 ml 20% hydrochloric acid. The organic solution of the neutral compounds was then evaporated at reduced pressure and the residue (12 g) yielded on distillation 9·7 g (39%) keto ester *II*, b.p. 145—146°C/0·5 Torr. For $C_{13}H_{14}O_3S$ (250·2) calculated: 62·39% C, 5·64% H, 12·79% S; found: 62·30% C, 5·68% H, 12·63% S.

The acid aqueous layer was refluxed for 5 h, the separated oil was cooled and extracted with benzene and the extract was distilled to recover 8·3 g (47%) of ketone *I*, b.p. 103—104°C/0·45 Torr, n_D^{23} 1·6215 (ref.[2] gives a b.p. of 119—120°C/1·5 Torr, n_D^{20} 1·6232). The acid aqueous phase was made alkaline with 20% solution of sodium hydroxide and the base *III* was isolated by extraction with benzene: 1·03 g (4·1%), b.p. 132°C/0·5 Torr. UV spectrum: λ_{max} 241 nm (log ε 4·271), 262 nm (3·773), 327 nm (3·446). IR spectrum: 743, 786 (1,2-disubstituted benzene), 1588 (Ar), 1682 cm^{-1} (Ar—CO). For $C_{14}H_{19}NOS$ (249·3) calculated: 67·44% C, 7·68% H, 5·62% N, 12·84% S; found: 67·07% C, 7·76% H, 5·43% N, 12·80% S. *Picrate*, m.p. 193—195°C (aqueous ethanol). For $C_{20}.H_{22}N_4O_8S$ (478·5) calculated: 50·21% C, 4·63% H, 11·71% N, 6·70% S; found: 50·06% C, 4·89% H, 11·84% N, 6,95% S.

5-Pyrrolidino-2,3-dihydro-1-benzothiepin (*V*)

A mixture of 44·5 g ketone *I*, 35·5 g pyrrolidine, 0·3 g *p*-toluenesulfonic acid and 200 ml benzene was refluxed for 16 h, the reaction water being separated in a separator for azeotropic distillation. After evaporation of the benzene and excess pyrrolidine, distillation of the residue yielded 50·6 g (88%) product, b.p. 140—145°C/1—1·3 Torr. For $C_{14}H_{17}NS$ (231·3) calculated: 72·70% C, 7·41% H, 6·06% N, 13·84% S; found: 72·90% C, 7·57% H, 5·84% N, 13·99% S. *Picrate*, m.p. 167—169°C (ethanol). For $C_{20}H_{20}N_4O_7S$ (460·4) calculated: 52·17% C, 4·38% H, 12·17% N, 6·95% S; found: 52·55% C, 4·54% H, 12·89% N, 7·24% S.

4-Benzyl-2,3-dihydro-4*H*-1-benzothiepin-5-one (*IV*)

A mixture of 8·1 g enamine *V*, 6·65 g benzyl chloride, 11·0 g ethyldicyclohexylamine[4] (b.p. 137—138°C/14 Torr) and 80 ml acetonitrile was heated under stirring for 11 h in a 110°C bath, acetonitrile was then distilled off, 100 ml 10% hydrochloric acid was added and the solution was refluxed for 7 h in a 120°C bath. After cooling, the separated oil was extracted with benzene, the extract was evaporated and the residue was subjected to fractional distillation. The first fraction to be recovered was ketone *I* (4·1 g), b.p. 115—118°C/1·5 Torr. Further, 2·6 g diffusely boiling fraction was obtained (up to 185°C/1·5 Torr) from which 0·35 g *ethyldicyclohexylamine hydrochloride* precipitated after dissolving in benzene. Its m.p. was 161·5—162·5°C (benzene–light petroleum. For $C_{14}H_{28}ClN$ (245·8) calculated: 68·40% C, 11·48% H, 14·42% Cl, 5·70% N; found: 68·09% C, 11·41% H, 14·66% Cl, 5·97% N.

The filtrate containing ketone *IV* was chromatographed on a column of alumina and the compound obtained by evaporation of the eluate was redistilled: b.p. 148°C/0·4 Torr. UV spectrum: λ_{max} 240 nm (log ε 4·264), 261 nm (3·785), 323 nm (3·466). IR spectrum: 700, 711, 741 and 751 (mono- and 1,2-disubstituted benzene), 1588, 1603 (Ar), 1680 cm^{-1} (Ar—CO). For $C_{17}.H_{16}OS$ (268·3) calculated: 76·10% C, 6·01% H, 11·93% S; found: 75·53% C, 5·95% H, 11·95% S.

5-[N-(2-Dimethylaminoethyl)hydroxylamino]-2,3-dihydro-1-benzothiepin (*VII*)

18·5 g 5-oximino-2,3-dihydro-4*H*-1-benzothiepin[7] were added to a solution of sodium (14 g) in 190 ml ethanol, followed by a dropwise addition of 16·4 g 2-dimethylaminoethyl chloride hydrochloride in 150 ml ethanol. The mixture was then refluxed for 2 h. After standing overnight, the ethanol was evaporated at reduced pressure, the residue was diluted with 100 ml water and extracted with benzene. The extract was decolourized with charcoal, dried and evaporated to yield 16·0 g of an inhomogeneous product. Chromatography of the sample on a thin layer of silica gel indicated that we were dealing here with a mixture of the starting oxime with two more polar compounds. Chromatography on a column of 500 g alumina and elution with benzene yielded 6·72 g of one of the more polar compounds which was treated with an ether solution of hydrogen chloride to yield the hydrochloride: m.p. 137—138°C (ethanol–ether). UV spectrum: λ_{max} 241 nm (log ε 4·193), 265 nm (3·890), 304 nm (3·324). IR spectrum: 756 and 769 (1,2-disubstituted benzene), 947 (N—O), 1607 (Ar), 1675 and 1740 (weak bands), 3390 cm^{-1}(OH?). For $C_{14}H_{21}ClN_2OS$ (300·9) calculated: 55·89% C, 7·04% H, 11·78% Cl, 9·31% N, 10·66% S; found: 55·93% C, 7·16% H, 11·72% Cl, 9·05% N, 10·48% S.

2-Phenyl-2,3,4,5-tetrahydropyrazolo(4,3-*d*)-1-benzothiepin-3-one (*VIII*)

A solution of 5·37 g keto ester *II* and 2·31 g phenylhydrazine in 10 ml ethanol was refluxed for 1 h and then ethanol was slowly distilled from the bath at 110°C (7 h). The residue was recrystallized from a mixture of benzene and ethanol: 5·4 g, m.p. 208—209°C. For $C_{17}H_{14}N_2OS$ (294·3) calculated: 69·37% C, 4·80% H, 9·52% N, 10·88% S; found: 69·00% C, 5·00% H, 9·43% N, 10·81% S.

7-Acetyl-2,3,4,5-tetrahydro-1-benzothiepin (*X*)

This was prepared in a 57% yield by a reaction of 2,3,4,5-tetrahydro-1-benzothiepin (ref.[10,11]) (*IX*) (b.p. 133—135°C/16 Torr, n_D^{22} 1·5930) with acetyl chloride and aluminium chloride in carbon disulfide; b.p. 150°C/1 Torr. Ref.[10] gives for a similarly prepared product a b.p. of 200—204°C at 20 Torr. *Oxime* XI was prepared in a 87% yield by a reaction of ketone with hydroxylamine hydrochloride in a mixture of pyridine and ethanol; m.p. 97·5—99°C (benzene–light petroleum). For $C_{12}H_{15}NOS$ (221·3) calculated: 65·14% C, 6·83% H, 6·33% N, 14·46% S; found: 65·08% C, 6·93% H, 6·30% N, 14·33% S.

7-Acetamido-2,3,4,5-tetrahydro-1-benzothiepin (*XII*)

A mixture of polyphosphoric acid (from 45 ml 85% phosphoric acid and 69 g phosphorus pentoxide) and 19·1 g oxime *XI* was heated for 10 min to 105°C and decomposed by pouring into water and ice. The precipitated product crystallized overnight in a quantitative yield: m.p. 119 to 121°C (benzene). UV spectrum: λ_{max} 232·5 nm (log ε 3·981), 273 nm (4·226). IR spectrum: 828 and 861 (1,2,4-trisubstituted benzene), 1587, 1620, 1640 (Ar and amide), 3100, 3200, 3224 and 3320 cm^{-1} (NH). For $C_{12}H_{15}NOS$ (221·3) calculated: 65·14% C, 6·83% H, 6·33% N, 14·46% S; found: 64·82% C, 6·82% H, 6·24% N, 14·18% S.

7-Amino-2,3,4,5-tetrahydro-1-benzothiepin (*XIII*)

A solution of 22·1 g amide *XII* in 100 ml ethanol was mixed with 100 ml 50% sulfuric acid and refluxed for 1 h and then poured into ice-cold water. The suspension formed was cooled and made alkaline with aqueous ammonia. The liberated base crystallized upon standing· 19·8 g, m.p. 51—54·5°C. It was dissolved in a hot mixture of 60 ml water and 20 ml concentrated sulfuric acid, the warm solution was filtered with charcoal and the filtrate was cooled. A total of 13·1 g

(58%) *sulfate* precipitated, m.p. 194—196°C (ethanol). For $C_{10}H_{13}NS.1/2\ H_2SO_4$ (228·3) calculated: 52·60% C, 6·18% H, 6·14% N, 21·07% S; found: 52·26% C, 6·22% H, 6·01% N, 20·99% S.

7-Hydroxy-2,3,4,5-tetrahydro-1-benzothiepin (*XIV*)

A suspension of 12·5 g sulfate of compound *XIII* in a mixture of 60 ml water and 20 ml concentrated sulfuric acid was diazotized with a solution of 3·86 g sodium nitrite in 10 ml water at 0—5°C, the mixture was left overnight at room temperature, diluted with 50 ml water and heated for 30 min on a boiling water bath. After cooling, the not completely pure product was isolated by extraction with benzene and by distillation: 4·7 g (48%), b.p. 130°C/0·4 Torr. For $C_{10}H_{12}OS$ (180·2) calculated: 66·65% C, 6·71% H, 17·76% S; found: 66·04% C, 6·52% H, 17·22% S.

7-(2,3-Epoxypropoxy)-2,3,4,5-tetrahydro-1-benzothiepin (*XV*)

4·5 g phenol *XIV* and 10·0 g epichlorohydrin were added to a solution of 2·0 g sodium hydroxide in 25 ml water. The solution was left for 2 days at room temperature, the separated oil was extracted with ether, the extract was evaporated and the residue heated for 45 min with 6 g potassium carbonate and 5 ml water on a boiling-water bath. After cooling, the separated oil was extracted with benzene and the extract distilled: 3·7 g (62%), b.p. 145—150°C/0·3 Torr. For $C_{13}H_{16}O_2S$ (236·3) calculated: 66·08% C, 6·83% H, 13·55% S; found: 65·70% C, 6·95% H, 12·98% S.

7-(3-Isopropylamino-2-hydroxypropoxy)-2,3,4,5-tetrahydro-1-benzothiepin (*XVI*)

A mixture of 3·6 g epoxide *XV*, 5 ml isopropylamine and 20 ml ethanol was left for 4 days at room temperature. The volatile fractions were evaporated on a water bath, the residue was dissolved in methanol and, applying an ether solution of hydrogen chloride, the base was converted to the *hydrochloride*; 4·6 g (91%) m.p. 181—182°C (ethanol–ether). For $C_{16}H_{26}ClNO_2S$ (331·9) calculated: 57·90% C, 7·90% H, 10·68% Cl, 4·22% N, 9·66% S; found: 57·89% C, 8·05% H, 10·58% Cl, 3·97% N, 9·55% S.

5-Phenyl-2,3,4,5-tetrahydro-1-benzothiepin-5-ol (*XVII*) and 5-Phenyl-2,3-dihydro-1-benzothiepin (*XX*)

Reaction of 3·6 g lithium wire with 33 g bromobenzene in 120 ml ether (3 h, nitrogen atmosphere) led to a solution of phenyllithium. Within 1 h, 30 g ketone *I* was added under stirring (an exothermic reaction), the mixture was stirred for 90 min at room temperature and, after standing overnight, it was decomposed with 80 ml water. Treatment of the ether phase by distillation yielded 9·8 g fraction, boiling at 173°C/0·8 Torr and further 32·4 g fraction (75%) boiling at 173—183°C/1 Torr. The product for analysis was redistilled, b.p. 178—179°C/0·6 Torr. It is the alcohol *XVII*. For $C_{16}H_{16}OS$ (256·3) calculated: 74·98% C, 6·29% H, 12·49% S; found: 75·39% C, 6·41% H, 12·24% S.

The first fraction, a mixture of ketone *I* and alcohol *XVII*, was dissolved in 20 ml ethanol, the solution was made acid with three drops of concentrated hydrochloric acid and left to stand overnight at room temperature. The precipitate was 2·7 g olefin *XX*, m.p. 112·5—113°C (ethanol). UV spectrum: λ_{max} 250 nm ($\log \varepsilon$ 4·258). IR spectrum: 709, 751 and 775 cm^{-1} (monosubstituted and 1,2-disubstituted benzene). For $C_{16}H_{14}S$ (238·4) calculated: 80·63% C, 5·92% H, 13·45% S; found: 80·37% C, 5·86% H, 13·06% S.

5-Phenyl-2,3,4,5-tetrahydro-1-benzothiepin (*XVIII*)

A mixture of 50 ml acetic acid, 6·3 g red phosphorus and 2·7 g iodine was left for 20 min at room temperature and then treated with 31·6 g carbinol XVII in 50 ml acetic acid and 2 ml water. The

mixture was refluxed under stirring for 7·5 h, filtered while hot and the filtrate was poured into a solution of 13 g sodium sulfite in 500 ml water. The precipitated product was recrystallized from ethanol: 28·4 g (96%), m.p. 77—78°C. UV spectrum: λ_{max} 218 nm (log ε 4·202), 263 nm (3·744). IR spectrum: 710 and 765 (monosubstituted and 1,2-disubstituted benzene), 1583 and 1602 cm^{-1} (Ar). For $C_{16}H_{16}S$ (240·3) calculated: 79·97% C, 6·71% H, 13·32% S; found: 79·69% C, 6·74% H, 13·56% S.

N-(3,3-Diphenylbutyl)dimethylamine (*XXIII*)

2·3 g sodium was added to 80 ml tetrahydrofuran and 12·8 g naphthalene and the spontaneously heated mixture was stirred for 2·5 h. Then 18·17 g 1,1-diphenylethane[13] was added (b.p. 87 to 90°C/0·4 Torr, n_D^{25} 1·5690) in 15 ml tetrahydrofuran, the mixture was stirred for further 2 h at room temperature and then 10·8 g 2-dimethylaminoethyl chloride was added over a period of 10 min. After 10 min of refluxing it was decomposed by pouring onto ice and extracted with ether. The extract was shaken with a solution of 30 ml concentrated hydrochloric acid in 120 ml water, the acid aqueous solution was evaporated to dryness at reduced pressure, the noncrystalline hydrochloride was converted in the usual way to the base (12·17 g) which was neutralized with 8·0 g maleic acid in 30 ml ethanol. Addition of ether precipitated a *hydrogen maleate*: 19·4 g, m.p. after several crystallizations from ethanol: 183—187°C. For $C_{22}H_{27}NO_4$ (369·4) calculated: 71·52% C, 7·37% H, 3·79% N; found: 71·42% C, 7·44% H, 3·65% N.

5-(3-Dimethylaminopropyl)-5-phenyl-2,3,4,5-tetrahydro-1-benzothiepin (*XIX*)

Similarly to the preceding case, 5·75 g of compound *XVIII* were alkylated with 3·0 g 3-dimethylaminopropyl chloride (3·1 g naphthalene, 0·55 g sodium, 45 ml tetrahydrofuran). A total of 3·45 g crude base was obtained which was distilled to yield 1·35 g (17%) pure product boiling at 165°C at 0·4 Torr. For $C_{21}H_{27}NS$ (325·4) calculated: 77·50% C, 8·36% H, 4·30% N, 9·83% S; found: 77·45% C, 8·79% H, 3·91% N, 9·58% S. *Hydrogen sulfate* was prepared from an acetone solution of the base by treatment with dilute sulfuric acid: m.p. 205—208°C (ethanol). For $C_{21}H_{29}.NO_4S$ (423·5) calculated: 59·56% C, 6·90% H, 3·31% N, 15·12% S; found: 59·52% C, 6·88% H, 3·30% N, 15·41% S.

3-Bromo-5-phenyl-2,3-dihydro-1-benzothiepin (*XXI*)
and 3,3-Dibromo-5-phenyl-2,3-dihydro-1-benzothiepin (*XXII*)

A mixture of 2·48 g olefin *XX*, 1·85 g N-bromosuccinimide and 100 ml tetrachloromethane was refluxed for 3 h. After cooling, it was filtered and the filtrate was evaporated. The residue was boiled with 6·4 g potassium acetate in 100 ml ethanol to attempt dehydrohalogenation. After evaporating the mixture and separating the residue between water and benzene, treatment of the organic phase yielded 3·57 g of a compound containing bromine. The compound was chromatographed on neutral alumina and elution with light petroleum yielded 1·0 g solid fraction, a part of which was soluble in boiling methanol. Crystallization from methanol produced the monobromo derivative *XXI*, m.p. 103·5—104·5°C. For $C_{16}H_{13}BrS$ (317·3) calculated: 60·57% C, 4·13% H, 10·11% S; found: 60·73% C, 4·19% H, 10·19% S. The methanol-insoluble fraction was recrystallized from hexane and was found to be the dibromo derivative *XXII*, m.p. 132—134°C (decomp.). For $C_{16}H_{12}Br_2S$ (396·2) calculated: 48·51% C, 3·05% H, 8·10% S; found: 49·07% C, 2·62% H, 8·31% S.

4-Phenyl-4-(phenylthio)butyric Acid (*XXVIII*)

22·1 g thiophenol and 32·4 g 4-phenylbutyrolactone[16] (*XXVI*) (b.p. 133°C/2 Torr) were added to a solution of 4·6 g sodium in 100 ml ethanol and the mixture was refluxed under stirring for 4 h. Ethanol was then evaporated, the residue was dissolved in 300 ml water, the solution was filtered and the filtrate was made acid with 30 ml concentrated hydrochloric acid; 34·8 g (64%), m.p. 124—126°C (changes from 95°C) (ethanol). UV spectrum: λ_{max} 214 nm (log ε 4·147), 255 nm (3·696). IR spectrum: 701, 741, 760 (monosubstituted benzene), 931, 1237, 1318, 1713 (COOH), 1583 cm^{-1}(Ar). For $C_{16}H_{16}O_2S$ (272·3) calculated: 70·57% C, 5·92% H, 11·75% S; found: 70·45% C, 5·97% H, 11·65% S.

4-Phenyl-7-methyl-1-tetralone (*XXXI*)

A mixture of polyphosphoric acid from 120 g phosphorus pentoxide and 80 ml 85% phosphoric acid, 20·0 g acid *XXVIII* and 200 ml toluene was refluxed for 8 h under stirring. After cooling, the reaction mixture was poured into ice-cold water, the toluene layer was separated and the aqueous one was extracted with benzene. The combined organic phases were washed with 5% sodium hydroxide, dried with $MgSO_4$ and evaporated. A total of 17·8 g of a mixture of neutral compounds was obtained, from which 14·5 g distilled between 140—220°C/1·2 Torr. The distillate was dissolved in 150 ml ethanol, a solution of 16·0 g semicarbazide hydrochloride and 19·0 g potassium acetate in 30 ml water was added and the mixture was refluxed for 4·5 h. Ethanol was then evaporated, the residue separated between water and benzene, the benzene layer was evaporated and the remaining oil was dissolved in a small amount of cyclohexane to yield 3·2 g crystalline semicarbazone which was twice recrystallized from a mixture of benzene and cyclohexane: m.p. 150—155°C. UV spectrum: λ_{max} 219 nm (log ε 4·408), 282 nm (4·292). IR spectrum: 700, 735 (monosubstituted benzene), 1496 (Ar), 1585 (C=N conjugated), 1695 ($CONH_2$), 3260 and 3481 cm^{-1} (NH_2 and NH). For $C_{18}H_{19}N_3O$ (293·4) calculated: 73·69% C, 6·53% H, 14·33% N; found: 73·66% C, 6·60% H, 14·17% N. A mixture of 1·46 g semicarbazone, 8·0 g dihydrate of oxalic acid and 25 ml water was refluxed for 7 h. The separated oil was cooled and isolated by extraction with chloroform (1·16 g) and by distillation; b.p. 160°C/2 Torr, m.p. 76·5—77·5°C (light petroleum). According to spectra and analyses it is the ketone *XXXI*. IR spectrum (CCl_4): 711 (monosubstituted benzene), 1290 (CO in a ring), 1500 and 1615 (Ar), 1690 cm^{-1} (CO conjugated). NMR spectrum: ϑ 8·00 (singlet, 1 H in position 8 of the tetraline skeleton), 7·60—6·85 (multiplet, 7 H, other aromatic protons), 4·13 (triplet, 1 H in position 4 of the tetraline skeleton), 3·00—2·00 (multiplet, 4 H of the CH_2 groups) 2·35 (singlet, 3 H of methyl). For $C_{17}H_{16}O$ (236·3) calculated: 86·40% C, 6·83% H; found: 86·52% C, 6·88% H.

2-Dimethylaminoethyl 4-phenyl-4-(phenylthio)butyrate (*XXXIII*)

13·6 g acid *XXVIII* was added to a solution of 1·15 g sodium in 100 ml ethanol followed after dissolving by 5·9 g 2-dimethylaminoethyl chloride. The mixture was refluxed for 3 h, ethanol was evaporated and the residue was separated between water and ether. The organic phase was dried with Na_2SO_4 and evaporated. The residue was dissolved in a small amount of ethanol, a solution of 3·5 g maleic acid in ethanol was added and, by adding ether, 7·5 g (33%) *hydrogen maleate* precipitated: m.p. 109°C (ethanol). For $C_{24}H_{29}NO_6S$ (459·5) calculated: 62·73% C, 6·36% H, 3·05% N, 6·97% S; found: 63·05% C, 6·35% H, 3·00% N, 6·92% S.

4-(2,4,6-Trimethylphenyl)butyrolactone (*XXVII*)

58·6 g 3-(2,4,6-trimethylbenzoyl)propionic acid[17] (*XXV*) (m.p. 108°C) was added in 600 ml 5% solution of sodium hydroxide. The solution was treated with 10·1 g sodium borohydride

in 30 ml water, the mixture was stirred for 1 h at room temperature, then heated for 4 h on a boiling-water bath, made acid with hydrochloric acid and heated for another hour. After cooling, the separated oil was extracted with benzene, the extract was washed with 5% sodium carbonate (acidification of the washings recovered 11·0 g of the starting compound *XXV*) and distilled: 41·0 g (76%), b.p. 155°C/1·5 Torr, m.p. 56—58°C (ether–light petroleum). UV spectrum: λ_{max} 219 nm ($\log \varepsilon$ 3·989). IR spectrum: 890 (solitary H at the benzene ring), 1573 and 1611 (Ar), 1771 cm^{-1} (γ-lactone). For $C_{13}H_{16}O_2$ (204·3) calculated: 76·44% C, 7·90% H; found: 76·49% C, 7·80% H.

4-(4-Chlorophenylthio)-4-(2,4,6-trimethylphenyl)butyric Acid (*XXIX*)

28·3 g 4-chlorothiophenol were added to a solution of 4·5 g sodium in 150 ml ethanol and the solution formed was evaporated to dryness *in vacuo*. The residue was mixed with 150 ml dimethylformamide and 40·4 g lactone *XXVII*, the mixture was stirred for 13 h in a water bath at 100 to 110°C and dimethylformamide was distilled at reduced pressure. The residue was dissolved in water, the solution was washed with benzene, made acid with dilute hydrochloric acid and the volatile components removed by steam-distillation. On cooling, an acid precipitated and was recrystallized from benzene: 52·9 g (77%) m.p. 97—99°C (ethanol). UV spectrum: λ_{max} 217 nm ($\log \varepsilon$ 4·337), 234·5 nm (4·175), 265 nm (3·910). IR spectrum: 816, 850, 890 (1,4-disubstituted and 1,2,3,5-tetrasubstituted benzene), 1607 (Ar), 1691 cm^{-1} (COOH). For $C_{19}H_{21}ClO_2S$ (348·9) calculated: 65·41% C, 6·07% H, 10·16% Cl, 9·19% S; found: 65·22% C, 6·00% H, 10·17% Cl, 9·37% S.

4-(2,4,6-Trimethylphenyl)-7-methyl-1-tetralone (*XXXII*)

A mixture of polyphosphoric acid (from 70 g phosphorus pentoxide and 40 ml 78% phosphoric acid), 14·0 g acid *XXIX* and 80 ml toluene was refluxed under stirring for 6 h in a 110°C bath. It was then decomposed by pouring into ice-cold water, the toluene phase was separated and the aqueous one extracted with benzene. The combined organic phases were washed with 10% sodium hydroxide and water, dried (Na_2SO_4) and evaporated. The residue (11 g) was shown to be a mixture of several compounds on thin-layer chromatography on silica gel. Chromatography of the mixture on a column of alumina yielded bis(*p*-chlorophenyl)disulfide (m.p. 70 to 71°C) and further a compound which was free of sulfur and chlorine and melted at 92—94°C (methanol). UV spectrum: λ_{max} 213 nm ($\log \varepsilon$ 4·514), 250·5 nm (4·095), 300 nm (3·502). IR spectrum: 810, 820, 850, 896 (1,2,4-trisubstituted benzene and 1,2,3,5-tetrasubstituted benzene), 1510, 1611 (Ar), 1686 cm^{-1} (CO conjugated). NMR spectrum: ϑ 7·90 (singlet, 1H in position 8 of the tetraline skeleton), 7·40—6·70 (multiplet, other aromatic protons), 4·15 (triplet, 1H in position 4 of the tetraline skeleton), 2·80—2·10 (multiplet, CH_2 groups), 2·30 (methyl groups). For $C_{20}H_{22}O$ (278·4) calculated: 86·28% C, 7·97% H; found: 86·17% C, 7·45% H.

The detailed pharmacological testing of XIX *was done by Dr J. Metyšová and Dr J. Metyš, that of compounds* VII *and* XVI (*from the point of view of cardiovascular activity*) *by Dr V. Trčka and Dr M. Vaněček of the pharmacological department of this Institute. Evaluation of the antimicrobial activity was done by Dr J. Turinová at the bacteriological department of the Institute (headed by Dr A. Šimek). The analytical estimations were done at the analytical department of this Institute (headed by Dr J. Körbl) by Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech and Mrs A. Slavíková.*

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