NEUROTROPIC AND PSYCHOTROPIC AGENTS. LVIII.*

8-HYDROXY-10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b*, *f*] THIEPIN, O-SUBSTITUTION DERIVATIVES AND SOME RELATED COMPOUNDS

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Demethylation of 8-methoxy-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*IIa*) with pyridine hydrochloride produced phenolketone *IIb* which was O-alkylated to ketones *IIc*—*IIf*. These served for the synthesis of 8-ethoxy, 8-n-butoxy, 8-benzyloxy and 8-(2-pyridyloxy) derivatives of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ic*—*If*). Debenzylation of *Ie* with sodium in 1-butanol led to aminophenol *Ib*. The same compound was obtained by demethylation of 8-methoxy-10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IVa*) with boron tribromide, subsequent substitution reaction with 1-methylpiperazine and hydrolysis. Products obtained in the reaction of 8-methoxy-11-bromo-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*XVIII*) with 1-methylpiperazine were studied. The ethoxy derivative *Ic* is a highly active neuroleptic, ethers *Id*—*If* are somewhat weaker and display a dissociation of the central depressant from the cataleptic activity, with emphasis on the latter.

In an earlier communication of this series[1] we described the synthesis of 8-methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ia*) (octometothepin) which displayed a high degree of neuroleptic activity. From the point of view of relationships between structure and activity it was desirable to study compounds that would be analogous to *Ia* and in position 8 would contain larger alkoxyl groups. The analogue with a free hydroxyl group in position 8 (*Ib*) was promising for two reasons: *1.* as another potential neuroleptic, *2.* as a potential metabolite of the compound unsubstituted in position 8, *i.e.* perathiepin[2–4]. The present communication thus deals first of all with the preparation of 8-ethoxy- (*Ic*), 8-n-butoxy- (*Id*), 8-benzyloxy-(*Ie*) and 8-(2-pyridyloxy) (*If*)-analogues of *Ia* and further with the synthesis of the 8-hydroxy derivative of perathiepin (*Ib*).

The key intermediate of the first part of the work was 8-hydroxy-11*H*-dibenzo-[*b*,*f*]thiepin-10-one (*IIb*) which was prepared by decomposition of the diazonium salt obtained from 8-amino-11*H*-dibenzo[*b*,*f*]thiepin-10-one[5,6] or by demethylation of 8-methoxy-11*H*-dibenzo[*b*,*f*]thiepin-10-one[1] (*IIa*) with pyridine hydrochloride at 200°C. More suitable for preparative purposes was the demethylation method.

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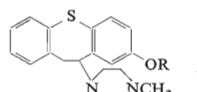
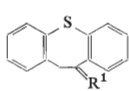
For transformation of phenol *IIb* to phenol ethers *IIc–IIe*, a suitable method was alkylation with ethyl iodide, n-butyl bromide or benzyl chloride in boiling acetone in the presence of potassium carbonate. In the case of benzylation, compound *IIb* was treated also with benzyl chloride in a sodium ethoxide solution in ethanol. A mixture resulted from which the desired phenol ether *IIe* was isolated as a minor product. The main product was the doubly benzylated 8-benzyloxy-11-benzyl-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*VI*). Reaction of phenol *IIb* with 2-bromopyridine was carried out in boiling pyridine in the presence of potassium carbonate and cupric oxide; the main product was the 8-(2-pyridyloxy) derivative *IIf*.



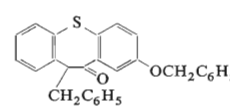
I

In formulae *I–VIII*: *a*, R = CH_3, *b*, R = H, *c*, R = CH_2CH_3, *d*, R = $(CH_2)_3CH_3$, *e*, R = $CH_2C_6H_5$, *f*, R = 



II, R^1 = O *IV*, R^1 = 

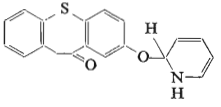
III, R^1 =  *V*, R^1 =



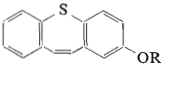
VI

Ketones *IIc–IIf* were reduced with sodium borohydride in aqueous ethanol to the alcohols *IIIc–IIIf*. The same method applied to phenol ketone *IIb* yields a mixture of compounds from which the pure diol *IIIb* (its preparation was described earlier using a different method[5]) was isolated in an insignificant yield only after chromatography. During hydrogenation of pyridyloxy ketone *IIf* on palladium in acetic acid two hydrogen atoms were consumed and the reaction stopped but the expected splitting of the pyridyloxy group did not take place[7]. The product isolated in the form of a crystalline hydrochloride retained the keto group; according to the NMR spectrum, the pyridine ring was partly saturated (Formula *VII*). By treatment with anhydrous hydrogen chloride in benzene at room temperature alcohols *IIIc–IIIe* yielded the corresponding 10-chloro derivatives *IVc–IVe*. For transformation of alcohol *IIIf* to the chloro derivative *IVf*, we used a similar reaction in chloroform; the primarily formed hydrochloride was decomposed by treatment

with alkali. On the other hand, attempts at preparing the 10-chlorophenol *IVb* did not produce a characterized substance: during reaction of diol *IIIb* with hydrogen chloride in chloroform, a mixture of products is formed from which the desired compound *IVb* could not be isolated in a pure state. Treatment with anhydrous hydrogen bromide of the methoxy alcohol *IIIa* in chloroform results in the unstable bromo derivative *Va* which eliminates readily hydrogen bromide. This prevented its preparation in a pure form. In a reaction with pyridine hydrochloride it is demethylated but simultaneously undergoes total dehydrobromination so that it yields 2-hydroxydibenzo[*b*,*f*]thiepin (*VIIIb*).



VII



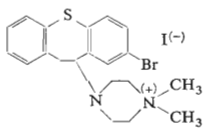
VIII

Substitution reaction of the chloro derivatives *IVc*–*IVf* with 1-methylpiperazine in boiling chloroform yielded the desired bases *Ic*–*If*. In a smaller extent, elimination reactions occur which results in compounds *VIII*, of which *VIIIc*–*VIIIe* have been isolated and characterized.

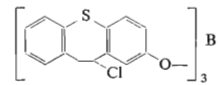
In the second part of this work, we set out to prepare 8-hydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*Ib*). For the first time, this compound was encountered during attempts at converting 8-bromo-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[8] to the Grignard reagent and at its further processing. The above brominated base did not react with magnesium in boiling tetrahydrofuran. The attempt at initiating the reaction with methyl iodide was not successful since the corresponding quaternary salt *IX* was formed immediately. On the other hand, when using a small amount of ethyl bromide, the reaction took place and the corresponding Grignard reagent was prepared. The reaction proceeded very slowly and the reaction mixture was not protected from contact with air. Apparently, the Grignard reagent reacted with atmospheric oxygen and thus a phenolic hydroxyl was formed[9]. Selenium added to the reaction mixture (in attempts at preparing the 8-methylseleno derivative of perathiepin[6]) did not participate in the reaction and the isolated product was characterized by analyses and spectra as not completely pure phenol *Ib*. In further work we attempted to obtain this phenol by demethylation of the methoxy derivative *Ia* but with no success. In the reaction with pyridine hydrochloride at 200°C demethylation takes place but is accompanied by elimination of methylpiperazine so that the resulting compound is 2-hydroxydibenzo[*b*,*f*]thiepin (*VIIIb*). In attempts at demethylation with sodium borohydride and iodine in ethanol[10] or with boron tribromide in dichloromethane[11] the desired

reaction practically did not take place and the starting compound *Ia* was recovered; in this connection, several novel salts of base *Ia* were characterized.

As another precursor of preparation of phenol *Ib* the benzyl ether *Ie* came into consideration. In an attempt at its debenzylation by hydrogenation on palladium in ethyl acetate in the presence of triethylamine no hydrogen was consumed. On the other hand, during heating of benzyl ether *Ie* with excess Raney nickel in an ethanolic solution the molecule was completely destroyed, the basic product having been identified as 1-methyl-4-ethylpiperazine[12]. Its formation must be explained by an alkylation of the primarily formed 1-methylpiperazine by the ethanol present. Only on heating the benzyl ether *Ie* with sodium in 1-butanol did the desired debenzylation take place and phenol *Ib* was formed. The same compound was obtained by a third method where the methoxy chloride[1] *IVa* was demethylated in the presence of boron tribromide in chloroform[11], the crude boric ester *X* was condensed with 1-methylpiperazine and the crude product was hydrolyzed by boiling in water. The resulting compound *Ib* has the properties of an internal salt: the base shows a high melting point and is poorly soluble in lipophilic solvents, its IR spectrum shows a band at 2690 cm^{-1} which is typical of an ammonium salt.

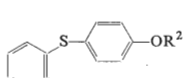


IX



X

In connection with this work, some of the intermediates were prepared by novel procedures. Thus, 2-(4-methoxyphenylthio)benzyl alcohol[1] (*XI*) was prepared by reduction of 2-(4-methoxyphenylthio)benzoic acid[1] either with diborane or with sodium bis(2-methoxyethoxy)dihydroaluminate (analogy in ref.[13,14]). 2-(4-Methoxyphenylthio)phenylacetic acid[1] (*XII*) was prepared by condensation of 4-methoxythiophenol[15] with 2-iodophenylacetic acid[6,14]. Analogously to the 4-chlorophenylthio series[14], we tried to apply Willgerodt's reaction to the preparation of acid *XII*. 2-(4-Methoxyphenylthio)benzoic acid[1] was converted with the aid of thionyl chloride

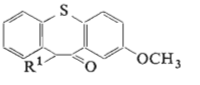


XI, $R^1 = CH_2OH$, $R^2 = CH_3$
XII, $R^1 = CH_2CO_2H$, $R^2 = CH_3$
XIII, $R^1 = COCl$, $R^2 = CH_3$
XIV, $R^1 = COCH_3$, $R^2 = CH_3$

XV, $R^1 = COCSN$ (O), $R^2 = CH_3$
XVI, $R^1 = CH_2CSN$ (O), $R^2 = CH_3$
XVII, $R^1 = CH_2COOH$, $R^2 = H$

to chloride *XIII* with which the ethoxymagnesium malonate ester was acylated; hydrolysis of the crude product with a mixture of acetic acid and sulfuric acid gave acetophenone derivative *XIV* (ref.[16] describes a different method of preparation). Reaction of this ketone with sulfur and morpholine results in a basically similar product as noted in the 4-chlorophenylthio series[14]. A mixture is formed the crystallization of which gave two products, identified as oxothiomorpholide *XV* and thiomorpholide *XVI*. Both these compounds are mentioned in the work of Kimoto and coworkers[16] but without full characterization. The formation of this mixture makes Willgerodt's reaction inapplicable even in this instance. Demethylation of acid *XII* with pyridine hydrochloride led to the phenol acid *XVII*.

Bromination of ketone *IIa* in chloroform results in 11-bromo ketone *XVIII*.



XVIII, $R^1 = Br$

XIX, $R^1 =$ 

XX, $R^1 = =O$

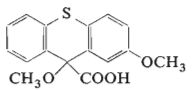
Its substitution reaction with 1-methylpiperazine does not proceed as smoothly as described for other analogous cases in some Geigy patents[17]. On the contrary, a course similar to that in the 8-unsubstituted series[2] was observed. In addition to the basic product, the main fraction of which is apparently represented by the piperazine derivative *XIX* (not characterized here), a considerable amount of a mixture of neutral compounds is formed, from which the diketone *XX* was isolated by crystallization. This diketone undergoes readily a benzil rearrangement and the hydroxy acid formed is etherified at the tertiary hydroxyl even during crystallization from methanol. In agreement with this, we isolated a product from the mother liquor after diketone *XX* which, after crystallization from methanol, was identified with the aid of analysis and spectra as 2,9-dimethoxythioxanthene-9-carboxylic

TABLE I

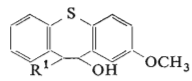
Pharmacological Properties of Piperazine Derivatives *Ia*—*If*
Doses in mg/kg.

Compound	Acute toxicity LD_{50} *i.v.*	Rotating rod ED_{50} *i.v.*	Catalepsy ED_{50} *i.p.*
Ia[1]	38	0·049	1·3
Ib	37	0·31	4·5
Ic	53	0·052	2·0
Id	59	1·4	8·2
Ie	38	1·2	5·4
If	54	1·2	5·4
Octoclothepin	46	0·06	2·4
Chlorpromazine	52	0·585	8·6

acid (*XXI*) (for completely analogous transformations[2,18]). In an attempt at preparing maleate from the crude base *XIX* only 1-methylpiperazine [di(hydrogen maleate)] was obtained. This indicates a ready cleavage of the benzyl—N bond in base *XIX*. Reduction of amino ketone *XIX* with diborane, generated either in the reaction of sodium borohydride with boron trifluoride or of sodium borohydride with acetic acid, gives again rise to a mixture of neutral and basic compounds. The principal neutral product formed was the diol *XXII*, the IR spectrum of which shows at a greater dilution a hydroxyl band at 3627 cm^{-1} and another band of a bound hydroxyl group at 3575 cm^{-1} so that it is believed to have a *cis*-configuration (an analogous situation exists with the *cis*- and *trans*-9,10-dihydroxy-9,10-dihydrophenanthrenes[19]). The basic fraction yielded a crystalline maleate, analyses and IR spectrum of which support the view that it is the amino alcohol *XXIII*. A similar amino alcohol unsubstituted in position 8 was described in an earlier publication[2] and in patents of Geigy[20] where compounds of the same type are included.



XXI



XXII, $R^1 = OH$

XXIII, $R^1 =$ 

Table I shows the pharmacological properties of piperazine derivatives *Ia*—*If*, including octoclothepin[8] and chlorpromazine as standards. All the compounds were applied intravenously (or intraperitoneally in the catalepsy test) in the form of salts, the values in the table referring to the base. In addition to acute toxicity for mice, expressed by the conventional mean lethal dose (LD_{50}), the table contains the mean effective dose (ED_{50}) in the rotating-rod test in mice which reflects disturbances of motor coordination and hence actually a central depressant activity, and also the mean effective doses in the catalepsy test in rats (ED_{50}). It may be seen that the novel ethoxy derivative *Ic* is almost equally active a neuroleptic as octometothepin[1] *Ia* and that both are somewhat more effective than octoclothepin. With the other compounds, both with phenol *Ib* and the ethers *Id*—*If*, one may observe a relatively much decreased central depressant activity while the cataleptic activity is reduced only little. It may be said that the compounds are more cataleptic than centrally depressant as compared with *Ia*, *Ic* and octoclothepin. This shift toward cataleptic activity is most pronounced with benzyl ether *Ie* and with pyridyl ether *If* which are about 20 times weaker central depressants than *Ia* and *Ic* but only 2—3 times less active cataleptogens than *Ia* and *Ic*.

The quaternary salt *IX* was evaluated at the affiliated unit of this institute at Rosice n/L. under the direction of Dr F. Hradil and Dr J. Němec using methods of pharmacological screening.

Upon oral application, the substance shows an acute toxicity LD_{50} of 2500 mg/kg; in the *in vivo* tests it was applied in a *p.o.* dose of 300 mg/kg. In this dose it has no effect in the rotating-rod test and showed a potentiation of thiopental narcosis and a trace of vasodilatory effect. It provides further evidence for the profound influence in the pharmacodynamics of a highly centrally active amine that its conversion to a quaternary salt may have (earlier this was shown for perathiepin methiodide[2]).

The compounds were further evaluated by Dr A. Šimek and Dr J. Turinová as to their antimicrobial activity *in vitro* using a standard series of microorganisms in the bacteriological department of this institute. Compounds *Ic—Ie* and *IX* are inhibitory at concentrations of 10—25 μg/ml toward *Streptococcus* β-*haemolyticus*, *Staphylococcus pyogenes aureus* and, at a concentration of 25—100 μg/ml, toward *Mycobacterium tuberculosis* H 37 Rv.

EXPERIMENTAL

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

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

A. Suspension of 2·0 g 8-amino-11*H*-dibenzo[*b,f*]thiepin-10-one[5,6] in 40 ml water and 2·5 ml sulfuric acid was diazotized at 3—5°C with a solution of 0·7 g $NaNO_2$ in 5 ml water. After 30 min of stirring at this temperature the solution was added dropwise to a boiling solution of 12 g sulfuric acid in 250 ml water. After cooling, it was extracted with ether, from the ether layer the phenolic product was extracted with 100 ml 5% NaOH, the alkaline solution was made acid with dilute hydrochloric acid and the precipitated product was recrystallized from a mixture of benzene and ethanol; 1·45 g (72%), m.p. 212—215°C (benzene); at 170—185°C the crystal modification changes. UV spectrum: λ_{max} 239 nm (log ε 4·34), 256 nm infl. (3·98), 356 nm (3·52). IR spectrum: 742 (1,2-C_6H_4), 819 and 898 (1,2,4-C_6H_3), 1221 (phenolic OH), 1598 (Ar), 1661 (CO—Ar), 3385 cm^{-1} (OH). For $C_{14}H_{10}O_2S$ (242·2) calculated: 69·42% C, 4·16% H, 13·22% S; found: 69·58% C, 4·20% H, 13·24% S.

B. Conc. HCl (300 ml) was added to a solution of 250 ml pyridine in 250 ml ethanol and the hydrochloride solution formed was evaporated *in vacuo*. The residue was heated to 200°C, the melt at this temperature was combined with 44·2 g methoxy ketone[1] *IIa* and the mixture stirred for 1 h. After cooling to 130°C, 600 ml water was added, the mixture left to stand overnight and filtered. The crude product was boiled with 300 ml benzene and, after distilling off 100 ml of the solvent and cooling, it was again filtered; 38·3 g (92%), m.p. 205—213°C, after recrystallization 212—215°C (benzene). For $C_{14}H_{10}O_2S$ (242·2) calculated: 69·42% C, 4·16% H, 13·22% S; found: 69·94% C, 4·11% H, 12·94% S. The product is identical with the compound obtained as under *A*.

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

A mixture of 6·2 g hydroxy ketone *IIb*, 3·6 g K_2CO_3, 4·8 g ethyl iodide and 40 ml acetone was refluxed for 40 h. After evaporation of acetone, the residue was divided between 200 ml water and a mixture of benzene and ether (100/100 ml), the organic phase was washed with 15% NaOH and evaporated: 6·75 g (97%), m.p. after recrystallization 112—114°C (cyclohexane or ethanol). UV spectrum: λ_{max} 238 nm (log ε 4·35), 257 nm (4·03), 352 nm (3·56). IR spectrum: 748 (1,2-C_6H_4) 820 and 880 (1,2,4-C_6H_3), 1225 (Ar—O—R), 1600 (Ar), 1670 cm^{-1} (Ar—CO). For $C_{16}H_{14}O_2S$ (270·3) calculated: 71·10% C, 5·22% H, 11·84% S; found: 70·76% C, 5·29% H, 12·10% S.

8-(n-Butoxy)-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*IId*)

From 7·5 g *IIb* and 5·1 g n-butyl bromide, a total of 5·7 g (62%) product was obtained in analogy with the foregoing case: m.p. 61—62°C (ethanol). UV spectrum: λ_{max} 239 nm (log ε 4·37), 256 nm infl. (4·04), 352 nm (3·53). IR spectrum: 750 and 760 (1,2-C_6H_4), 821 and 882 (1,2,4-C_6H_3), 1220, 1271 and 1317 (Ar—O—R), 1591 (Ar), 1665 cm^{-1} (Ar—CO). For $C_{18}H_{18}O_2S$ (298·3) calculated: 72·46% C, 6·08% H, 10·73% S; found: 72·38% C, 6·07% H, 10·92% S.

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

From 15·0 g *IIb* and 9·4 g benzyl chloride there were obtained in analogy with preparation of *IIc* 13·8 g (67%) product; m.p. 101·5—102·5°C (cyclohexane). UV spectrum: λ_{max} 239 nm (log ε 4·40), 257 nm infl. (4·08), 351 nm (3·55). IR spectrum: 700 (C_6H_5), 750 and 760 (1,2-C_6H_4), 825 and 880 (1,2,4-C_6H_3), 1226, 1270, 1305 (Ar—O—R), 1590 (Ar), 1670 cm^{-1} (Ar—CO). NMR spectrum: δ 6·90—8·00 (m, 12 H, aromatic protons), 5·06 (s, 2 H, $ArCH_2O$), 4·37 (s, 2 H, $ArCH_2$ in the ring). For $C_{21}H_{16}O_2S$ (332·3) calculated: 75·89% C, 4·85% H, 9·63% S, found: 76·00% C, 4·97% H, 9·38% S.

8-Benzyloxy-11-benzyl-11*H*-dibenzo[*b*,*f*]thiepin-10-one (VI)

Hydroxyketone *IIb* (5·1 g) and 2·8 g benzyl chloride were added to a solution of 0·61 g Na in 60 ml ethanol and the mixture was refluxed for 5 h. After evaporation of the ethanol, the residue was divided between benzene and 5% NaOH, the organic phase was separated and evaporated. The residue (5·2 g) is according to thin-layer chromatography on silica gel a mixture of about 6 components. Chromatography on alumina and crystallization led to a separation of two components in a pure state. The more polar fraction yielded 0·98 g ketone *IIe*, m.p. 101·5—102·5°C (cyclohexane). The less polar fraction yielded 1·45 g product, m.p. 112—113°C (ethanol). UV spectrum: λ_{max} 239·5 nm (log ε 4·43), 258 nm infl. (4·04), 353 nm (3·59). IR spectrum: 705 (C_6H_5), 750 and 755 (1,2-C_6H_4), 830 and 875 (1,2,4-C_6H_3), 1225 and 1270 (Ar—O—R), 1590 (Ar), 1680 cm^{-1} (Ar—CO). NMR spectrum: δ 6·95—8·00 (m, 17 H, aromatic protons), 5·10—5·50 (m, 1 H Ar—CH in the ring), 5·04 (s, 2 H, $ArCH_2O$), 3·1—4·2 (m, 2 H, Ar—CH_2—C). For $C_{28}H_{22}O_2S$ (422·5) 79·60% C, 5·25% H, 7·16% S; found: 80·06% C, 5·40% H, 7·30% S.

8-(2-Pyridyloxy)-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*IIf*)

A mixture of 7·27 g hydroxyketone *IIb*, 5·22 g 2-bromopyridine, 6·2 g K_2CO_3, 0·96 g CuO and 40 ml pyridine was refluxed under stirring for 3 h. After filtration, the pyridine was evaporated at reduced pressure and the residue was chromatographed on a column of alumina (400 g, activity II). After separation of a small fraction of the least polar substance, benzene was used for eluting 6·2 g (65%) of the desired product which was converted with an ether solution of hydrogen chloride to the hydrochloride, m.p. 103—106°C (ethanol–ether). UV spectrum: λ_{max} 223 nm (log ε 4·44), 263 nm (4·28), 296 nm (3·79). IR spectrum: 740, 770, and 782 (Ar—4 H), 842 (1,2,4-C_6H_3), 1287 (Ar—O—Ar), 1510, 1582, 1612 (Ar), 1660 and 1675 (Ar—CO), 1820, 1878, 1930, 2000 and 2500 cm^{-1} (NH^+). For $C_{19}H_{14}ClNO_2S$ (355·8) calculated: 64·13% C, 3·96% H, 9·96% Cl, 3·94% N, 9·01% S; found: 63·47% C, 4·03% H, 9·62% Cl, 3·94% N, 9·00% S.

8-Ethoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*IIIc*)

A solution of 0·85 g $NaBH_4$ in 5 ml water with 3 drops of 15% NaOH was added dropwise to 5·45 g ketone *IIc* in 80 ml ethanol. The mixture was stirred for 1 h at 50°C, left to stand overnight, re-

fluxed for 3 h and ethanol was then evaporated. The residue was divided between water and chloroform, the organic phase was washed with 5% hydrochloric acid and water and evaporated. The residue crystallized from ethanol: 4·8 g (87%), m.p. 74—76°C. NMR spectrum: δ 6·90—7·75 (m, 6 H, aromatic protons in positions 1,2,3,4,6 and 7), 6·70 (dd, 1 H, aromatic proton in position 9), 5·43 (dd, J = 9·0; 5·0 Hz, 1 H in ArCH—O), 4·0 (q, 2 H, CH_2O), 3·05—3·70 (m, 2 H, $ArCH_2$), 2·25 (bs, 1 H, OH), 1·35 (t, 3 H, C—CH_3). For $C_{16}H_{16}O_2S$ (272·3) calculated: 70·57% C, 5·92% H, 11·76% S; found: 70·40% C, 5·84% H, 11·67% S.

8-(n-Butoxy)-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*IIId*)

Reduction of 5·22 g ketone *IId* yielded in analogy to the foregoing case almost the theoretical amount of the product, m.p. 90—91°C (ethanol). IR spectrum (KBr): 755 (1,2-C_6H_4), 829 and 855 (1,2,4-C_6H_3), 1015 and 1234 (Ar—O—R), 1063 (CHOH), 1596 (Ar) and 3260 cm^{-1} (OH). For $C_{18}H_{20}O_2S$ (300·3) calculated: 71·98% C, 6·71% H, 10·66% S; found: 72·07% C, 6·83% H, 10·52% S.

8-Benzyloxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*IIIe*)

Reduction of 13·81 g ketone *IIe* yielded in analogy to the above cases an almost theoretical yield of alcohol *IIIe*, m.p. 111—113°C (ethanol). IR spectrum (KBr): 696 (C_6H_5), 751 (1,2-C_6H_4), 811 and 880 (1,2,4-C_6H_3), 1012 and 1262 (Ar—O—R), 1055 (CHOH), 1598 (Ar), 3350 cm^{-1} (OH). For $C_{21}H_{18}O_2S$ (334·4) calculated: 75·43% C, 5·43% H, 9·58% S; found: 74·98% C, 5·53% H, 9·69% S.

8-(2-Pyridyloxy)-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*IIIf*)

Reduction of 4·8 g ketone *IIf* yielded similarly to the above cases 2·94 g (61%) alcohol *IIIf*, m.p. 130—131·5°C (benzene–light petroleum). UV spectrum: λ_{max} 270 nm (log ε 4·20); IR spectrum (KBr): 749 and 779 (Ar—4 H), 819 and 895 (1,2,4-C_6H_3), 1052 (CHOH), 1244, 1267 and 1296 (Ar—O—Ar), 1567 and 1589 (Ar), 3430 cm^{-1} (OH). NMR spectrum: δ 8·15 (dd, J = 5·0; 2·0 Hz, 1 H, aromatic proton in the vicinity of pyridine N), 6·75—7·90 (m, 10 H, other aromatic protons), 5·34 (bs, 1 H, after D_2O dd, J = 8·0; 4·0 Hz, Ar—CH—O), 3·65 (dd, 1 H, J = 14·0; 4·0 Hz) and 3·15 (dd, 1 H, J = 14·0; 8·0 Hz) $ArCH_2$, 3·00 (bs, 1 H, OH). For $C_{19}H_{15}NO_2S$ (321·4) calculated: 71·00% C, 4·70% H, 4·36% N, 9·98% S; found: 70·64% C, 4·85% H, 4·09% N, 9·60% S.

8,10-Dihydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*IIIb*)

Reduction of 8·15 g hydroxy ketone *IIb* with 2·2 g $NaBH_4$ was carried out as in the foregoing cases. After evaporation of the ethanol the mixture was combined with 50 ml water and made acid with hydrochloric acid. The precipitate was dissolved in chloroform and applied to a column of 300 g alumina (activity II). The product *IIIb* was eluted with ethanol: 4·35 g (53%), m.p. 136 to 138°C (benzene). It is identical with the product prepared[5] by decomposition of the diazonium salt obtained from 8-amino-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin.

8-(1,2-Dihydro-2-pyridyloxy)-11*H*-dibenzo[*b,f*]thiepin-10-one (*VII*)

A solution of 0·57 g hydrochloride of ketone *IIf* in 40 ml acetic acid was hydrogenated on palladium (0·17 g $PdCl_2$, 0·5 g charcoal) at normal temperature and pressure until cessation of hydrogen absorption. After filtration, the solution was evaporated at reduced pressure, the base was

liberated from the residue with 5% $NaHCO_3$ and isolated by extraction with a mixture of benzene and ether: 0·46 g oil. Using an ether solution of hydrogen chloride, the hydrochloride was prepared: m.p. 108—110°C (ethanol–ether). UV spectrum: λ_{max} 220 nm (log ε 4·37), 241 nm (4·34), 262 nm (4·18), 340 nm (3·62). IR spectrum (KBr): 745 and 765 (1,2-C_6H_4), 819 and 848 (1,2,4-C_6H_3), 1293 (Ar—O—R), 1515, 1595, 1608 (Ar), 1625 (C=C), 1678 (Ar—CO), 1886, 1940, 2010, 2300 and 2380 (NH_2^+), 3420 cm^{-1} (NH). NMR spectrum: (CD_3SOCD_3): δ 8·20 (m, 1 H, aromatic proton in position 9), 7·00—8·00 (m, 10 H, remaining aromatic protons and olefinic protons of the dihydropyridine residue), 6·67 (s, NH), 4·40 (s, 2 H, $ArCH_2CO$). For $C_{19}H_{16}ClNO_2S$ (357·9) calculated: 63·77% C, 4·51% H, 3·91% N; found: 63·80% C, 4·23% H, 3·89% N.

8-Ethoxy-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*IVc*)

Anhydrous, powdery $CaCl_2$(1 g) was added to a solution of 4·2 g alcohol *IIIc* in 50 ml benzene and the suspension was saturated for 3·5 h with anhydrous HCl. After standing overnight it was filtered, the filtrate was evaporated and the residue recrystallized from cyclohexane: 4·1 g (92%), m.p. 89—90°C, and after conversion of needles to prisms again 96—96·5°C. For $C_{16}H_{15}ClOS$ (290·8) calculated: 66·08% C, 5·20% H, 12·19% Cl, 11·03% S; found: 65·86% C, 5·22% H, 12·48% Cl, 10·75% S.

8-(n-Butoxy)-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*IVd*)

As in the preceding case, this was obtained from the alcohol *IIId* in a practically theoretical yield; m.p. 69—70°C (cyclohexane). For $C_{18}H_{19}ClOS$ (318·9) calculated: 67·80% C, 6·00% H, 11·12% Cl, 10·06% S; found: 67·66% C, 6·05% H, 11·06% Cl, 10·23% S.

8-Benzyloxy-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*IVe*)

As in the preceding cases, it was obtained from alcohol *IIIe* in a 95% yield; m.p. 117—119°C (benzene–cyclohexane). For $H_{21}H_{17}ClOS$ (352·9) calculated: 71·48% C, 4·85% H, 10·05% Cl, 9·09% S; found: 71·76% C, 4·85% H, 9·78% Cl, 9·04% S.

8-(2-Pyridyloxy)-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*IVf*)

$CaCl_2$ (1 g) was added to a solution of 1·97 g alcohol *IIIf* in 70 ml chloroform and the suspension was saturated for 2 h with anhydrous HCl. After standing overnight, it was filtered and the filtrate was evaporated. The remaining oily hydrochloride was decomposed with aqueous $NaHCO_3$ and the base was isolated by extraction with ether. The crude product crystallized from cyclohexane: 1·20 g (58%), m.p. 84—87°C. IR spectrum (KBr): 750 and 780 (Ar—4 H), 840 and 898 (1,2,4-C_6H_3), 1250 (Ar—O—Ar), 1575 and 1590 cm^{-1} (Ar). NMR spectrum: δ 8·15 (dd, 1 H, aromatic proton in the vicinity of pyridine N), 6·75—7·80 (m, 10 H, remaining aromatic protons), 5·75 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CHCl), 3·94 (dd, J = 14·0; 4·0 Hz) and 3·60 (dd, J = 14·0; 9·0 Hz, 2 H, $ArCH_2$). For $C_{19}H_{14}ClNOS$ (339·8) calculated: 67·15% C, 4·15% H, 10·43% Cl, 4·12% N, 9·44% S; found: 67·24% C, 4·34% H, 10·47% Cl, 3·93% N, 9·40% S.

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

A solution of 4·1 g chloride *IVc* and 10 ml 1-methylpiperazine in 10 ml chloroform was refluxed for 9 h. After evaporation of the solvent it was divided between benzene and water, the benzene solution was washed with water and shaken with 60 ml dilute hydrochloric acid (1 : 2). The pre-

cipitated hydrochloride was filtered, washed with benzene, suspended in the acid aqueous phase of the filtrate, made alkaline to liberate the base and this was isolated by extraction with chloroform; 4·2 g oil. Neutralization with methanesulfonic acid in ethanol with an addition of ether yielded 5·4 g di(methanesulfonate), m.p. 213–215°C (aqueous ethanol–ether). For $C_{23}H_{34}N_2O_7S_3$ (546·7) calculated: 50·53% C, 6·27% H, 5·12% N, 17·60% S; found: 50·44% C, 6·53% H, 5·32% N, 17·41% S. Evaporation of the benzene phase after removal of basic components by shaking with hydrochloric acid yielded 0·64 g of oily 2-ethoxydibenzo[*b,f*]thiepin (*VIIIc*) which did not crystallize even after chromatography on Al_2O_3. UV spectrum: λ_{max} 242 nm (log ε 4·30), 262 nm (3·82), 294 nm (3·76). IR spectrum (film): 748 (1,2-C_6H_4), 820 and 876 (1,2,4-C_6H_3), 1 275 (Ar—O—Ar), 1 592 cm^{-1} (Ar). NMR spectrum: δ 6·70–7·60 (m, 9 H, aromatic and olefinic protons), 3·96 (q, J = 7·0 Hz, 2 H, CH_2O), 1·33 (t, J = 7·0 Hz, 3 H, C—CH_3).

8-(n-Butoxy)-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Id*)

In analogy with the preceding case, 4·90 g chloride *IVd* gave rise to 5·00 g (85%) oily base I*d* which was converted to di(methanesulfonate) monohydrate: 6·08 g, m.p. 161–163° (ethanol–ether). For $C_{25}H_{40}N_2O_8S_3$ (592·8) calculated: 50·65% C, 6·80% H, 4·73% N, 16·23% S; found: 50·44% C, 6·67% H, 4·68% N, 16·26% S. In a yield of 0·68 g the neutral reaction product was isolated: 2-(n-butoxy)dibenzo[*b,f*]thiepin (*VIIId*) which does not crystallize even after chromatography on alumina. NMR spectrum: δ 7·10–7·60 (m, 5 H, aromatic protons in positions 4,6,7,8 and 9), 7·02 (s, 2 H, CH=CH), 6·85 (dd, J = 9·0; 2·0 Hz, 1 H, aromatic proton in position 3), 6·76 (d, 1 H aromatic proton in position 1), 3·89 (t, J = 6·0 Hz, 2 H, OCH_2), about 1·55 (m, 4 H, remaining CH_2 groups of the butyl), 0·92 (t, J = 5·0 Hz, 3 H, C—CH_3).

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

As in preceding cases, 12·43 g chloride *IVe* yielded 11·35 g (78%) base *Ie*, m.p. 131·5–132°C (ethanol). NMR spectrum: δ 7·00–7·60 (m, 11 H, aromatic protons in positions 1, 2. 3, 4, 6 and 9 and phenyl), 6·72 (dd, J = 9·0; 2·0 Hz, 1 H, aromatic proton in position 7), 4·99 (s, 2 H, $ArCH_2O$), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·44 and 2·60 (2 m, 8 H, CH_2 groups of piperazine), 2·25 (s, 3 H, N—CH_3). For $C_{26}H_{28}N_2OS$ (416·6) calculated: 74·96% C, 6·78% H, 6·72% N, 7·70% S; found: 74·96% C, 6·79% H, 6·64% N, 7·83% S.

Di(methanesulfonate)dihydrate, m.p. 186–187°C (ethanol–ether). For $C_{28}H_{40}N_2O_9S_3$ (644·8) calculated: 52·15% C, 6·25% H, 4·34% N, 14·91% S; found: 51·97% C, 5·87% H, 4·25% N, 15·06% S. As the neutral reaction product, 2-benzyloxydibenzo[*b,f*]thiepin (*VIIIe*) was isolated in a yield of 3·28 g. It crystallized from ethanol, m.p. 85°C. UV spectrum: λ_{max} 241·5 nm (log ε 4·31), 262 nm (4·42), 293 nm (3·75). IR spectrum (KBr): 693 and 736 (C_6H_5 and 1,2-C_6H_4), 795, 828 and 870 (1,2,4-C_6H_3), 1 041 and 1 245 (Ar—O—R), 1 589 cm^{-1} (Ar). NMR spectrum: δ 6·80–7·60 (m, 7 H, aromatic protons of the tricyclic skeleton), 7·37 (s, 5 H, phenyl), 6·98 (s, 2 H, CH=CH), 4·98 (s, 2 H, $ArCH_2O$). For $C_{21}H_{16}OS$ (316·3) calculated: 79·73% C, 5·10% H 10·12% S; found: 80·19% C, 5·30% H, 10·15% S.

8-(2-Pyridyloxy)-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*If*)

A mixture of 3·85 g oily hydrochloride of *IVf*, 10 ml chloroform and 10 ml 1-methylpiperazine was refluxed for 7 h. After cooling, it was diluted with benzene and washed several times with water. The organic phase was then shaken with excess 10% hydrochloric acid, the separated acid solution was made alkaline with aqueous ammonia and the base was extracted with benzene; 3·0 g oil. Dimaleate (hemihydrate): m.p. 106–108°C (ethanol–ether). For $C_{32}H_{34}N_3O_{9,5}S$ (644·7) calculated: 59·61% C, 5·32% H, 6·52% N, 4·97% S; found: 59·66% C, 5·35% H, 6·55% N, 5·44% S.

2-Hydroxydibenzo[*b,f*]thiepin (*VIIIb*)

A. 1 g $CaCl_2$ was added to a solution of 2·5 g alcohol[1] *IIIa* in 50 ml chloroform and the suspension was saturated for 3 h with anhydrous HBr. After standing overnight, it was filtered, the filtrate was washed with water, dried with $CaCl_2$ and evaporated; 2·9 g oily bromide *Va*. From 1·5 g pyridine the hydrochloride was precipitated in ether with gaseous HCl, the ether was evaporated and, after adding 0·7 g bromide *Va*, the mixture was heated for 1 h to 200°C. After cooling, 50 ml water was added and extracted with chloroform. The product was extracted from the organic phase with 15% NaOH, from which it was liberated by acidification and isolated by extraction with chloroform: 0·45 g, m.p. 130—131°C (cyclohexane). UV spectrum: λ_{max} 290 nm (log ε 3·76), 263 nm (4·38), 240 nm (4·26), 222 nm (4·51). IR spectrum: 746 (1,2-C_6H_4), 790, 818 and 886 (1,2,4-C_6H_3). 950 and 1 288 (phenol), 1 472, 1 586 and 1 608 (Ar), 3 320 cm^{-1} (OH). NMR spectrum: δ 6·60—7·60 (m, 9 H, aromatic and olefinic protons), 4·75 (bs, 1 H, OH). For $C_{14}H_{10}OS$ (226·2) calculated: 74·33% C, 4·46% H, 14·15% S; found: 74·27% C, 4·52% H, 14·12% S. *B*. A mixture of 13·6 g pyridine hydrochloride and 4·6 g dihydrochloride of base[1] *Ia* was heated for 1 h to 195—200°C. After cooling, the melt was divided between 50 ml water and 50 ml benzene. Evaporation of the benzene phase yielded 1·55 g (62%) phenol *VIIIb*, m.p. 128—130°C which is identical with the compound prepared according to *A*.

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

Base, m.p. 94—96°C (light petroleum) (previously[1] a m.p. of 80—81·5°C was given for the product crystallized from cyclohexane). NMR spectrum: δ 6·90—7·60 (m, 6 H, aromatic protons in positions 1, 2, 3, 4, 6 and 9), 6·58 (dd, J = 8·5; 3·5 Hz, 1 H, aromatic proton in position 7), 3·93 (s, 1 H, Ar—CH—N), 3·85 and 3·12 (d, J = 8·0 Hz, 2 H, $ArCH_2$), 3·70 (s, 3 H, O—CH_3), 2·68 (m, 4 H, CH_2 groups of piperazine nearer the skeleton), 2·37 (m, 4 H, remaining CH_2 groups of piperazine), 2·26 s, 3 H, N—CH_3). For $C_{20}H_{24}N_2OS$ (340·4) calculated: 70·56% C, 7·11% H, 8·23% N, 9·40% S; found: 70·38% C, 7·07% H, 7·91% N, 9·56% S.

Monomethanesulfonate, m.p. 184—186°C (ethanol–ether). For $C_{21}H_{28}N_2O_4S_2$ (436·5) calculated: 57·79 C, 6·47% H, 6·42% N, 14·67% S; found: 57·72% C, 6·49% H, 6·15% N, 14·68% S.

Di(*methanesulfonate*) (*hemihydrate*), m.p. 199—200° (ethanol–ether). For $C_{22}H_{33}N_2O_{7.5}S_3$ (541·7) calculated: 48·78% C, 6·14% H, 5·17% N, 17·76% S; found: 48·82% C, 6·11% H, 4·93% N, 17·72% S.

Dihydrodichloride (*hemihydrate*), m.p. 223—225°C in the capillary (ethanol–ether). For $C_{20}.H_{27}Cl_2N_2O_{1.5}S$ (422·4) calculated: 56·87% C, 6·44% H, 16·79% Cl, 6·63% N, 7·59% S; found: 56·97% C, 6·23% H, 16·66% Cl, 6·40% N, 7·44% S.

Dihydrobromide, m.p. 213—214°C under decomposition (aqueous ethanol). For $C_{20}H_{26}.Br_2N_2OS$ (502·3) calculated: 47·82% C, 5·22% H, 31·82% Br, 5·58% N, 6·38% S; found: 47·83% C, 5·22% H, 32·42% Br, 5·60% N, 6·42% S.

1-Methyl-4-ethylpiperazine

Raney nickel W-2, prepared from 30 g alloy, was suspended in 100 ml ethanol, 1·92 g base *Ie* was added and the mixture was refluxed under stirring for 10 h. After filtration and evaporation of the filtrate, a total of 1·5 g of residue was obtained, from which, through addition of 0·5 g maleic acid and crystallization of the product to a constant melting point, 0·5 g di(hydrogenmaleate) was obtained; m.p. 190—191°C (ethanol). For $C_{15}H_{24}N_2O_8$ (360·4) calculated: 49·99% C, 6·71% H, 7·77% N; found: 50·07% C, 6·76% H, 7·77% N. Reaction of an aqueous solution of this salt with

a solution of sodium picrate resulted in the dipicrate, m.p. 284°C in the capillary under decomposition (water). NMR spectrum (CD_3SOCD_3): δ 8·71 (s, 4 H, aromatic protons of picric acid). 3·50 (m, 8 H, CH_2 groups of piperazine), 3·28 (q, J = 8·0 Hz, 2 H, CH_2 group of ethyl), 2·96 (s, 3 H, N—CH_3), 1·25 (t, J = 8·0 Hz, 3 H, C—CH_3). For $C_{19}H_{22}N_8O_{14}$ (586·5) calculated: 38·91% C, 3·78% H, 19·11% N; found: 39·27% C, 3·84% H, 19·35% N. Ref.[12] described the formation of 1-methyl-4-ethylpiperazine by a different procedure and mentions monopicrate as its salt.

1,1-Dimethyl-4-[8-bromo-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl]piperazinium Iodide (*IX*)

This was obtained by a reaction of the base of 8-bromo-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin[8] with methyl iodide in tetrahydrofuran; m.p. 261—264°C (aqueous ethanol). For $C_{20}H_{24}BrIN_2S$ (531·3) calculated: 45·21% C, 4·55% H, 23·89% I, 5·27% N, 6·04% S; found: 45·34% C, 4·51% H, 23·88% I, 4·86% N, 6·42% S.

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

A. Ethyl bromide (0·12 ml) was added to a mixture of 20 ml tetrahydrofuran, 0·21 g magnesium, 3·13 g base of 8-bromo-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin[8] and a small amount of iodine. The mixture was refluxed for 5 h. After 48 h of standing (without elimination of air) 0·63 g selenium was added, the mixture was refluxed for 1 h, cooled, diluted with ether, decomposed with excess hydrochloric acid and filtered. The acid aqueous phase was separated from the filtrate, made alkaline with 20% NaOH and, after adding excess 20% solution of NH_4Cl, it was extracted with chloroform. After evaporation of the extract, 2·45 g of a residue was obtained. This was dissolved in 5 ml ethanol. On standing, 0·24 g compound precipitated, apparently not completely pure base *Ib* — m.p. 239—243°C under decomposition (ethanol). UV spectrum: λ_{max} 242 nm (log ε 3·94), 268·5 nm (3·71), 292·5 nm (3·53). IR spectrum: 760 (1,2-C_6H_4), 780, 810 and 881 (1,2,4-C_6H_3), 1002 and 1300 (Ar—O—), 1567 cm^{-1} (Ar). For $C_{19}H_{22}N_2OS$ (326·4) calculated: 69·92% C, 6·79% H, 8·58% N, 9·82% S; found: 70·60% C, 6·92% H, 8·16% N, 9·78% S.

B. Sodium (2·5 g) was gradually added to a solution of 1·33 g base *Ie* in 25 ml 1-butanol and the mixture was refluxed for 1 h until the sodium dissolved. After adding further 10 ml 1-butanol it was refluxed for 1·5 h, cooled, decomposed with 100 ml water and acidified with hydrochloric acid. After separation of the organic phase, the acid aqueous phase was made alkaline with aqueous ammonia and the product was extracted with chloroform. Evaporation of the extract yielded a residue which was crystallized from ethanol to 0·38 g base *Ib*, m.p. 258—260°C, under decomposition. IR spectrum is identical with that of the product prepared according to *C*.

C. A solution of 6·7 g boron tribromide in 10 ml chloroform was added dropwise over a period of 5 min at 10—15°C to a solution of 7·4 g *IVa* (ref.[1]) in 30 ml chloroform. The mixture was stirred for 6 h, left to stand overnight and heated for 15 min to 60°C whereupon it was cooled to 20°C. 1-Methylpiperazine (15 ml) was then added and refluxed for 8 h. After 48 h of standing the chloroform was distilled off, the residue was combined with 40 ml ethanol and 20 ml water and the mixture was refluxed for 4 h. Ethanol was then evaporated: 3·25 g crude base *Ib* which is poorly soluble in benzene and ethanol. After several crystallizations from a larger volume of ethanol it melted at 257—259°C under decomposition. IR spectrum: 760 (1,2-C_6H_4), 780, 810 and 882 (1,2,4-C_6H_3), 1005 and 1300 (Ar—O—), 1570 and 1610 (Ar), 2690 cm^{-1} (NH^+). For $C_{19}H_{22}N_2OS$ (326·4) calculated: 69·92% C, 6·79% H, 8·58% N, 9·82% S; found: 69·82% C, 6·97% H, 8·96% N, 9·68% S. On applying ether solution of HCl to a chloroform solution of the base, dihydrochloride is precipitated, m.p. 207—209°C (aqueous ethanol–ether). IR spectrum

(KBr): 752 (1,2-C_6H_4), 830, 880 and 895 (1,2,4-C_6H_3), 1290 (Ar—OH), 1575, 1610 (Ar), 2450 (NH^+), 3200 cm^{-1} (OH). For $C_{19}H_{24}Cl_2N_2OS$ (393·4) calculated: 57·14% C, 6·05% H, 17·75% Cl, 7·02% N, 8·03% S; found: 57·17% C, 6·19% H, 17·39% Cl, 6·81% N, 7·91% S.

2-(4-Methoxyphenylthio)benzyl Alcohol (*XI*)

A. $NaBH_4$ (3·4 g) was slowly added to a mixture of 7·8 g 2-(4-methoxyphenylthio)benzoic[1] acid and 60 ml tetrahydrofuran. The mixture was cooled to 20°C and, within 15 min, a solution of 3 ml boron trifluoride etherate in 20 ml tetrahydrofuran was added under stirring. The mixture was stirred for 1 h at room temperature and then refluxed for 3 h. After standing overnight, it was decomposed with a mixture of 20 ml 5% HCl and 100 ml water, the organic phase was separated and the aqueous one extracted with 200 ml ether. The combined organic phases were washed with 5% NaOH, dried with $MgSO_4$ and evaporated: 6·8 g (92%), m.p. 49—50°C (ether–light petroleum). For $C_{14}H_{14}O_2S$ (246·3) calculated: 68·28% C, 5·73% H, 12·99% S; found: 68·39% C, 5·97% H, 12·97% S. For a product obtained by reduction with $LiAlH_4$ a m.p. of 47·5—48·5°C was reported earlier[1].

B. Sodium bis(2-methoxyethoxy)dihydroaluminate (1200 ml 50% solution in benzene) was added dropwise under stirring over a period of 3 h to a suspension of 390 g 2-(4-methoxyphenylthio)benzoic acid[1] in 1500 ml benzene. The solution was stirred for 1 h at room temperature and then, over a period of 90 min, 2000 ml 10% NaOH was added dropwise, the separated benzene phase was washed with water, dried with $MgSO_4$ and gave 318 g (87%), b.p. 180—190°C/0·8 Torr. After inoculation, the product crystallizes, m.p. 48°C, and is identical with the product obtained under *A*.

2-(4-Methoxyphenylthio)phenylacetic Acid (*XII*)

A mixture of 20·2 g 2-iodophenylacetic acid[6,14], 11·8 g 4-methoxythiophenol[15], 160 ml water, 16 g KOH and 1 g freshly reduced copper was refluxed for 8 h under stirring. After filtration while hot, the filtrate was made acid: 16·4 g (81%) crude product which, after crystallization from aqueous ethanol, melts at 102—105°C. For acid *XII* obtained by hydrolysis of the nitrile, a m.p. of 103—104°C was reported before[1].

2-(4-Methoxyphenylthio)benzoyl Chloride (*XIII*)

A mixture of 26·5 g 2-(4-methoxyphenylthio)benzoic acid[1], 260 ml benzene, 24 ml thionyl chloride and 2 drops of dimethylformamide was refluxed for 2 h and then evaporated *in vacuo*. The residue crystallized from cyclohexane: 26·3 g (93%), m.p. 96—97°C. IR spectrum: 770 (1,2-C_6H_4), 838 (1,4-C_6H_4), 1251 (Ar—O—R), 1588 and 1590 (Ar), 1722 and 1752 cm^{-1} (ArCOCl). For $C_{14}H_{11}ClO_2S$ (278·8) calculated: 60·32% C, 3·98% H, 12·72% Cl, 11·50% S; found: 60·44% C 3·95% H, 12·54% Cl, 11·64% S.

2-(4-Methoxyphenylthio)acetophenone (*XIV*)

A solution of 13·0 g chloride *XIII* in 30 ml ether and 20 ml dioxane was added to a solution of diethyl ethoxymagnesium malonate (from 7·7 g diethyl malonate, 1·2 g magnesium, 6·3 ml ethanol and 0·1 ml CCl_4 in 20 ml ether). The mixture was refluxed for 1 h and left to stand overnight. Then it was decomposed by adding 35 ml 10% sulfuric acid, the organic phase was washed with water and evaporated. The residue was combined with 15 ml acetic acid, 10 ml water and 2 ml sulfuric acid and the mixture was refluxed for 12 h. After cooling, it was made alkaline

with 20% NaOH and the product was isolated by extraction with benzene: 8·9 g (74%), m.p. 99–101·5°C (ethanol). Japanese authors[16] gave for the product obtained by a different procedure, a m.p. of 100–101°C. UV spectrum: λ_{max} 230·5 nm (log ε 4·48), 266 nm (3·93), 335 nm (3·60). IR spectrum (KBr): 762 (1,2-C_6H_4), 831 (1,4-C_6H_4), 1022 and 1250 (Ar—O—R), 1590 (Ar), 1660 cm^{-1} (Ar—CO). NMR spectrum: δ 7·86 (m, 1 H, aromatic proton in the vicinity of the keto group), 7·50 (d, J = 9·0 Hz, 2 H, aromatic protons in the anisol ring in the vicinity of the sulfur atom), 6·92 (d, J = 9·0 Hz, 2 H, aromatic protons in the anisol ring in the vicinity of the oxygen atom), 6·80–7·30 (m, 3 H, remaining aromatic protons), 3·80 (s, 3 H, OCH_3), 2·61 (s, 3 H, $COCH_3$). For $C_{15}H_{14}O_2S$ (258·3) calculated: 69·73% C, 5·46% H, 12·41% S; found: 69·67% C, 5·45% H, 12·44% S.

Thiomorpholide of 2-(4-Methoxyphenylthio)phenylacetic Acid (*XVI*) and Thiomorpholide of 2-(4-Methoxyphenylthio)phenylglyoxylic Acid (*XV*)

Mixture of 4·3 g acetophenone *XIV*, 0·8 g sulfur and 2·3 ml morpholine was heated for 10 h at 150°C. From the mixture, the following compounds were isolated by fractional crystallization: Thiomorpholide *XVI*, m.p. 73–76°C (ethanol). Ref.[16] shows 79–81°C. NMR spectrum: δ 7·24 (d, J = 9·0 Hz, 2 H, aromatic protons in the anisol part in the vicinity of the S atom), 7·00–7·60 (m, 4 H, aromatic protons 1,2-C_6H_4), 6·85 (d, J = 9·0 Hz, 2 H, remaining aromatic protons in the anisol ring), 4·34 (s, 2 H, CH_2CS), 4·35 and 3·75 (2 t, 4 H, CH_2OCH_2), 3·75 (s, 3 H, OCH_3), 3·39 (s, 4 H, CH_2NCH_2). For $C_{19}H_{21}NO_2S_2$ (359·4) calculated: 63·50% C, 5·89% H, 3·90% N, 17·82% S; found: 63·11% C, 5·84% H, 3·67% N, 17·70% S. Oxothiomorpholide *XV* (benzene–light petroleum), m.p. 167–168°C. Ref.[16] gives 165–166°C. NMR spectrum: δ 7·90 (m, 1 H, aromatic proton in the vicinity of CO), 7·55 (d, J = 9·0 Hz, 2 H, aromatic protons in the anisol part in the vicinity of the S atom), 6·90–7·50 (m, 3 H, remaining aromatic protons in 1,2-C_6H_4), 7·00 (d, J = 9·0 Hz, 2 H, remaining aromatic protons in the anisol part), 4·35 and 3·90 (2 t, 4 H, CH_2OCH_2), 3·85 (s, 3 H, OCH_3), 3·71 (s, 4 H, CH_2NCH_2). For $C_{19}H_{19}$-$.NO_3S_2$ (373·4) calculated: 61·12% C, 5·13% H, 3·75% N, 17·12% S; found: 61·39% C, 5·15% H, 3·51% N, 16·73% S.

2-(4-Hydroxyphenylthio)phenylacetic Acid (*XVII*)

The acid *XII* was heated with pyridine hydrochloride to 200°C similarly to the preparation of *IIb* (Method *B*); m.p. 184–186°C (benzene–ethanol). IR spectrum: 750 (1,2-C_6H_4), 830 (1,4-C_6H_4), 1220 (C—O), 1494, 1585 and 1595 (Ar), 1720 (COOH), 3100 and 3390 cm^{-1} (OH). NMR spectrum (CD_3SOCD_3): δ 11–12 (m, 2 H, OH and COOH), 6·70–7·50 (m, 8 H, aromatic protons), 3·75 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{12}O_3S$ (260·3) calculated: 64·60% C, 4·64% H, 12·32% S; found: 64·44% C, 4·37% H, 12·04% S.

8-Methoxy-11-bromo-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*XVIII*)

A solution of 7·7 g bromine in 20 ml chloroform was added dropwise under stirring over a period of 75 min to a solution of 12·3 g ketone[1] *IIa* in 60 ml chloroform. After 5 min of stirring, the solution was washed with water, dried with $MgSO_4$, and evaporated. The remaining oil (15·4 g) crystallized from 10 ml ethanol to 12·5 g (78%) product: m.p. 115–116·5°C (ethanol). UV spectrum: λ_{max} 239 nm (log ε 4·36), 265 nm (4·02), 354 nm (3·60). IR spectrum: 757 (1,2-C_6H_4), 829 and 870 (1,2,4-C_6H_3), 1029, 1227, 1273 and 1323 (Ar—O—R), 1598 (Ar), 1682 cm^{-1} (Ar—CO). For $C_{15}H_{11}BrO_2S$ (335·2) calculated: 53·74% C, 3·31% H, 9·57% S; found: 54·38% C, 3·48% H, 9·68% S.

2-Methoxydibenzo[*b,f*]thiepin-10,11-dione (*XX*)

A mixture of 11·8 g bromo ketone *XVIII*, 20 ml 1-methylpiperazine, 50 ml benzene and 50 ml ether was left to stand for 7 days at room temperature. It was then washed with water and the water insoluble bases were extracted with excess 5% HCl. From the acid solution, the base was liberated with 15% NaOH and isolated by benzene extraction: 3·5 g amorphous base *XIX*. The organic phase containing neutral and acid reaction products was evaporated and the residue (5·7 g) was recrystallized from cyclohexane: 2·8 g red crystals of the diketone *XX*, m.p. 106·5—107·5°C. UV spectrum: λ_{max} 217 nm (log ε 4·25), 236 nm (4·24), 246 nm (4·25), 266 nm (4·13), 275 nm (4·09), 296 nm (3·60), 364 nm (3·65). IR spectrum: 755 (1,2-C_6H_4), 835 and 882 (1,2,4-C_6H_3), 1 242 (Ar—O—R), 1 590 (Ar), 1 680 and 1 695 cm^{-1} (Ar—CO). NMR spectrum: δ 7·30—7·90 (m, 5 H, aromatic protons in positions 4,6,7,8 and 9), 7·25 (d, J = 3·0 Hz, 1 H, aromatic proton in position 1), 6·95 (dd, J = 9·0; 3·0 Hz, 1 H, aromatic proton in position 3), 3·75 (s, 3 H, OCH_3). For $C_{15}H_{10}O_3S$ (270·3) calculated: 66·65% C, 3·73% H, 11·86% S; found: 67·08% C, 3·77% H, 11·94% S.

Evaporation of the mother liquor after diketone *XX* and crystallization of the residue from methanol and then from a mixture of methanol and ethanol yielded 2·05 g yellow crystals melting at 110—115°C which were identified as 2,9-dimethoxythioxanthene-9-carboxylic acid (*XXI*). IR spectrum: 745 (1,2-C_6H_4), 841 and 874 (1,2,4-C_6H_3), 1 031 (Ar—O—R), 1 080 (OH), 1 172 (C—O), 1 238 and 1 274 (Ar—O—R), 1 560 and 1 595 (Ar), 1 680 (Ar—COOH), 3 380 cm^{-1} (OH). NMR spectrum: δ 8·18 (m, 1 H, aromatic proton in position 8), 7·00—7·70 (m, 5 H, aromatic protons in positions 1, 4, 5, 6 and 7), 6·80 (q, J = 9·0; 2·5 Hz, 1 H, aromatic proton in position 3), 5·45 (s, 1 H, disappears after D_2O, COOH), 3·79 (s, 3 H, Ar—OCH_3), 3·15 (s, 3H, 9-OCH_3). For $C_{16}H_{14}O_4S$ (302·4) calculated: 63·56% C, 4·67% H, 10·60% S; found: 63·73% C, 4·77% H, 10·43% S.

cis-2-Methoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10,11-diol (*XXII*)

Acetic acid (2·3 ml) was added dropwise at 20—30°C to a solution of 1·08 g crude base *XIX* in 15 ml tetrahydrofuran containing 0·37 g $NaBH_4$. The mixture was refluxed for 2 h, cooled, decomposed with 15% NaOH and the product was extracted with benzene. Washing of the extract with dilute hydrochloric acid removed the basic compounds and, after evaporation of the solution, a total of 0·28 g diol *XXII* was obtained: m.p. 171—172·5 °C (benzene). IR spectrum (KBr): 758 (1,2-C_6H_4), 808 and 883 (1,2,4-C_6H_3), 1 088 (CHOH), 1 578 and 1 602 (Ar), 3 330 (bound OH) 3 480 cm^{-1} (free OH). The IR spectrum of the compound at high dilution (about 0·0001%) in CCl_4 shows a band of a free hydroxyl group at 3 627 cm^{-1} and an intense band of a bound OH group at 3 575 cm^{-1}. On the basis of comparison and analogies with spectra of *cis*- and *trans*-9,10-dihydroxy-9,10-dihydrophenanthrenes[19], the present diol is of *cis*-configuration (the *trans*-isomer would probably contain only a band of the free OH group). NMR spectrum: (CD_3SOCD_3): δ 7·05—7·65 (m, 6 H, aromatic protons in positions 1, 4, 6, 7, 8, 9), 6·78 (q, J = 9·0; 3·0 Hz, 1 H, aromatic proton in position 3), 5·10—5·80 (m, 4 H, ArCH(OH)—CH(OH)Ar; after D_2O 2 bs at 5·38 and 5·23, 2 H, Ar—CH—CH—Ar), 3·71 (s, 3 H, OCH_3). NMR spectrum and the Dreiding's model of the *cis*-compound represent further evidence for the correctness of the configuration ascribed. The 10,11-C—H bonds in the cis-diol show a dihedral angle of about 90° which is confirmed by the absence of their spin-spin interaction in the NMR spectrum. On the other hand, the *trans*-diol with a dihedral angle of about 150°, should have the interaction constant J of approx. 8 Hz. For $C_{15}H_{14}O_3S$ (274·3) calculated: 65·69% C, 5·15% H, 11.68% S; found: 66·09% C, 5·19% H, 11·52% S.

8-Methoxy-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XXIII*)

$NaBH_4$ (0·52 g, 95%) was added at 20°C to a solution of 2·25 g crude base *XIX* in 20 ml tetrahydrofuran. This was followed by the addition, over a period of 5 min, of 1·7 ml boron trifluoride etherate. The mixture was stirred for 3 h, then it was diluted with 40 ml ether and decomposed with 15% NaOH. The organic phase was washed with water and with 5% hydrochloric acid. The neutral product obtained by evaporation (0·10 g, m.p. 171—172·5°C after crystallization from benzene) is diol *XXII*. Alkalinization of the acid aqueous solution with aqueous ammonia liberated the base (0·55 g) and neutralization with maleic acid converted it to maleate, m.p. 207—208°C under decomposition (ethanol). IR spectrum (KBr): 760 (1,2-C_6H_4), 833 and 870 (1,2,4-C_6H_3), 1152 (CHOH), 1225 (Ar—O—R), 1596, 1618 (Ar), 1677 (COOH), 1705 (COO^-), 2300 and 2450 (NH^+), 3450 cm^{-1} (OH). For $C_{24}H_{28}N_2O_6S$ (472·6) calculated: 61·00% C, 5·97% H, 5·93% N, 6·78% S; found: 60·91% C, 5·82% H, 5·59% N, 6·80% S.

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