NEUROTROPIC AND PSYCHOTROPIC COMPOUNDS. LV.*

NEW SYNTHESES OF 8-CHLORO-10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b,f*] THIEPIN AND RELATED COMPOUNDS

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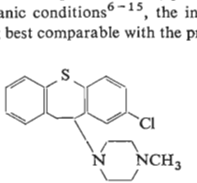
New preparations of intermediates of the synthesis of compound *I* are described: alcohol *III*, acid *VI* and ketone *VII*. The product of reaction of the acetophenone derivative *XVIII* with morpholine and sulfur is the oxothiomorpholide *XX*. Reaction of di(4-chlorophenyl) sulfide with aluminium chloride and oxalyl chloride yielded 2,7-dichlorothioxanthone (*XXV*); an analogous reaction with chloroacetyl chloride yielded compound *XXVI*. Heating of ketone *VII* with salts of 1 methylpiperazine to 180–200°C *in vacuo* gives rise to enamine *XXVII*. Conditions for a substitution reaction of chloride *IX* with 1-methylpiperazine were found under which the elimination reaction (yielding olefin *XXIX*) is suppressed. Reduction of carbamate *XXVIII* by complex hydrides yields *I*. New salts of base *I* were prepared, of which dibenzoyl-(+)-tartrate and (+)-tartrate were used for resolving the racemic base *I* to its antipodes; pharmacodynamically, both antipodes and the racemate are rather similar. Preparation of 2-chloro-10,11-dihydrodibenzo[*b,f*]-thiepin (*XXX*) *via* reduction of ketone *VII* with hydrazine was studied. As by-product, the heptacyclic pyrrole *XXXI* was obtained.

Some time ago[1–3] we described the preparation of 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin ("octoclothepin") (*I*) by a substitution reaction of 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin (*IX*) with 1-methylpiperazine. The product showed a high neuroleptic activity which substantiated its clinical testing and introduction into therapeutical practice[4] (Clotepin^R-Spofa). The compound was studied in detail[5] pharmacologically and toxicologically, further from the point of view of pharmacokinetics, metabolism and possible teratogenic effect. Clinically, octoclothepin had a good therapeutical effect, particularly toward psychoses of the schizophrenic type and toward manic conditions[6–15], the intensity of its therapeutical effect as well as of the side reaction being best comparable with the properties of perphenazine[16].



I

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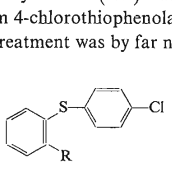
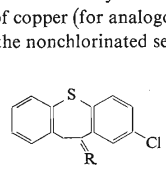
In the present study we deal first with variations of the individual phases of synthesis of *I*, proceeding from 2-iodobenzoic acid[17] and 4-chlorothiophenol[18] and continuing *via* intermediates[2] *II*–*IX*. The objective was to simplify the procedure and to increase its efficiency. In some cases the aim was reached, in others we encountered unexpected results and novel products, to be described below. First of all, attention was concentrated on seeking feasible ways of preparing alcohol *III* which was obtained so far only by reduction of acid *II* with lithium aluminium hydride[2,3]. A possible approach is represented by the application of sodium bis(2-methoxyethoxy)-dihydroaluminate[19] as reducing agent which provides stable yields of more than 90% (as was described for the selenium analogue[20]). For the reduction, one can also use an agent prepared from sodium borohydride and aluminium chloride in tetrahydrofuran but the yield is relatively low. For characterization,alcohol *III* was converted to 4-nitrobenzoate *X*.

In further work, we sought ways of preparing acid *VI* that would not require the hydride reduction step. Condensation of 2-iodophenylacetic acid (this became available through a recently described reaction of phenylacetic acid with thallium(III) trifluoroacetate and potassium iodide[21]) with 4-chlorothiophenol[18] gives a 65% yield of acid *VI* (methodically, the introduction of 2-iodophenylacetic acid into this type of synthesis was recently described[22]). In subsequent experiments, it was attempted to use as intermediate the readily available 2-tolyl 4'-chlorophenyl sulfide[23] (*XV*), the radical halogenation of which promised a feasible approach to compounds of the type of chloride *IV*. The reaction sequence was tested first in the nonchlorinated series. Phenyl 2-tolyl sulfide[24] (*XI*) was converted by bromine at 150–165°C or even better by N-bromosuccinimide in boiling tetrachloromethane and in the presence of dibenzoyl peroxide to 2-phenylthiobenzyl bromide (*XII*) (its preparation was described recently[25], proceeding from the corresponding alcohol and hydrobromic acid). Conversion to the crude nitrile *XIII* was done in the usual way[26], the nitrile yielding upon alkaline hydrolysis 2-(phenylthio)phenylacetic acid[26] (*XIV*). The experience obtained was then applied to the 4'-chloro series. The starting 2-tolyl 4'-chlorophenyl sulfide (*XV*) was prepared by a reaction of 2-tolyldiazonium sulfate with sodium 4-chlorothiophenolate in the presence of copper (for analogous methods see[27]). Its treatment was by far not as smooth as in the nonchlorinated series. Bromi-



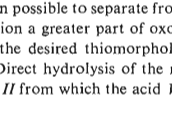
II, R = COOH
III, R = CH_2OH
IV, R = CH_2Cl
V, R = CH_2CN
VI, R = CH_2COOH



VII, R = O
VIII, R = <H/OH
IX, R = <H/Cl

nation with bromine and bromosuccinimide yields nonhomogeneous products, the distillation of which is accompanied by partial decomposition so that the isolation of pure bromide *XVI* was not successful. The crude product of bromination was converted to acid *VI via* nitrile *V* but the total yield of 23% is not satisfactory from the preparative point of view.

A possibility for the preparation of acid *VI* is provided by Willgerodt's reaction[28,29] which was recently applied by Japanese authors[30] to the preparation of unsubstituted acid *XIV* and of its 4'-methoxy derivative. When it was found impossible to reproduce the preparation of the starting 2-(phenylthio)acetophenone (*XVII*) described by these authors through the reaction of 2-chloroacetophenone with sodium thiophenolate, another preparation procedure of the starting compound was preferred for the chlorinated series. Acylation of the ethoxymagnesiummalonic ester with 2-(4-chlorophenylthio)benzoyl chloride[18] and subsequent hydrolysis of the product led to 2-(4-chlorophenylthio)acetophenone (*XVIII*). Using this compound, Willgerodt's reaction with sulfur and morpholine was carried out at 150—160°C which provided a mixture of two neutral products at a ratio of about 3 : 1 (according to thinlayer chromatography). After column chromatography on alumina only a minor component was obtained in a crystalline state. The compound in question had the formula $C_{18}H_{16}ClNO_2S_2$ which, upon alkaline hydrolysis, yields the acid *II*, *i.e.* a lower homologue of the desired acid *VI*. The facts, together with the spectra, led to the conclusion that the product is oxothiomorpholide *XX*. The product of this type was detected and characterized during Willgerodt's reaction for the first time by Dauben and Rogan[31] when using acetylmesitylene, *i.e.* a sterically hindered ketone. Also the present ketone *XVIII* is sterically considerably hindered and, also, the Japanese authors[30] mentioned the formation of "oxothiomorpholides" which they did not characterize further. The formation of the oxothiomorpholides is apparently the first step occurring during Willgerodt's reaction. In the case of steric hindrance of the keto group the second stage cannot fully set in, *viz.* reduction of the keto group. In the present case, it was then possible to separate from the crude products of Willgerodt's reaction, by seeding and crystallization a greater part of oxothiomorpholide while the remaining oily product, composed mainly of the desired thiomorpholide *XIX*, was converted by alkaline hydrolysis to the desired acid *VI*. Direct hydrolysis of the mixture of compounds *XIX* and *XX* results in a mixture of acids *VI* and *II* from which the acid *VI* can be isolated only with substantial losses on crystallization.



X, $R^1 = 4\text{-}CH_2OCOC_6H_4NO_2$, $R^2 = Cl$
XI, $R^1 = CH_3$, $R^2 = H$
XII, $R^1 = CH_2Br$, $R^2 = H$
XIII, $R^1 = CH_2CN$, $R^2 = H$
XIV, $R^1 = CH_2CO_2H$, $R^2 = H$

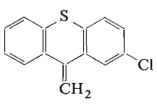
XV, $R^1 = CH_3$, $R^2 = Cl$
XVI, $R^1 = CH_2Br$, $R^2 = Cl$
XVII, $R^1 = COCH_3$, $R^2 = H$
XVIII, $R^1 = COCH_3$, $R^2 = Cl$
XIX, $R^1 = CH_2CSN\langle O \rangle$, $R^2 = Cl$

XX, $R^1 = COCSN\langle O \rangle$, $R^2 = Cl$

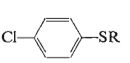
The method of choice for the preparation of ketone *VII* remains the cyclization of acid *VI* with polyphosphoric acid[1-3]. The nonchlorinated ketone[26] was prepared

analogously (see[32]).* A novel method of preparation of ketones of this type[33,34], consisting in a reaction of *o*-(chlorosulfenyl)phenylacetyl chloride with benzene and aluminium chloride, can be hardly considered in the case of ketone *VII*. On the other hand, some promise is held by the oxidation of olefins with thallic nitrate, taking place with a rearrangement of the skeleton and yielding ketones[35]. Thermal dehydration of 2-chloro-9-methylthioxanthen-9-ol[18] led to 2-chloro-9-methylenethioxanthene (*XXI*) which, through the above oxidation, yielded a mixture of predominating amount of ketone *VII* (isolated by crystallization and characterized) and of a smaller amount of isomeric 2-chloro-10-ketone[36].

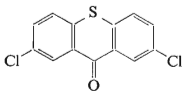
Another potential intermediate of synthesis of ketone *VII* was seen in di(2-phenylacetyl-4-chlorophenyl) disulfide, the preparation of which was attempted by the Friedel-Crafts reaction of di-(4-chlorophenyl) disulfide[37] (*XXII*) with phenylacetyl chloride. Instead of the expected reaction, cleavage took place, the products of which were 4-chlorothiophenol[18] and a novel (4-chlorophenyl)thiophenyl acetate (*XXIII*). A similar reaction course was reported by Herz and Tarbell[38] in an attempt to acetylate diphenyl disulfide with acetyl chloride. In this connection, attempts were made to perform the Friedel–Crafts reaction with bis(4-chlorophenyl) sulfide[39] (*XXIV*). When using oxalyl chloride and aluminium chloride in dichloromethane we aimed at 2,8-dichlorodibenzo[*b,f*]thiepin-10,11-dione; however, we obtained 2,7-dichlorothioxanthone[36] (*XXV*). Its formation is accounted for by decarbonylation of the primarily formed diketone (decarbonylation of α-diketones of this type do not seem to appear in the literature[40]) rather than *via* a benzil rearrangement[41]). Reaction of sulfide *XXIV* with chloroacetyl chloride and aluminium chloride in di-



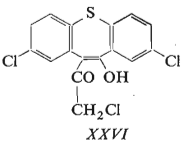
XXI



XXII, R = 4-SC_6H_4Cl
XXIII, R = $COCH_2C_6H_5$
XXIV, R = 4-C_6H_4Cl



XXV



XXVI

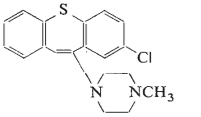
* For calling their attention to the dissertation and making it available to them, the authors are indebted to Prof. A. Lüttringhaus, Albert-Ludwigs-Universität, Freiburg im Breisgau, GFR.

chloromethane was an attempt at a direct preparation of 2,8-dichloro-11*H*-dibenzo-[*b*,*f*]thiepin-10-one[36]. Besides the starting compound the only crystalline compound obtained was one with formula $C_{16}H_9Cl_3O_2S$, the composition of which suggests that two molecules of chloroacetyl chloride participated in the reaction, one of them reacting at both reactive ends (an increment of only 1 chlorine atom). The UV spectrum indicates rich conjugation and a dibenzo[*b*,*f*]thiepin chromophore. The peak at 1640 cm^{-1} in the IR spectrum indicates the presence of a CO—C=C—OH fragment with the keto group in a hydrogen bond. On the basis of all these facts we assume the primarily desired course of reaction with subsequent attack of the second molecule of chloroacetyl chloride at the bridge formed. As probable structure of the product we suggest *XXVI* where both the IR spectrum (in Nujol) and the UV spectrum (in methanol solution) support the fixed enol form.

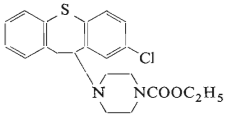
For the final step of synthesis of base *I*, *i.e.* a substitution reaction of the dichloro derivative *IX* with excess 1-methylpiperazine, we reported in an earlier paper[2] a yield of only 25% when working without and 53% when working with boiling chloroform. It was found subsequently that the ratio of substitution and elimination depends on the quality of the 1-methylpiperazine used. Beside this starting base, obtained *via* 1-(ethoxycarbonyl)piperazine[42], we used also methylpiperazine prepared by methylation of piperazine monohydrochloride with dimethyl sulfate[43]. It was found later that the product thus obtained contains a variable amount of 1,4-dimethylpiperazine which increases considerably the fraction of elimination in the reaction with chloride *IX*. In this way one must explain the low yields of analogous reactions in some of our further work[36,44–51]. When using completely pure 1-methylpiperazine[52,53], reaction with chloride *IX* produced as much as 83% yield of substitution. The neutral product then represents a mixture of chloride *IX* and of the elimination product *XXIX* where one or the other component predominates, depending on the conditions used.

Base *I* can be further prepared by reduction of enamine[54] *XXVII*, reduction of carbamate[55] *XXVIII* by hydride agents[56], methylation of the 10-piperazine analogue with a free secondary amino group[57], reaction of 8-chloro-10-[bis(2-chloroethyl)-amino]-10,11-dihydrodibenzo[*b*,*f*]thiepin with methylamine[55]. In the experimental section a modified method of preparing enamine *XXVII* is described, the procedure being superior to the ways described before[54,58,59]. It consists in heating a mixture of ketone *VII* with mono-salts of 1-methylpiperazine (monohydrochloride, monomethanesulfonate, mono-*p*-toluenesulfonate) to 180–200°C *in vacuo*. Reaction water is removed much faster than in the classical way of preparing enamines[54] so that the reaction is terminated in 2–4 h and enamine *XXVII* is obtained in the form of maleate in a yield of 50–60%. The possibility of formation of enamine *XXVII* by simple heating of ketone *VII* with the salts of 1-methylpiperazine was suggested by the high central depressant and neuroleptic activity of the crude melts thus obtained. It is probable that this technically advantageous method of enamine preparation is a generally useful one. Reduction of carbamate *XXVIII* was carried out either with lithium aluminium hydride or with sodium bis(2-methoxyethoxy)dihydroaluminate. Several new salts of base *I* are also described, the monomethane-

sulfonate and dimethanesulfonate being the only ones readily soluble in water and hence suited for preparation of injection solutions. Using basic dibenzoyl(+)-tartrate an unsuccessful attempt was made to resolve the racemic base *I*. Resolution was achieved by crystallization of neutral dibenzoyl-(+)-tartrate (yielding the laevorotatory base *I*), and of (+)-tartrate (yielding the dextrorotatory base *I*).



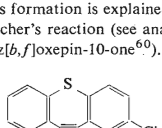
XXVII



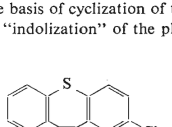
XXVIII

Whereas cold aqueous solutions of octoclothepin (*I*) salts (*e.g.* methanesulfonate) are stable, the molecule is completely cleaved in the presence of excess, dilute or conc. HCl at the boiling temperature, the neutral product being a noncrystalline substance, characterized by chromatography on a thin layer as a mixture of 2-chlorodibenzo[*b,f*]thiepin (*XXIX*) and of 8,10-dichloride (*IX*) at an approximate ratio of 1 : 3. It was not possible to separate this mixture by crystallization. Cleavage of *I* takes place also in the presence of excess formic acid; this gives rise again to an oily neutral product, according to chromatography apparently dibenzo[*b,f*]thiepin (*XXIX*) but the substance could not be induced to crystallize even on seeding with authentic[2] *XXIX*. The NMR spectrum showed it to be a mixture of two compounds, one of them displaying olefinic protons (apparently *XXIX*), the other a singlet corresponding to the $-CH_2CH_2-$ fragment which is attributed to the presence of 2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XXX*). The instability of the octoclothepin (*I*) molecule in boiling formic acid accounts also for the unsuccessful preparation of *I* by Leuckart's reaction of ketone *VII* with 1-methylpiperazine; compound *I* is then formed in a yield of about 2% (see the result of a similar experiment in the 8-nonchlorinated series[41]).

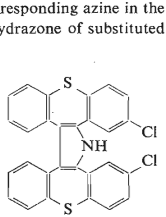
For the sake of comparison we prepared 2-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XXX*) by Huang-Minlon's reduction of ketone *VII*. As by-product, we isolated a substance not melting below 360°C and poorly soluble, which according to the mass spectrum and analyses has the formula $C_{28}H_{15}Cl_2NS_2$. The IR spectrum shows a sharp intense band at 3420 cm^{-1}, corresponding to the NH group. In agreement with this, the NMR spectrum displays besides the multiplet of aromatic and conjugated olefinic protons one proton disappearing on deuterization which might correspond to the NH group. The substance is assumed to have the structure of *XXXI* and its formation is explained on the basis of cyclization of the corresponding azine in the sense of Fischer's reaction (see analogous "indolization" of the phenylhydrazone of substituted 11*H*-dibenz[*b,f*]oxepin-10-one[60]).



XXIX

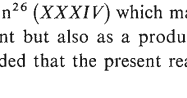


XXX

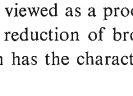


XXXI

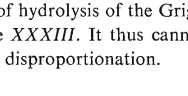
The ready solubility of methanesulfonates of base *I* suggested the preparation of a similar salt of "perathiepin"[26,41] (*XXXII*). The previously prepared 10-bromodibenzo[*b*,*f*]thiepin[41] (*XXXIII*) was taken into a Grignard reaction. In boiling tetrahydrofuran the compound (*XXXIII*) reacts slowly with magnesium. Subsequent treatment with acetone and processing of the reaction mixture yielded a substance which, however, is not the expected dibenzo[*b*,*f*]thiepin-8-yl-dimethylcarbinol[61]. The same compound is formed without addition of acetone. We are thus dealing with a product of interaction of bromide *XXXIII* with magnesium and tetrahydrofuran and of subsequent hydrolysis as indicated by the empirical formula $C_{18}H_{18}O_2S$. Using the spectra, the product was identified as 10-(1,4-dihydroxybutyl) dibenzo[*b*,*f*]-thiepin (*XXXV*). Even if cleavage of ethers by Grignard's reagents has been occasionally observed and the cleavage of oxides is a generally occurring reaction[62] no analogy was found for the reaction observed here where the cleavage of the ether must be accompanied by oxidation. To explain the reaction one must be aware of the fact that the second reaction product (in about a 50% yield) was dibenzo[*b*,*f*]-thiepin[26] (*XXXIV*) which may be viewed as a product of hydrolysis of the Grignard reagent but also as a product of reduction of bromide *XXXIII*. It thus cannot be excluded that the present reaction has the character of disproportionation.



XXXII



XXXIII, R = Br
XXXIV, R = H



XXXV

The octoclothepin(*I*) enantiomers were compared pharmacologically with the racemate in basic tests. Acute toxicity was determined in mice upon intravenous application: LD_{50} is 38 mg/kg for (+)-I, 31 mg/kg for (−)-*I*, and 38 mg/kg for (±)-*I*. The motor coordination of mice in the rotating-rod test 30 min after intravenous application is affected as expressed by the mean effective dose ED_{50}: 0·11 mg/kg for (+)-I, 0·13 mg/kg for (−)-*I*, and 0·13 mg/kg for (±)-*I*. In the catalepsy test in rats after intraperitoneal application, the ED_{50} is 2·5 mg/kg for (±)-*I*. The same dose of (+)-*I* brings about catalepsy in 7 rats out of 10, and the same dose of (−)-*I* causes catalepsy in 6 out of 10 rats. In all the three tests the substances were applied in the form of maleate solutions, the values being expressed per base. It may be seen that the enantiomers and racemate of octoclothepin (*I*) do not differ from each other in toxicity or in the depressant effect. In the catalepsy test, there is an indication of a higher effect of the optically active forms in comparison with the racemate. However, since this appeared with both antipodes, one cannot draw any conclusions on the stereospecificity of the effect.

The lacking stereospecificity of octoclothepin effect and further the higher activity of enamine[54,58] might lead to the conclusion that compounds *I* and *XXVII* exert their pharmacodynamic effect in the form of the same cleavage product, devoid

of a centre of chirality. The product might be the ketone *VII*, which is evidently formed by acid hydrolysis of *XXVII* and which might be formed from octoclothepin (*I*) by enzyme N-oxidation at the nitrogen nearer the skeleton and by subsequent cleavage of the C—N bond. For this reason, ketone *VII* was subjected to testing by methods of general pharmacological screening. It was found that its toxicity (LD_{50}) upon oral application is higher than 2·5 g/kg. It was then applied in most tests at a dose of 300 mg/kg *p.o.* In this dose it showed no signs of central or vegetative neurotropic effects and did not affect blood circulation. Only a suggestion of a diuretic effect was noted. This principally negative finding does not completely refute the justification of the view expressed above since in the tests carried out the ketone *VII* which is practically water-insoluble was applied per os when it was apparently resorbed only to a minute extent.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block. The samples were dried in the usual way. UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200 G spectrophotometer and NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR-60 (Zeiss, Jena) spectrometer.

2-(4-Chlorophenylthio)benzyl alcohol (*III*)

A. A benzene solution (62 ml) of sodium bis(2-methoxyethoxy)dihydroaluminate (1 ml containing 0·632 g reagent) was added dropwise under stirring over a 60 min period to a suspension of 20·0 g 2-(4-chlorophenylthio)benzoic acid[18] (*II*) in 200 ml benzene. The mixture was stirred for 3 h at room temperature and decomposed by adding dropwise 100 ml of 10% NaOH. The benzene layer was separated, washed with water, dried with K_2CO_3 and evaporated. A total of 17·3 g (91%) crude product was obtained which was distilled to produce 15·3 g of a fraction boiling at 176—178°C/0·5 Torr. For $C_{13}H_{11}ClOS$ (250·7) calculated: 62·27% C, 4·42% H, 14·14% Cl; found: 62·33% C, 4·68% H, 13·92% Cl. On further standing the compound crystallized slowly, m.p. 34—35°C which is in agreement with our previous finding[2]. 4-*Nitrobenzoate* (X) was prepared from alcohol *III* and from 4-nitrobenzoyl chloride in pyridine at 30°C; m.p. 121—122°C (yellow prisms from acetone). For $C_{20}H_{14}ClNO_4S$ (399·8) calculated: 60·07% C, 3·53% H, 8·86% Cl, 3·50% N, 8·02% S; found: 60·25% C, 3·53% H, 8·95% Cl, 3·41% N, 8·13% S. *B.* A solution of 1·0 g aluminium chloride in 8 ml tetrahydrofuran was added dropwise under stirring to a mixture of 60 ml tetrahydrofuran, 8·0 g acid *II* and 2·0 g sodium borohydride. The mixture was refluxed for 4·5 h, cooled and decomposed with 100 ml 5% HCl. It was extracted with benzene, the extract washed with 5% NaOH, dried with $MgSO_4$ and distilled; 4·1 g (55%), b.p. 170°C/0·9 Torr, m.p. 34—35°C. Acidification of the alkaline washing solution recovered 2·6 g of the starting acid *II*.

2-(Phenylthio)benzyl Bromide (*XII*)

A. Bromine (16·8 g) was added dropwise under stirring over a period of 2 h to 20·0 g phenyl 2-tolyl sulfide (*XI*) (b.p. 157—160°C/12 Torr[24]) at 150—165°C under illumination with a 200 W light bulb. After cooling, the product was dissolved in 100 ml benzene, the solution was washed with water and with 5% $NaHCO_3$ dried with $CaCl_2$ and evaporated: 27·0 g (approximately the

theoretical amount). Distillation revealed inhomogeneity; the greatest part (10·2 g) distilled at 140—160°C/0·5 Torr. For $C_{13}H_{11}BrS$ (279·2) calculated: 28·63% Br; found: 28·83% Br. *B.* A mixture of 100 ml tetrachloromethane, 20·0 g sulfide *XI*, 18·8 g N-bromosuccinimide and 1·0 g dibenzoyl peroxide was refluxed for 40 h under illumination with a 200 W light bulb. After standing overnight, it was filtered and the filtrate distilled: 20·7 g (74%), b.p. 140—160°C/0·5 Torr. Redistillation yielded 14·0 g of a product boiling at 146—148°C/0·2 Torr. For $C_{13}H_{11}BrS$ (279·2) calculated: 55·92% C, 3·97% H, 28·63% Br, 11·48% S; found: 55·45% C, 4·04% H, 28·81% Br, 11·69% S.

2-(Phenylthio)phenylacetonitrile (*XIII*)

A mixture of 12·1 g bromide *XII* (b.p. 146—148°C/0·2 Torr), 4·8 g NaCN, 25 ml ethanol and 15 ml water was refluxed for 8 h. After evaporation of the ethanol, the residue was divided between 100 ml benzene and 100 ml water, the benzene layer was washed with water, dried with $MgSO_4$ and distilled: 7·3 g (75%), b.p. 154°C/0·25 Torr. For $C_{14}H_{11}NS$ (225·3) calculated: 6·22% N; found: 5·89% N. Alkaline hydrolysis of this product[26] yielded 4·15 g (48%) 2-(phenylthio)phenylacetic acid (*XIV*), m.p. 120—123°C (benzene). In mixture with the previously prepared product[26] (m.p. 123°C) it melts without depression.

2-Tolyl 4'-chlorophenyl Sulfide (*XV*)

4-Chlorothiophenol (50 g) and 30 g copper powder were added to a solution of 40 g NaOH in 250 ml water. A solution of 2-tolyl diazonium sulfate obtained by diazotation of 37 g 2-toluidine in a mixture of 600 ml water, 150 g ice and 43 g H_2SO_4 with the aid of 26 g sodium nitrite in 200 ml water and by subsequent addition of 55 g crystalline sodium acetate in 100 ml water, was added to the above suspension over a period of 90 min at 5°C. The mixture was stirred for 1 h at 5°C and for 2 h at room temperature. After standing overnight it was made acid with HCl, 50 g zinc powder was added and the mixture was refluxed for 1 h on a boiling-water bath. After cooling, it was extracted with ether, the extract was filtered, thoroughly washed with 5% NaOH, followed with dilute HCl and water, dried with $MgSO_4$ and distilled: 49·5 g (62%), b.p. 183—190°C/10 Torr Redistillation yielded a product boiling at 122—123°C/0·25 Torr. For $C_{13}H_{11}ClS$ (234·7) calculated: 66·51% C, 4·72% H, 15·11% Cl, 13·66% S; found: 66·79% C, 4·83% H, 14·89% Cl, 13·44% S.

2-(4-Chlorophenylthio)acetophenone (*XVIII*)

A solution of 40 g 2-(4-chlorophenylthio)benzoyl chloride[18] (m.p. 82°C) in 150 ml ether was added dropwise under stirring to a solution of diethyl ethoxymagnesiummalonate (prepared from 24 g diethyl malonate, 3·65 g magnesium, 19 ml ethanol and 0·5 g tetrachloromethane in 65 ml ether). The mixture was stirred for 1 h at room temperature and then refluxed for 3 h. After standing overnight it was decomposed with 100 ml 10% H_2SO_4, the ether layer was separated, filtered and evaporated. The residue (59 g) was dissolved in 60 ml acetic acid, 30 ml water and 7 ml H_2SO_4 was added and the mixture was refluxed for 8 h. After standing overnight, the precipitated crude product was filtered, dissolved in a mixture of 150 ml benzene and 150 ml ether, the solution was washed with 10% NaOH to remove acid fractions and evaporated; 33·0 g (88%), m.p. 96—98°C (methanol). UV spectrum: λ_{max} 257·5 nm ($\log \varepsilon$ 3·94), 277 nm (3·67), 303 nm (3·59). IR spectrum (KBr): 771 (1,2-C_6H_4), 819 (1,4-C_6H_4), 1 583 (Ar), 1 680 cm^{-1} (Ar—CO). NMR spectrum: δ 7·86 (multiplet, 1 H, Ar—H in *o*-position to acetyl), 7·44 (singlet, 4 H, protons of chlorophenyl), 6·80—7·30 (multiplet, 3 H, remaining aromatic protons), 2·61 (singlet, 3 H, $COCH_3$). For $C_{14}H_{11}ClOS$ (262·8) calculated: 64·00% C, 4·22% H, 13·50% Cl, 12·20% S; found: 63·80% C, 4·23% H, 13·46% Cl, 11·98% S.

Thiomorpholide of 2-(4-Chlorophenylthio)phenylglyoxylic Acid (*XX*)

A mixture of 10·0 g ketone *XVIII*, 1·90 g sulfur and 10·0 g morpholine was refluxed for 4 h at 150–160°C. After cooling, the mixture was dissolved in 100 ml benzene, the solution was washed with water, dried with K_2CO_3 and evaporated. The residue (14·0 g) does not crystallize. A sample (4·0 g) was chromatographed on a column of 120 g neutral alumina (activity II), eluting with benzene. One of the more polar fractions crystallized, m.p. 184–185°C (yellow prisms from benzene). On seeding the solution of the remaining residue in a mixture of ethanol and benzene with this solid product, a total of 2·7 g substance was obtained, m.p. 184–185°C. UV spectrum: λ_{max} 227 nm (log ε 4·40), 269 nm (4·28), 344 nm (3·79). IR spectrum (KBr): 746 (1,2-C_6H_4), 819 (1,4-C_6H_4), 1 114 (ether), 1 507 (N—C═S), 1 551 and 1 582 (Ar), 1 642 cm^{-1} (Ar—CO—CS—N). NMR spectrum: δ 7·90 (multiplet, 1 H Ar—H in *o*-position toward CO group), 7·41 (singlet, 4 H, aromatic protons of chlorophenyl), 6·80–7·50 (multiplet, 3 H, remaining aromatic protons), 4·25 and 3·85 (triplets, 4 H, CH_2OCH_2), 3·66 (singlet, 4 H, CH_2NCH_2). The crystalline substance is oxothiomorpholide XX. For $C_{18}H_{16}ClNO_2S_2$ (377·9) calculated: 57·21% C, 4·27% H, 9·38% Cl, 3·71% N, 16·97% S; found: 57·92% C, 4·31% H, 9·49% Cl, 3·37% N, 16·60% S. As proven by hydrolysis, the noncrystallizing product from the mother liquor after compound *XX* is the crude thiomorpholide *XIX*.

2-(4-Chlorophenylthio)benzoic Acid (*II*)

The oxothiomorpholide *XX* (1·5 g) was hydrolyzed by boiling for 3 h with a solution of 2·0 g KOH in 2 ml ethanol (130–140°C bath). After evaporation of the ethanol, the product was dissolved in water and the solution after filtration made acid with 3M-HCl. A total of 0·90 g product melting at 242–243°C (ethanol) was obtained and was identified as acid *II* (described[18] m.p. 239–242°C, in mixture with this product it melts without depression). For $C_{13}H_9ClO_2S$ (264·7) calculated: 58·99% C, 3·43% H, 13·39% Cl, 12·11% S; found: 58·93% C, 3·46% H, 12·98% Cl, 12·13% S.

2-(4-Chlorophenylthio)phenylacetic Acid (*VI*)

A. 4-Chlorothiophenol[18] (1·5 g) was added to a solution of 2·0 g KOH in 20 ml water, the solution was heated to 50°C and 0·2 g copper powder was added, followed with 2·60 g 2-iodophenylacetic acid[22]. The mixture was refluxed under stirring in a 130–140°C bath, cooled and filtered, and the filtrate was made acid with 3M-HCl. The crude product (m.p. 90–105°C) was obtained in the theoretical amount (2·80 g). Recrystallization from 4 ml 90% ethanol yielded 1·70 g (65%) pure substance, melting at 115–116°C. In a mixture with authentic[2] acid *VI* it melts without depression. For $C_{14}H_{11}ClO_2S$ (278·8) calculated: 60·32% C, 3·97% H, 12·72% Cl, 11·50% S; found: 60·57% C, 4·12% H, 12·72% Cl, 11·61% S. *B*. Sulfide *XV* (20 g) was brominated with N-bromosuccinimide as in the preparation of *XII* (according to *B*). Analogous treatment yielded 17·0 g crude bromide *XVI*, b.p. 140–160°C/0·3–1·0 Torr (calculated: 25·48% Br; found: 20·14% Br). The product (16·0 g) was processed with sodium cyanide similarly to the preparation of *XIII*; a total of 14·1 g crude nitrile *IV* (residue) was obtained which was hydrolyzed under alkaline conditions as described before[2]. A total of 5·5 g (23% referred to sulfide *XV*) of not completely pure acid *VI* was obtained: m.p. 111–113°C. *C*. Crude thiomorpholide *XIX* (2·60 g) was hydrolyzed for 3 h by boiling with 2·0 g KOH in 4 ml ethanol in a 130–140°C bath. After evaporation of ethanol the product was dissolved in 50 ml water, the solution was filtered and the filtrate made acid with 3M-HCl; 1·3 g recrystallized acid *VI*, m.p. 116–117°C (benzene). In mixture with authentic[2] acid *VI* it melts without depression. According to analysis it retains the solvent so that it is a solvate with $^1/_3$ benzene molecule. For $C_{16}H_{13}ClO_2S$ (304·8) calculated: 63·05% C, 4·30% H, 11·63% Cl, 10·52% S; found: 62·95% C, 4·28% H, 11·82% Cl, 10·82% S.

2-Chloro-9-methylenethioxanthene (*XXI*)

Crude tertiary alcohol[18] prepared by a reaction of 12·4 g 2-chlorothioxanthone[18] with methylmagnesium iodide (14·2 g methyl iodide, 2·43 g magnesium) in 60 ml ether was distilled *in vacuo*: 6·0 g, b.p. 150—160°C/0·8 Torr. The product resists attempts at crystallization and is sensitive to atmospheric oxygen; the oxidation product is 2-chlorothioxanthone[18] (m.p. 153—155°C). NMR spectrum: δ 7·15—7·80 (multiplet, 8 H, aromatic protons and one of the protons of the $=CH_2$ group), 5·60 (doublet, 1 H, $J = 2·0$ Hz, the other proton of the $=CH_2$ group). Mass spectrum gives a molecular weight of 244. For $C_{14}H_9ClS$ (244·8) calculated: 68·70% C, 3·71% H, 14·49% Cl, 13·10% S; found: 68·61% C, 3·96% H, 14·61% Cl, 13·09% S.

8-Chloro-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*VII*)

A solution of 1·50 g thallium(III) nitrate[35] in 20 ml methanol was added to a solution of 0·90 g *XXI* in 60 ml methanol and the mixture was left overnight at room temperature. The precipitated thallium(I) nitrate was then filtered, the filtrate was extracted for 5 min with 100 ml 1M-H_2SO_4 and extracted with benzene. The extract was dried with calcium chloride and evaporated. The oil obtained (0·80 g) contains according to the IR spectrum the ketone *VII* together with 10 to 20% 2 chloro isomer[36]. IR spectrum (KBr) of pure 2-chloro-11*H*-dibenzo[*b*,*f*]thiepin-10-one[36]: 750 (1,2-C_6H_4), 813 and 875 (1,2,4-C_6H_3), 1560 and 1586 (Ar), 1670 cm^{-1} (Ar—CO). For an approximate estimation of the 2-isomer content in the mixture bands at 792, 899 and 1195 cm^{-1} were used, which are missing in the spectrum of *VII* (ref.[2]). After dissolving the mixture in a small amount of cyclohexane, 0·40 g ketone *VII* crystallized which after recrystallization from ethanol melts at 125—126°C and, in mixture with authentic[2] ketone *VII*, it melts without depression. For $C_{14}H_9ClOS$ (260·7) calculated: 64·49% C, 3·48% H, 13·60% Cl, 12·30% S; found: 64·15% C, 3·63% H, 13·46% Cl, 12·37% S.

Bis(4-chlorophenyl) disulfide (*XXII*)

This was obtained as a by-product during preparation of larger batches of 4-chlorothiophenol by reduction of 4-chlorobenzenesulfochloride according to ref.[18]. It remains as a nonvolatile residue after steam distillation of 4 chlorothiophenol; m.p. 72—74°C. Ref.[37] gives for the product of oxidation of 4-chlorothiophenol with nitric acid a m.p. of 71°C. For $C_{12}H_8Cl_2S_2$ (287·2) calculated: 50·18% C, 2·80% H, 24·69% Cl, 22·33% S; found: 50·50% C, 2·67% H, 24·34% Cl, 22·16% S.

(4-Chlorophenyl)thiolphenylacetate (*XXIII*)

A mixture of phenylacetic acid (27·2 g) and 36 g thionyl chloride was left for 30 min at 80°C, was evaporated, the residue was dissolved in 50 ml carbon disulfide and the solution was added under stirring to a suspension of 39·0 g aluminium chloride in a solution of 28·7 g disulfide *XXII* in 100 ml carbon disulfide. The mixture was refluxed under stirring for 6 h at 60°C, cooled, and poured into a mixture of 300 g ice and 25 ml HCl and extracted with 100 ml chloroform. The organic phase was evaporated, the residue dissolved in 300 ml benzene, the solution washed with 150 ml 10% NaOH, dried with K_2CO_3 and evaporated. The residue (39 g) was distilled in vacuo (0·5 Torr) to obtain 14·7 g volatile fractions. After dissolving in benzene and washing with 10% NaOH, the alkaline aqueous extracts were combined, acidified with H_2SO_4 and steam-distilled. This produced 4·5 g 4-chlorothiophenol melting at 51—53°C (it melts without depression in mixture with an authentic preparation[18]). Evaporation of the benzene solution yielded 9·4 g oil which crystallized within 48 h of standing: thiol ester *XXIII*; m.p. 63—65°C (needles from

light petroleum). For $C_{14}H_{11}ClOS$ (262·7) calculated: 64·00% C, 4·22% H, 13·50% Cl, 12·20% S; found: 64·64% C, 4·30% H, 13·25% Cl, 12·21% S. The nonvolatile fractions of the reaction product (24 g) were chromatographed on a column of alumina but none of the fractions obtained crystallized.

2,7-Dichlorothioxanthone (*XXV*)

A solution of 1·3 g di(4-chlorophenyl) sulfide[39] (*XXIV*) and 1·3 g oxalyl chloride in 10 ml dichloromethane was slowly added to a suspension of 2·0 g aluminium chloride in 5 ml dichloromethane (dried with P_2O_5). The mixture was left for 36 h at room temperature, decomposed with a mixture of ice and dilute HCl. After extraction with chloroform the extract was washed with water, dried with $CaCl_2$ and evaporated. The residue (0·90 g) of crude ketone *XXV* was recrystallized from chloroform whereafter it melted at 252—254°C (yellow needles). In mixture with the authentic product[36] it melts without depression. For $C_{13}H_6Cl_2OS$ (281·2) calculated: 55·63% C, 2·15% H, 25·22% Cl, 11·41% S; found: 55·64% C, 2·22% H, 25·74% Cl, 11·74% S (ref.[63]).

2,8-Dichloro-10-(chloroacetyl)-11-hydroxydibenzo[*b,f*]thiepin (*XXVI*)

Di(4-chlorophenyl) sulfide[39] (*XXIV*) (10·2 g) was added to a suspension of 5·9 g aluminium chloride in 25 ml dichloromethane and, under cooling with ice-cold water, a solution of 4·5 g chloroacetyl chloride (b.p. 105°C) in 15 ml dichloromethane was added dropwise over 20 min. The mixture was stirred for 30 min at room temperature, refluxed for 3 h, cooled, and decomposed with ice cold dilute HCl. The mixture was then extracted with a mixture of benzene and chloroform. The extract was washed with dilute NaOH, dried with K_2CO_3 and evaporated. The crystalline residue (10·2 g) was extracted with boiling benzene, the greater part of it being dissolved. Treatment of the extract recovered 4·9 g of the starting *XXIV* (m.p. 96—98°C). The benzene-insoluble fraction was recrystallized from a mixture of chloroform and light petroleum: 2·1 g, m.p. 216—217°C. UV spectrum: λ_{max} 220 nm (log ε 4·40), 247 nm (4·21), 273 nm (4·01), 323 nm (4·05). IR spectrum: 702, 753, 771 and 789 (C—Cl), 829 and 845 (1,2,4-C_6H_3), 1279 and 1389 (OH in hydrogen bond), 1570 (Ar), 1601 (Ar and C=C), 1640 cm^{-1} (CO—C=C—OH). For $C_{16}H_9Cl_3O_2S$ (371·7) calculated: 51·70% C, 2·44% H, 28·62% Cl, 8·63% S; found: 51·44% C, 2·52% H, 28·76% Cl, 8·45% S.

8-Chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*I*)

A. A mixture of 10·0 g dichloride[2] *IX*, 10·8 g 1-methylpiperazine[52] and 40 ml chloroform was refluxed for 32 h. The previously described[2] procedure yielded 10·2 g (83%) base *I*, m.p. 99—100°C (ethanol) which was neutralized with maleic acid to 12·3 g maleate melting at 202—204°C. The neutral product (2·2 g) was the dichloride *IX*. When the amount of 1-methylpiperazine was decreased to 7·2 g, the amount of chloroform to 5 ml, and the reaction period was reduced to 8 h, the yield per base *I* dropped to 72%; the neutral fraction (2·6 g) is practically exclusively the elimination product *XXIX*. The NMR spectrum of base *I*: δ 6·8—7·8 (multiplet, 7 H of the aromatic ring protons), 2·9—4·1 (multiplet, 3 H of —CH_2CH—), 2·4—2·7 (multiplet, 8 H, CH_2 groups of piperazine), 2·26 (singlet, 3 H, N—CH_3). Di(hydrogenmaleate), m.p. 169—171°C (aqueous ethanol). For $C_{27}H_{29}ClN_2O_8S$ (577·0) calculated: 56·20% C, 5·07% H, 6·14% Cl, 4·86% N, 5·55% S; found: 56·16% C, 5·23% H, 6·31% Cl, 5·03% N, 5·74% S. Monomethanesulfonate, m.p. 224—225°C (ethanol), its solubility in water is greater than 10%. For $C_{20}H_{25}ClN_2O_3S_2$ (441·0) calculated: 54·47% C, 5·71% H, 8·04% Cl, 6·35% N, 14·54% S; found: 54·54% C, 5·86% H, 8·27% Cl, 5·96% N, 14·81% S. Dimethanesulfonate, m.p. 215—217°C (aqueous ethanol), solu-

bility in water also greater than 10%. For $C_{21}H_{29}ClN_2O_6S_3$ (537·1) calculated: 46·96% C, 5·44% H, 6·58% Cl, 5·22% N, 17·91% S; found: 46·81% C, 5·51% H, 6·72% Cl, 5·17% N, 17·70% S. Neutral citrate, m.p. 122—126°C (ethanol). For $C_{69}H_{77}Cl_3N_6O_{14}S_3$ (1418·9) calculated: 58·40% C, 5·60% H, 7·50% Cl, 5·92% N, 6·78% S; found: 58·24% C, 5·88% H, 7·96% Cl, 5·89% N, 7·18% S. 4,4'-Methylenebis(3-hydroxy-2-naphthoate)1 : 1, obtained by neutralization of base *I* with 4,4'-methylenebis(3-hydroxy-2-naphthoic) acid in dimethylformamide and subsequent dilution of the obtained solution with water, monohydrate, m.p. 190—200°C. For $C_{42}H_{39}ClN_2 \cdot .0_7S$ (751·3) calculated: 67·15% C, 5·23% H, 4·72% Cl, 3·73% N, 4·26% S; found: 67·41% C, 5·22% H, 4·99% Cl, 3·93% N, 4·65% S. Product 2 : 1 was obtained by boiling a solution of 12·0 g base *I* and 20 ml water in 1700 ml ethanol with 5·5 g acid until the solution cleared (4 h) and by subsequent crystallization; 14·05 g, m.p. 172—174°C under decomposition. For $C_{61}H_{58}Cl_2N_4 \cdot .O_6S_2$ (1078·1) calculated: 67·95% C, 5·42% H, 6·58% Cl, 5·20% N, 5·95% S; found: 67·48% C, 5·71% H, 6·50% Cl, 5·06% N, 5·95% S. Basic dibenzoyl-L-tartrate, crystallized from ethanol as dihydrate. On repeated crystallization it retains its specific rotation $[\alpha]_D^{20}$ —30° (1% solution in methanol) and m.p. 148—149°C under decomposition. Alkalinization yields racemic base *I*. For $C_{56}H_{60}Cl_2N_4O_{10}S_2$ (1084·1) calculated: 62·04% C, 5·58% H, 6·54% Cl, 5·17% N, 5·91% S; found: 62·26% C, 5·57% H, 6·82% Cl, 5·23% N, 5·93% S.

B. A mixture of 20 ml tetrahydrofuran, 1·0 g lithium aluminium hydride and 2·0 g carbamate[55] *XXVIII* was refluxed for 3 h, cooled and decomposed by successively adding 1 ml water, 1 ml 15% NaOH and 3 ml water, and finally diluted with 15 ml ether. After 15 min of standing it was filtered and the filtrate evaporated. The residue (1·7 g) crystallized from 4·5 ml ethanol and a small amount of water to 1·3 g (76%) base *I*, m.p. 99—100°C. For $C_{19}H_{21}ClN_2S$ (344·9) calculated: 66·16% C, 6·14% H, 9·29% S; found: 66·42% C, 6·45% H, 9·31% S. *C.* A solution of sodium bis(2-methoxyethoxy)dihydroaluminate (15 ml) in benzene (1 ml containing 0·632 g reagent) was added dropwise to a solution of 6·0 g carbamate[55] *XXVIII* in 60 ml benzene and the mixture was heated for 5 h to 60°C. After cooling, it was decomposed by adding dropwise 18 ml water, left to stand overnight to separate, and the organic phase was washed with 15% NaOH and water, dried with K_2CO_3 and evaporated. A total of 4·80 g (92%) base *I* was obtained, m.p. 99—100°C (ethanol). From 4·3 g of this base, neutralization with maleic acid (1·5 g) in 30 ml ethanol yielded 4·6 g maleate melting at 204—205°C (aqueous ethanol) (ref.[2] m.p. 206—207°C). For $C_{23}H_{25}ClN_2O_4S$ (461·0) calculated: 59·93% C, 5·47% H, 7·69% Cl, 6·08% N, 6·96% S; found: 60·16% C, 5·57% H, 7·70% Cl, 6·16% N, 7·14% S. *D.* Heating of a mixture of 5·0 g 1-methylpiperazine, 3·0 g ketone[2] *VII* and 5·0 g 100% formic acid for 8 h in a 190—200°C bath and usual processing[41] yielded 90 mg (2%) of base *I* (according to chromatography on a thin layer of alumina). *E.* Resolution of racemic compound *I* with dibenzoyl-(+)-tartaric acid: A solution of 29·0 g dibenzoyl-(+)-tartaric acid in 160 ml ethanol was added to a warm solution of 27·6 g racemic base *I* in 240 ml ethanol. The solution formed was left to stand for 12 h at room temperature. A total of 12·8 g neutral dibenzoyl-(+)-tartrate precipitated (m.p. 146—148°C, under decomposition; $[\alpha]_D^{20}$ —75°). Its rotation does not increase on recrystallization from aqueous ethanol. For $C_{37}H_{35}ClN_2O_8S$ (703·2) calculated: 63·19% C, 5·02% H, 3·98% N, 4·56% S; found: 62·68% C, 5·14% H, 4·26% N, 4·56% S. Decomposition of 6·5 g of this salt with aqueous ammonia and extraction with benzene yielded 3·54 g of (—)-base *I* which, after recrystallization from cyclohexane, melts at 110—112°C and has an $[\alpha]_D^{20}$ of —45° (1% solution in methanol). For $C_{19}H_{21}ClN_2S$ (344·9) calculated: 66·16% C, 6·14% H, 10·28% Cl, 8·12% N, 9·29% S; found: 66·20% C, 6·26% H, 10·36% Cl, 7·92% N, 9·17% S. Maleate of (—)-base *I*, m.p. 192—195°C (ethanol), $[\alpha]_D^{20}$ —29° (1%, methanol). For $C_{23}H_{25}ClN_2O_4S$ (461·0) calculated: 59·93% C, 5·47% H, 7·69% Cl, 6·08% N, 6·96% S; found: 59·95% C, 5·50% H, 7·86% Cl, 6·04% N, 7·22% S. *F.* Resolution of racemic compound *I* with (+)-tartaric acid: A solution of racemic base *I* (34·5 g) and 15·1 g (+)-tartaric acid in 400 ml hot ethanol was left for 24 h to stand at room temperature.

The precipitated basic (+)-tartrate was recrystallized twice from a 40-fold excess of 50% ethanol; 11·6 g, m.p. 228—232°C (under decomposition). For $C_{42}H_{48}Cl_2N_4O_6S_2$ (839·9) calculated: 60·06% C, 5·76% H, 8·44% Cl, 6·67% N, 7·63% S; found: 59·14% C, 5·96% H, 8·74% Cl, 6·39% N, 8·05% S. Decomposition of the salt with aqueous ammonia and extraction with benzene yielded 9·85 g of (+)-base *I* which recrystallized from light petroleum to a m.p. of 112—114°C and an $[\alpha]_D^{20}$ of +50° (1%, methanol). For $C_{19}H_{21}ClN_2S$ (344·9) calculated: 66·16% C, 6·14% H, 10·28% Cl, 8·12% N, 9·29% S; found: 66·27% C, 6·27% H, 10·51% Cl, 8·21% N, 9·48% S. Maleate of (+)-base *I*, m.p. 195—196°C (ethanol), $[\alpha]_D^{20}$ +35° (1%, methanol). For $C_{23}H_{25}ClN_2O_4S$ (461·0) calculated: 59·93% C, 5·47% H, 7·69% Cl, 6·08% N, 6·96% S; found: 59·58% C, 5·60% H, 7·90% Cl, 5·98% N, 6·99% S.

8-Chloro-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*XXVII*)

A mixture of 2·60 g ketone *VII*, 3·00 g 1-methylpiperazine and 5·16 g *p*-toluenesulfonic acid was heated for 1 h in an open vessel at 180—190°C and for 3 h *in vacuo* (10—20 Torr) in the same bath. After cooling, the melt was decomposed with 30 ml dilute aqueous ammonia (1 : 1) and the mixture was extracted with benzene. The extract was evaporated and the residue (3·1 g) was dissolved in 20 ml warm methanol. After 24 h of standing of the solution, 0·30 g precipitated ketone *VII* was filtered and the filtrate was evaporated at reduced pressure. The residue (2·61 g) was dissolved in 5 ml ethanol and the solution was neutralized with 0·90 g maleic acid. After 12 h of standing of the solution in a refrigerator, 2·80 g (61%) crude maleate of base *XXVII* precipitated (m.p. 208—210°C; for pure maleate a m.p. of 222—223°C was reported before[54]). According to a comparison of the crude base by thin-layer chromatography on alumina with a previously prepared product[54], the two substances are identical. On using 1-methylpiperazine monohydrochloride, the yield was 55%, on using 1-methylpiperazine monomethanesulfonate it was 54%.

2-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XXX*)

A mixture of 3·2 g ketone *VII*, 15 ml 40% hydrazine hydrate, 4·0 g KOH and 20 ml ethylene glycol was heated at first for 5 h in a 120°C bath and then for 7 h in a 210°C bath with simultaneous evaporation of the volatile fractions. After cooling, it was mixed with 100 ml water and extracted with ether. The extract was dried with $MgSO_4$ and evaporated. The oily residue (2·9 g) dissolved for the most part in a mixture of benzene and light petroleum; undissolved remained only 0·48 g substance. The filtrate was evaporated and the residue crystallized after adding ethanol: 1·8 g, m.p. 67°C (methanol). NMR spectrum: ϑ 6·90—7·55 (multiplet, 7 H of aromatic ring protons), 3·24 (singlet, 4 H of CH_2CH_2). For $C_{14}H_{11}ClS$ (246·8) calculated: 68·14% C, 4·49% H, 14·37% Cl, 13·00% S; found: 68·10% C, 4·46% H, 14·25% Cl, 12·73% S. The undissolved fraction (0·48 g) was crystallized from a larger volume of a mixture of benzene and light petroleum. It does not melt below 360°C. UV spectrum: λ_{max} 274 nm (log ε 4·53), 333 nm (4·31). IR spectrum (KBr): 742 (1,2-C_6H_4), 810 and 868 (1,2,4-C_6H_3), 1 570 and 1 590 (Ar), 3 420 cm^{-1} (NH). The NMR spectrum displays a multiplet of aromatic protons and a broad singlet at ϑ 12·40 which disappears on deuterization (1 H, NH). Mass spectrum: molecular weight 500, empirical formula $C_{28}H_{15}Cl_2NS_2$. The substance is characterized as a solvate with $^1/_3$ benzene molecule. According to all these facts we are dealing here with 8,12-dichloro-10*H*-pyrrolo(2,3-l; 5,4-l′)di[dibenzo(*b,f*)-thiepin] (*XXXI*). For $C_{30}H_{17}Cl_2NS_2$ (526·5) calculated: 68·44% C, 3·25% H, 13·47% Cl, 2·66% N, 12·18% S; found: 68·40% C, 3·23% H, 13·62% Cl, 2·71% N, 12·31% S.

10-(4-Methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*XXXII*)

Methanesulfonate was prepared from a previously described base[26,41]; m.p. 173—174°C (ethanol). It dissolves in water to a more than 40% solution. For $C_{20}H_{26}N_2O_3S_2$ (406·6) calculated: 59·08% C, 6·45% H, 6·89% N, 15·77% S; found: 59·28% C, 6·44% H, 7·09% N, 15·71% S.

10-(1,4-Dihydroxybutyl)dibenzo[*b,f*]thiepin (*XXXV*)

A mixture of 0·42 g magnesium, 50 ml tetrahydrofuran, 5·0 g 10-bromodibenzo[*b,f*]thiepin[41] (*XXXIII*) and grains of iodine was refluxed for 3 h. The mixture was then combined with 4 ml acetone and the whole refluxed for 3 h. The volatile fractions were evaporated, the residue mixed with 60 ml ether and the mixture cooled and decomposed with a solution of 2·25 g ammonium chloride in 25 ml water. The organic phase was washed with water, dried with $MgSO_4$ and evaporated. The oily residue (4·3 g) after dissolving in 10 ml benzene and after adding 10 ml light petroleum yielded 0·80 g compound melting at 146—147°C (benzene). UV spectrum: λ_{max} 256 nm (log ε 4·28), 281 nm (3·66). IR spectrum: 755 (1,2-C_6H_4), 1 050 and 3 300 cm^{-1} (OH). The NMR spectrum (dimethyl sulfoxide-6^2H): ϑ 7·10—7·85 (multiplet, 9 H of aromatic protons and conjugated olefinic H), 5·44 (doublet, 1 H of the secondary alcoholic OH), 4·75 (multiplet, 1 H, —CH—O—), 4·32 (triplet, J = 5·0 Hz, 1 H, of the primary alcoholic OH), 3·32 (multiplet, 2 H of CH_2—O—), 1·52 (multiplet, 4 H of the remaining CH_2 groups in the chain). For $C_{18}H_{18}O_2S$ (298·3) calculated: 72·46% C, 6·08% H, 10·73% S; found: 72·75% C, 6·08% H, 10·73% S. The same compound was obtained in an approximately equal yield if the addition of acetone was omitted. Chromatography of the mother liquor after compound *XXXV* on a column of 120 g neutral alumina and elution with a mixture of benzene and light petroleum yielded 2·22 g fraction which was identified as dibenzo[*b,f*]thiepin (*XXXIV*), m.p. 85—88°C (yellow prisms); in a mixture with authentic product[26] (m.p. 87—88°C) it melts without depression.

The pharmacological tests of ketone VII *were done by Dr F. Hradil and Dr J. Němec at the unit of this institute at Rosice n/L. The mass spectra were recorded and interpreted by Dr M. Ryska, Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, Prague. The analytical estimations were done at the analytical department of this institute by Mr K. Havel, Mrs V. Šmídová, Mrs J. Komancová, Mrs A. Slavíková, Mrs E. Dvořáková and Mrs J. Hrdá, Mrs M. Hrubantová cooperated in the preparatory part of the work.*

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