POTENTIAL ORAL NEUROLEPTICS WITH PROTRACTED ACTION: 8-CHLORO-3,7-DIFLUORO-10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN AND FURTHER 3,7-SUBSTITUTED OCTOCLOTHEPIN AND DEHYDROCLOTHEPIN DERIVATIVES*

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Reactions of (2-bromo-4-fluorophenyl)acetic acid with 4-chloro-3-fluorothiophenol and 4-chloro-3-methoxythiophenol resulted in acids *IXa* and *IXd*. Reactions of 2-iodo-4-methoxybenzoic acid with the same thiophenols resulted in acids *Vb* and *Vc* which were converted to homologous acids *IXb* and *IXc*. Cyclization of acids *IXa*—*IXd* with polyphosphoric acid led to ketones *Xa*—*Xd* which were reduced to alcohols *XIa*—*XId* and converted to chlorides *XIIa*—*XIId*. Substitution reactions with 1-methylpiperazine gave rise to the title compound *Ia* and its analogues *Ib*—*Id*. Ketones *Xc* and *Xd* reacted with 1-methylpiperazine and titanium tetrachloride to enamines *IIIc* and *IIId*. Reduction of *IIId* to the dihydro derivative *Id* was studied. Attempts at demethylation of *Ib*—*Id* with boron tribromide to the corresponding phenolic bases were successful only in the case of *Ib*, giving rise to phenol *IV* (a potential metabolite of 7-fluorooctoclothepin). In cases *Ic* and *Id* the formation of a hydroxyl group in position 7 is accompanied by elimination of the basic part of the molecule, yielding in the case of series *d* phenolic olefin *XVI*. The 3,7-difluoro derivative *Ia* is highly depressant for mice, highly cataleptic for rats and, in higher doses, is effective in the antiapomorphine tests in rats and dogs; protraction of the action is particularly marked with the depressant effects. The phenolic derivative *IV* is also rather effective.

One of the biologically highly active metabolites of chlorpromazine is its 3,7-dihydroxy derivative[1–9]. The 3,7-dimethoxy derivative of chlorpromazine[10] is mentioned among the human metabolites of this neuroleptic[4] but it is apparently rather inactive biologically[11–16]. Continuing in our attempts to synthesize the highest possible number of potential hydroxylated metabolites of octoclothepin (8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin[17–19]) and employing the analogy with chlorpromazine[20,21] we set out to synthesize the 3,7-dihydroxy derivative of octoclothepin and its analogues where positions 3 and/or 7 would be blocked by fluorination. These attempts are described in this communication. They were only partly successful.

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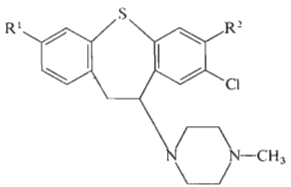
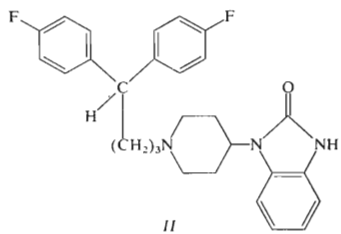
The 3,7-difluoro derivative of octoclothepin (*Ia*) possesses some structural features in common with "pimozide" (*II*), an oral neuroleptic of the group of N-[4,4-bis(4-fluorophenyl)butyl]piperidines with a slightly protracted action[22]. Its synthesis proceeded from (2-bromo-4-fluorophenyl)acetic acid[23] and 4-chloro-3-fluorothiophenol[24]. Reaction of this acid with the sodium salt of the thiol in dimethylformamide in the presence of anhydrous potassium carbonate and copper at 150°C yielded an oily and apparently nonhomogeneous acid *IX* which was cyclized with polyphosphoric acid in the presence of boiling toluene. Ketone *Xa* was obtained in a poor yield, the main product being a mixture of two neutral compounds which could not be separated even by chromatography on alumina. Reduction of ketone *Xa* with sodium borohydride in aqueous dioxane yielded alcohol *XIa* which was treated with hydrogen chloride in dichloromethane to give rise to chloride *XIIa*. Substitution reaction with 1-methylpiperazine in boiling chloroform produced a 84% yield of the basic product *Ia*. A by-product isolated in the reaction was identified as 2-chloro-3,7-difluorodibenzo[*b*,*f*]thiepin (*XIIIa*)

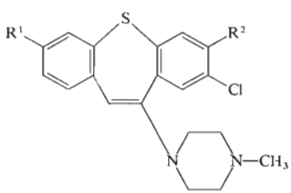


I

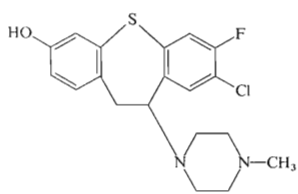


II

a, $R^1 = R^2 = F$
b, $R^1 = OCH_3$, $R^2 = F$
c, $R^1 = R^2 = OCH_3$
d, $R^1 = F$, $R^2 = OCH_3$

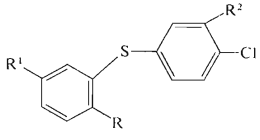


III

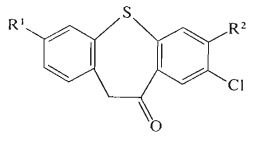


IV

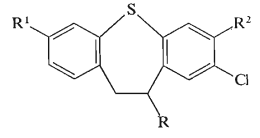
Synthesis of the 3-methoxy-7-fluoro derivative *Ib* proceeded also from 4-chloro--3-fluorothiophenol[24] which was condensed with 2-iodo-4-methoxybenzoic acid[20] in a boiling aqueous solution of potassium hydroxide in the presence of copper. The resulting acid was *Vb* and it was reduced with sodium dihydridobis(2-methoxyethoxy)aluminate in benzene to alcohol *VIb*. Reaction with thionyl chloride in the presence of pyridine gave rise to chloride *VIIb* which was not characterized and was directly converted in a reaction with sodium cyanide in dimethylformamide to nitrile *VIIIb* which was then subjected to alkaline hydrolysis to acid *IXb*. The acid was cyclized in a similar way as in series *a*, yielding a high amount of ketone *Xb*. Reduction to alcohol *XIb* was done with sodium borohydride in aqueous ethanol and the product was converted to chloride *XIIb* by the action of hydrogen chloride in benzene. A substitution reaction with 1-methylpiperazine had a similar course like in series *a*; crystalline base *Ib* was obtained, besides the elimination product, 2-chloro-3-fluoro-7-methoxydibenzo[*b*,*f*]thiepin (*XIIIb*). Treatment of base *Ib* with boron tribromide in dichloromethane resulted in demethylation, the primary product of which was hydrolyzed with hot aqueous–ethanolic solution of sodium hydroxide. The resulting phenolic base *IV* was converted to crystalline maleate. Even after liberation from the salt the base remains amorphous but the ^{1}H-NMR spectrum established its identity.



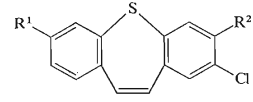
V, R = COOH
VI, R = CH_2OH
VII, R = CH_2Cl
VIII, R = CH_2CN
IX, R = CH_2COOH



X



XI, R = OH
XII, R = Cl



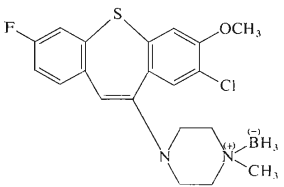
XIII

In series *c* the starting reaction was condensation of 2-iodo-4-methoxybenzoic acid[20] with 4-chloro-3-methoxythiophenol[25] in a boiling solution of potassium hydroxide in the presence of copper; a high yield of acid *Vc* was obtained. If a solution of 2-iodo-4-methoxybenzoic acid in aqueous potassium hydroxide in the presence of copper was left to stand overnight at room temperature, the thiol was added only then and the mixture was heated, the main product obtained was 4-methoxysalicylic acid[26,27]. Like in series *b*, acid *Vc* was converted to intermediates *VIc* to *VIIIc* and then to homologous acid *IXc*. Cyclization under conditions similar to those described before yielded ketone *Xc*. Like in series *a*, chloride *XIIc* was prepared *via* alcohol *XIc* which reacted with 1-methylpiperazine in boiling chloroform to yield 80% of the 3,7-dimethoxy derivative *Ic* besides a small amount of 2-chloro-3,7-dimethoxydibenzo[*b*,*f*]thiepin (*XIIIc*) formed by elimination. Reaction of ketone *Xc* with 1-methylpiperazine and titanium tetrachloride in boiling benzene yielded enamine *IIIc*.

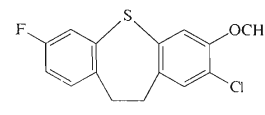
Attempts to demethylate *Ic* with boron tribromide or with the sodium salt of 4-chlorothiophenol in dimethylformamide did not produce identified products. Thiophenolate was found to be a N-dealkylating agent (the $C_{(10)}$—N bond in *Ic* is rather labile) rather than an O-demethylating one[28–31]. The mass spectrum of the product contains a molecular ion at *m/e* 290, corresponding to $C_{15}H_{11}ClO_2S$ (most likely 2-chloro-3-hydroxy-7-methoxydibenzo[*b*,*f*]thiepin) which is apparently a fragment formed by elimination of the 4-chlorophenylthio group by a thermal reaction. An ion of the same composition is found in the mass spectrum of the product of demethylation using boron tribromide but here, too, we are dealing with a fragment. When we took into account the negative result of the attempt to demethylate the 7-methoxy derivative of perathiepin[32], further attempts to prepare the 3,7-dihydroxy derivative of octoclothepin were stopped.

In series *d*, synthesis was started analogously by condensation of 2-bromo-4-fluorophenylacetic acid[23] with 4-chloro-3-methoxythiophenol[25] in dimethylformamide in the presence of potassium hydroxide, potassium carbonate and copper. Acid *IXd* was obtained in a relatively low yield; more important was the fraction of a noncrystallizing compound of acid character which contained substantial amounts of acid *IXd*. To cyclize it to ketone *Xd* with the aid of polyphosphoric acid in the presence of boiling toluene we used both crystalline acid *IXd* and the noncrystalline fractions. The ketone was obtained in both cases, the cyclization proceeding smoothly. The first sample of ketone *Xd* was obtained on shaking the benzene solution of crude acid *IXd* with concentrated sulfuric acid. Reduction of ketone *Xd* to alcohol *XId* and its conversion to chloride *XIId* were carried out in analogy to series *a*. The substitution reaction with 1-methylpiperazine in chloroform produces a fine yield of base *Id* along with the elimination product, 2-chloro-7-fluoro-3-methoxy dibenzo[*b*,*f*]thiepin (*XIIId*). A method similar to that used in series *c* converted ketone *Xd* to enamine *IIId*. The possibilities of reduction of this enamine to dihydrobase *Id* were then investigated. Catalytic hydrogenation on platinum in ethanol does not take place at all even in the presence of an equivalent of hydrogen chloride; cleavage

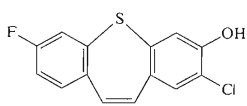
of enamine proceeds slowly, the product being ketone *Xd*. Reaction of enamine *IIId* with diborane (method in ref.[33]) under gentle conditions at 20°C and subsequent decomposition with aqueous sodium hydroxide gave rise to a single homogeneous product which was isolated and identified by analysis and spectra as methylpiperazine borane *XIV*. Hydrolysis with aqueous–ethanolic sodium hydroxide recovers a theoretical yield of pure enamine *IIId*. In a similar reaction of enamine *IIId* with diborane under more stringent conditions (refluxing of the reaction mixture) it is reduced to *Id* in a 25% yield. The by-products obtained were ketone *Xd*, alcohol *XId* and olefin *XIIId*. In an attempt to reduce enamine *IIId* with zinc and boiling acetic acid (method[34]) the molecule was cleaved and a mixture of neutral products was obtained which were separated by chromatography on a column of alumina. The most interesting product was the least polar compound which was identified as 2-chloro--7-fluoro-3-methoxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XV*). Only two compounds



XIV



XV



XVI

of this type are known at present[18,35] and both were obtained by reduction of the corresponding ketones with hydrazine in the Huang-Minlon modification. Another product was olefin *XIIId* from which the dihydro derivative *XV* could not completely be removed. Ketone *Xd* and alcohol *XId* were also eluted from the column. It was attempted to demethylate *Id* with boron tribromide in chloroform at room temperature. Besides unidentified products, the minor products characterized were 1-methylpiperazine (as crystalline dimaleate[36]) and 2-chloro-7-fluoro-3-hydroxydibenzo-[*b*,*f*]thiepin (*XVI*) which is formed by demethylation and simultaneous or sub-

sequent elimination of methylpiperazine. Hence again the instability[32] of the compound with a free hydroxyl in *para*-position with respect to the benzyl α-carbon carrying a piperazine residue was demonstrated. While it was possible to prepare 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin derivatives with a free hydroxyl in positions 2, 3, 6 and 8 (ref.[20,21,32,36–38]) it was not manageable to do so in position 7 (besides the present report, see also[25,32]).

Of the compounds prepared, the difluoro derivative *Ia*, the dimethoxy derivatives *Ic* and *IIIc*, the fluoromethoxy derivative *Id* and fluorophenol *IV* were subjected to an orientative pharmacological evaluation. Using oral application, the acute toxicity was determined in female mice, the incoordinating effect using the rotating-rod test in female mice and the cataleptic effect in female rats. The results are shown in the form of LD_{50} and ED_{50} values in Table I which includes pimozide[22], octoclothepin[17–19], the 3-fluoro derivative of octoclothepin[39] and the 7-fluoro derivative of octoclothepin[24] as standards. The ED_{50} values for ataxia were calculated at the time of maximum effect (the effect was examined at intervals of 15, 30, 45, 60, 90, and 120 min after administration of the compound) and the ED_{50} values for catalepsy were calculated from the optimum values obtained during the experiment (catalepsy was evaluated after 1 h and then in 30 min intervals for 5 h). All the three compounds containing methoxyl in position 7 (*Ic*, *Id*, *IIIc*) are uninteresting from the point

TABLE I

Pharmacological Properties of the Compounds Prepared on Oral Administration (mg/kg)

Compound[a]	Code No	Acute toxicity LD_{50}	Ataxia ED_{50}	Catalepsy ED_{50}
Ia	VÚFB-10·699	84	4·0	3·8
Ic	VÚFB-10·700	[b]	>100	[b]
Id	VÚFB-10·690	250	41	[c]
IIIc	VÚFB-10·701	360	47	>50[d]
IV	VÚFB-12·349	[b]	4·8	20[e]
Pimozide[22]		228[22]	21	1·3
Oct.[f]	VÚFB- 6·281	78	2·2	4·3
3-F-Oct.[g]	VÚFB- 9·470	28·5	0·8	3·8
7-F-Oct.[h]	VÚFB-10·122	>1 000	7·0	5·5

[a] The compounds were administered in the form of salts described in the Experimental; the values reported refer to the bases. [b] Not estimated. [c] The substance is inactive in the dose of 50 mg/kg. [d] The dose shown brings about catalepsy in 10% animals. [e] The dose of 10 mg/kg was cataleptic for 20% animals, the dose of 50 mg/kg for 90% animals. [f] Octoclothepin maleate[17–19]. [g] 3-Fluoro derivative of octoclothepin maleate[39]. [h] 7-Fluoro derivative of octoclothepin maleate[24].

of view of their effects; they are very slightly centrally depressant and they are inactive cataleptically. A high depressant activity was found in fluorophenol *IV* but it is surprisingly ineffective cataleptically. Fluorination of the 3-hydroxy derivative of octoclothepin[20] in position 7 decreases the depressant activity about 6 times, the cataleptic one about 10 times. The only interesting compound is the 3,7-difluoro derivative *Ia* which is about equally toxic as octoclothepin (the toxicity-increasing effect of 3-fluorination and the detoxicating effect of 7-fluorination compensate each other), shows about 50% of the effect of octoclothepin in the rotating-rod test while in the catalepsy test it is about equally effective whereby it matches the 3-fluoro derivative of octoclothepin. As compared with pimozide, in these acute tests *Ia* is about 3 times more toxic, 5 times more effective as depressant and 3 times less effective as cataleptic. Further detailed tests were carried out (using oral application) where the duration of the effects was investigated, using pimozide for comparison[22].

First of all, the antiapomorphine effect in male rats was examined using the test according to Janssen and coworkers[40,41]. Individual oral doses (10, 20, 40, and 80 mg/kg) were administered to ten-animal groups of rats in distilled water. Four h after application and then after 24 and 48 h, apomorphine hydrochloride was applied intravenously in a dose of 1·25 mg/kg and then chewing and agitation were investigated. The dose D_{50} which decreases the mean control value of the two parameters by 50% was determined in the individual time intervals. For *Ia* (all the values refer to the base) the D_{50} values for chewing and agitation are 19·4 and 16·8 mg/kg, respectively. After 24 h, *Ia* will depress apomorphine chewing with statistical significance at doses of 40 and 80 mg/kg, apomorphine agitation in a dose of 80 mg/kg; the effects wane after 48 h. Pimozide (*II*) was applied in a similar way (in a solution of tartaric acid) in doses of 1, 2·5, 5 and 10 mg/kg. In the interval of 4 h, the inhibition of chewing and agitation after all these doses was greater than 50%; the D_{50} for both parameters is thus lower than 1·0 mg/kg. At 24 h after administration, pimozide inhibits apomorphine chewing with statistical significance in all the doses described (D_{50} 4·0 mg/kg); apomorphine agitation is inhibited significantly from 2·5 mg/kg (D_{50} 3·9 mg/kg). The effects wane by 48 h.

The ED_{50} values for *Ia* and for pimozide referring to the catalepsy test in rats[42] are shown in Table I. With *Ia*, there is a cataleptic effect persisting after 24 h following a dose of 25 mg/kg with only 20% animals. On the other hand, with pimozide, one can compute the ED_{50} values even after 24 and 48 h (7·4 and 25 mg/kg). A dose of 25 mg/kg pimozide keeps 20% rats in a cataleptic state even after 72 h.

In connection with more detailed tests in mice, the locomotor activity was followed by the photo-cell method[43]. Changes in locomotor activity were examined at 1, 4, 24 and 48 h following oral administration of the compound. The D_{50} value decreasing the mean locomotor activity by 50% was determined at individual time

intervals. Compound *Ia* is highly effective in this test; 1 h after application, D_{50} was 0·32 mg/kg, 4 h 0·5 mg/kg, after 24 h the depressant effect is statistically significant still at doses of 0·5 and 1·0 mg/kg while after 48 h only in a dose of 2·5 mg/kg. For pimozide D_{50} was 1·6 mg/kg after 1 h, less than 1·0 mg/kg after 4 h while after 24 h it was significant only after a dose of 30 mg/kg. The effect disappears by 48 h.

The mean effective doses at the time of maximum effect (ED_{50}) for ataxia in the rotating-rod test in mice[44] are shown in Table I. To check the possible prolongation of effects, ataxia was also investigated after 24 and 48 h. With *Ia*, an ED_{50} of 10·5 mg/kg may still be found after 24 h; the incoordinating effect disappears by 48 h. Pimozide is little effective in this test and on using higher doses (50 and 100 mg/kg) some animals die on the 2nd and 3rd day which prevents an evaluation of the protracted effect to be made.

For a comparison of *Ia* and pimozide (*II*) the decisive test was that of the antiapomorphine effect in dogs (mongrels, females)[45]. A subcutaneous application of 0·31 mg/kg apomorphine hydrochloride caused vomiting in dogs. To observe the antiapomorphine effect, the two compounds under comparison (*Ia*, *II*) were applied orally in doses of 0·1 and 1·0 mg/kg. The mean frequency of vomiting and the percentage of animals with an emetic response were processed statistically before application and 24, 48 and 96 h after application of the compounds. *Ia* was found to block the emetic response in 50% dogs only in the higher dose of 1·0 mg/kg in a 24 h interval. The effect disappears by 48 h. Pimozide(*II*) is effective even in a lower

TABLE II

Antimicrobial Activity of the Octoclothepin Derivatives *in vitro* (the minimum inhibitory concentrations in μg/ml given)

Microorganism[a]	Compound[b]			
	Ia	*Ic*	*Id*	*IIIc*
Streptococcus faecalis	50	100	50	100
Staphylococcus pyogenes aureus	25	50	25	50
Escherichia coli	100	>100	>100	>100
Mycobacterium tuberculosis H37Rv	6·25	12·5	12·5	>100
Trichophyton mentagrophytes	25	50	25	50
Candida albicans	100	100	100	100
Aspergillus niger	>100	>100	100	>100

[a] In a concentration of 100 mg/ml the compounds were inactive against *Streptococcus* β-*haemolyticus*, *Pseudomonas aeruginosa* and *Proteus vulgaris*. [b] The compounds were tested in the form of salts described in the Experimental part.

dose (0·1 mg/kg; in 75% dogs after 24 h); a higher dose (1·0 mg/kg) inhibits the frequency of vomiting with statistical significance at intervals of 24 (100%) and 48 h (75%) while after 96 h the effect is slight (25%) and then gradually disappears. The emetic response of dogs was fully blocked in all animals (8/8) after 1 mg/kg pimozide 24 h after application. The detailed comparison of *Ia* with pimozide thus shows that *Ia* is more effective in tests of central depressant activity where a prolongation of effects may be seen. On the other hand, pimozide is more active neuroleptically and its effect is more intense in the appropriate tests and is more protracted than that of *Ia*.

Compounds *Ia*, *Ic*, *Id*, and *IIIc* were tested at the bacteriological department of this institute (Dr J. Turinová, Dr A. Čapek) for antimicrobial activity *in vitro* using a standard set of microorganisms. The results are shown in Table II in the form of minimum inhibitory concentrations in μg/ml. The relatively high antituberculotic activity of *Ia* should be mentioned here.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at 0·5 Torr over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded in a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) in a Tesla BC 487 (80 MHz) spectrometer and the mass spectra in a MS 902 (AEI) spectrometer. The homogeneity of compounds was checked by thin-layer chromatography on silica gel (Silufol).

2-(4-Chloro-3-fluorophenylthio)-4-methoxybenzoic Acid (*Vb*)

A solution of 41 g KOH in 460 ml water was combined with, one by one, 32·5 g 4-chloro-3-fluorothiophenol[24], 55·6 g 2-iodo-4-methoxybenzoic acid[20] and 1·0 g "molecular" copper and the mixture was refluxed under stirring for 7 h. On the following day, 2 litres water were added to dissolve the precipitated potassium salt, the mixture was heated to 70°C and filtered with charcoal. The filtrate was acidified with hydrochloric acid, cooled and left to stand until 48 g (77%) product precipitated (m.p. 194—198°C). Its sample was recrystallized for analysis from aqueous ethanol, m.p. 204—206°C. UV spectrum: λ_{max} 256 nm infl. (log ε 4·13), 282 nm infl. (3·86). IR spectrum: 780, 825, 850, 886, 901 (2 adjacent and solitary Ar—H), 923, 1331 (COOH), 1231, 1246 (ArO.CH_3), 1470, 1552, 1577, 1596 (Ar), 1671 (Ar—COOH), 2560, 2670 cm^{-1} (COOH). For $C_{14}H_{10}ClFO_3S$ (312·7) calculated: 53·76% C, 3·22% H, 11·34% Cl, 6·07% F, 10·25% S; found: 53·62% C, 3·21% H, 11·34% Cl, 5·93% F, 10·50% S.

2-(4-Chloro-3-methoxyphenylthio)-4-methoxybenzoic Acid (*Vc*)

Like in the preceding case, 96·4 g 2-iodo-4-methoxybenzoic acid[20] and 65·5 g 4-chloro-3-methoxythiophenol[25] were left to react in a solution of 56 g KOH in 500 ml water in the presence of 5 g copper. The hot mixture obtained was directly filtered, the filtrate was acidified and the precipitated product was recrystallized from a mixture of ethanol and benzene; 94·2 g (88%), m.p. 215 to

216°C. UV spectrum: λ_{max} 237·5 nm (log ε 4·53), 260 nm infl. (4·14), 291 nm (3·95), infl. 310 nm (3·74). IR spectrum: 810, 820, 855 (2 adjacent and solitary Ar—H), 912 (COOH), 1 234 ($ArOCH_3$), 1481, 1550, 1580, 1592 (Ar), 1730 (ArCOOH), 2565 cm^{-1} (COOH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·98 (d, J = 8·0 Hz, 1 H, 6-H), 7·58 (d, J = 8·0 Hz, 1 H, 5′-H), 7·45 and 6·20 (2 mcs, J = 2·5 Hz, 2 H, 3,2′-H_2), 7·15 and 6·80 (2 mcd, J = 8·0; 2·5 Hz, 2 H, 5,6′-H_2), 3·90 and 3·65 (2 s, 6 H, 2 OCH_3). For $C_{15}H_{13}ClO_4S$ (324·8) calculated: 55·47% C, 4·03% H, 10·92% Cl, 9·87% S; found: 55·71% C, 4·06% H, 10·99% Cl, 9·86% S.

In another experiment, 125 g 2-iodo-4-methoxybenzoic acid[20] was dissolved in a solution of 76 g KOH in 700 ml water and then 7 g Cu was added. The mixture was left to stand overnight at room temperature. Then 83·4 g 4-chloro-3-methoxythiophenol[25] was added and the mixture processed as before. After filtration and acidification, the crude acid obtained was recrystallized from a mixture of benzene and acetone. A total of 39·5 g product melting at 160—161°C was obtained and was identified as 4-methoxysalicylic acid which is reported[26,27] to have m.p. of 151·5 and 161°C, respectively. Evaporation of the mother liquor yielded 66 g of an acid mixture; attempts at its resolution by crystallization were not successful.

2-(4-Chloro-3-fluorophenylthio)-4-methoxybenzyl Alcohol (*VIb*)

A suspension of 34 g acid *Vb* in 275 ml benzene was combined under stirring over a period of 30 min with 75 ml 60% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate added dropwise at 30—40°C. The mixture was stirred for 3 h at room temperature, decomposed by adding 300 ml 10% solution of NaOH, shaken and the benzene layer was separated. After washing with water and drying with $MgSO_4$, benzene was evaporated at reduced pressure; 26·4 g (82%) product which was used for further work. A sample for analysis was distilled; b.p. 160 to 170°C/0·5 Torr. IR spectrum (film): 817, 861, 890, 901 (2 adjacent and solitary Ar—H), 1057 (CH_2OH), 1240, 1289 ($ArOCH_3$), 1483, 1571, 1603 (Ar), 2850 (OCH_3), 3380 cm^{-1} (OH). For $C_{14}H_{12}ClFO_2S$ (298·8) calculated: 56·28% C, 4·05% H, 11·87% Cl, 6·36% F, 10·73% S; found: 56·59% C, 4·14% H, 11·61% Cl, 6·29% F, 10·79% S.

2-(4-Chloro-3-methoxyphenylthio)-4-methoxybenzyl Alcohol (*VIc*)

Like in the preceding case, 94·2 g acid *Vc* was reduced with 213 ml 55% benzene solution of sodium dihydridobis(2-methoxyethoxy)aluminate in 600 ml benzene. A total of 91·3 g (98%) product was obtained, a sample of which was redistilled for analysis; b.p. 215°C/1·5 Torr. IR spectrum (film): 800, 869 (2 adjacent and solitary Ar—H), 1028, 1050 (CH_2OH), 1249, 1279 ($ArOCH_3$), 1480, 1570, 1595 (Ar), 3440 cm^{-1} (OH). For $C_{15}H_{15}ClO_3S$ (310·8) calculated: 10·32% S; found: 10·41% S.

2-(4-Chloro-3-fluorophenylthio)-4-methoxyphenylacetic Acid (*IXb*)

A solution of 22·2 g alcohol *VIb* in 7·0 g pyridine was cooled to 10°C and stirred at that temperature for 20 min while 10·2 g $SOCl_2$ was being added. The mixture was left to stand for 1 h at room temperature, diluted with 180 ml benzene and stirred for 2 h at room temperature. On the next day, it was heated for 1 h to 35—40°C, cooled to 10°C and decomposed by slowly adding 50 ml ice-cold water. The benzene layer was separated, washed with 1M-HCl, with cold 5% NaOH, and with water. Then it was dried with $MgSO_4$, filtered with charcoal and evaporated at reduced pressure; 21·8 g (92%) crude chloride *VIIb* which was not further purified but was directly dissolved in 50 ml dimethylformamide, 10·2 g NaCN was added and the mixture was heated to 105—110°C for 8 h under stirring. The volatile fractions were evaporated at reduced pressure,

the residue was diluted with 250 ml benzene, the solution was washed with water, dried with $MgSO_4$, filtered with charcoal and evaporated *in vacuo*; 17·2 g (81%) crude nitrile *VIIIb*. A solution of 15·0 g crude *VIIIb* in 75 ml ethanol was combined with 15 g KOH in 75 ml water and the mixture was refluxed for 12 h. Ethanol was then evaporated at reduced pressure and the turbid solution was washed with ether. After cooling, it was acidified with hydrochloric acid which led to precipitation of 14·3 g (90%) crude acid *IXb* which crystallized from benzene as a solvate with one-half molecule of benzene; m.p. 98—100°C. IR spectrum: 809, 840, 859, 899 (2 adjacent and solitary Ar—H), 942 (COOH), 1 032 and 1 050 ($ArOCH_3$), 1 241 and 1 250 ($ArOCH_3$ and COOH), 1 500, 1 569, 1 600 (Ar), 1 700, 2 560, 2 670, 2 735 cm^{-1} (COOH). ^{1}H-NMR spectrum: δ 11·25 (bs, 1 H, COOH), 7·32 (s, 3 H, 0·5 C_6H_6), 6·60—7·30 (m, 6 H, Ar—H), 3·70 (s, 5 H, $ArCH_2$ and OCH_3). For $C_{15}H_{12}ClFO_3S + 1/2\ C_6H_6$ (365·8) calculated: 59·10% C, 4·13% H, 9·69% Cl, 5·19% F, 8·77% S; found: 58·91% C, 4·12% H, 9·58% Cl, 5·01% F, 8·99% S.

2-(4-Chloro-3-methoxyphenylthio)-4-methoxyphenylacetic Acid (*IXc*)

Like in the preceding case, a reaction of 91 g alcohol *VIc* with 40·5 g $SOCl_2$ in a mixture of 30 ml pyridine and 30 ml chloroform yielded 86 g crude chloride *VIIc* which was subjected to the action of 25 g NaCN in 400 ml dimethylformamide at 90°C and converted to nitrile *VIIIc* (58·5 g, b.p. 230°C/0·8 Torr). Hydrolysis with 50 g KOH in a mixture of 200 ml ethanol and 60 ml water yielded 62 g (62% with respect to starting *VIc*) crude acid *IXc*, m.p. 52—65°C. Crystallization from a mixture of benzene and cyclohexane yielded a solvate with one-half molecule cyclohexane; m.p. 50—65°C, and then again at 114—116°C. IR spectrum: 798, 834, 868 (2 adjacent and solitary Ar—H), 1 483, 1 578 (Ar), 1 240 ($ArOCH_3$), 945, 1 702, 2 670 cm^{-1} (COOH). ^{1}H-NMR spectrum: δ 9·80 (bs, 1 H, COOH), 6·50—7·40 (m, 6 H, Ar—H), 3·80 and 3·75 (2 s, 8 H, $ArCH_2$ and 2 OCH_3), 1·42 (s, CH_2 of cyclohexane). For $C_{16}H_{15}ClO_4S + 1/2\ C_6H_{12}$ (380·9) calculated: 59·91% C, 5·56% H, 9·31% Cl, 8·42% S; found: 60·29% C, 5·24% H, 9·36% Cl, 8·91% S.

2-(4-Chloro-3-methoxyphenylthio)-4-fluorophenylacetic Acid (*IXd*)

A mixture of 240 ml dimethylformamide, 36·2 g 4-chloro-3-methoxythiophenol[25], 39·6 g (2--bromo-4-fluorophenyl)acetic acid[23], 20 g KOH, 10 g K_2CO_3 and 6 g Cu was refluxed under stirring for 15 h in a 170°C bath. After evaporation of the volatile fractions the residue was dissolved in water, the solution was filtered and the filtrate was acidified with hydrochloric acid. The separated oily and nonhomogeneous acid was isolated by extraction with benzene; 34·6 g (besides *IXd*, the product also contains the starting bromofluoro acid). Crystallization from ethanol yielded 13·8 g acid *IXd*, m.p. 115—118°C; analytical sample, m.p. 118—119°C (aqueous ethanol). IR spectrum: 805, 815, 835, 849, 875, 890, 901 (2 adjacent and solitary Ar—H), 932, 1 707, 2 560, 2 660, 2 740 (COOH), 1 245 ($ArOCH_3$), 1 490, 1 580 cm^{-1} (Ar). For $C_{15}H_{12}ClFO_3S$ (326·8) calculated: 55·13%C, 3·70% H, 10·85% Cl, 5·81% F, 9·81% S; found: 55·25% C, 3·71% H, 10·99% Cl, 5·99% F, 9·80% S. Evaporation of the mother liquor yielded further 20·8 g oily nonhomogeneous acid which was also used for cyclization.

8-Chloro-3,7-difluorodibenzo[*b,f*]thiepin-10(11*H*)-one (*Xa*)

A solution of C_2H_5ONa (180 ml ethanol and 8·6 g Na) was combined with 40 g 2-bromo-4-fluorophenylacetic acid[23] and 32·6 g 4-chloro-3-fluorothiophenol[24], the mixture was homogenized, ethanol was removed by distillation (the remainder *in vacuo* on a 150°C bath). The residue was combined with 240 ml dimethylformamide, 10 g K_2CO_3 and 6 g Cu. The mixture was refluxed under stirring for 11 h in a 150°C bath, filtered, dimethylformamide was evaporated *in vacuo*,

the residue was diluted with water, acidified and extracted with benzene. The acid fraction of the benzene extract was transferred to excess 20% NaOH by shaking, the solution of sodium salts was acidified with hydrochloric acid and extracted with benzene. Evaporation of the extract yielded 33·0 g crude acid *IXa* which is contaminated with the starting bromofluoro acid. The entire amount of the product (33·0 g) was dissolved in 300 ml toluene, the solution was added to polyphosphoric acid (from 90 g P_2O_5 and 45 ml 85% H_3PO_4) and the mixture was refluxed under stirring for 16 h. The toluene layer was then separated by decanting, the residue in the flask was washed with further toluene, the combined toluene solutions were washed with 5% NaOH and water, dried with $MgSO_4$ and evaporated. The residue (34 g) is nonhomogeneous and was crystallized from ethanol to yield 9·6 g ketone *Xa*, m.p. 131—133°C (ethanol–benzene). UV spectrum: λ_{max} 243 nm (log ε 4·21), 265 nm (3·97), 324 nm (3·49). IR spectrum: 813, 841, 871 (2 adjacent and solitary Ar—H), 1 229, 1 260 (C—F), 1 490, 1 558, 1 581 (Ar), 1 674 cm^{-1} (Ar—CO). ^{1}H-NMR spectrum: δ 8·20 (d, J = 7·0 Hz, 1 H, 9-H), 6·80—7·50 (m, 4 H, remaining Ar—H), 4·26 (s, 2 H, $ArCH_2CO$). For $C_{14}H_7ClF_2OS$ (296·7) calculated: 56·67% C, 2·38% H, 11·95% Cl, 12·81% F, 10·81% S; found: 56·87% C, 2·41% H, 12·00% Cl, 13·01% F, 10·84% S. Evaporation of the mother liquor yielded 22·1 g oily substance which is a mixture of ketone *Xa* and another compound with a similar R_F; the mixture could not be separated by chromatography on a column of 500 g alumina (activity II).

8-Chloro-7-fluoro-3-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Xb*)

This was obtained like in the preceding case by cyclization of 14·0 g acid *IXb* with the aid of 140 g polyphosphoric acid (the stock acid was prepared from 500 ml 85% H_3PO_4 and 800 g P_2O_5) in the presence of 65 ml boiling toluene using a reaction period of 5 h. Processing of the toluene phase resulted in 9·7 g (73%) product melting at 175—178°C; analytical sample, m.p. 179—182°C (ethanol). UV spectrum: λ_{max} 236 nm (log ε 4·41), infl. 260 nm (4·10), infl.289 nm (3·66), 327 nm (3·52). IR spectrum (KBr): 797, 820, 863, 909 (2 adjacent and solitary Ar—H), 1 029, 1 046, 1 228 1 298 ($ArOCH_3$), 1 547, 1 584, 1 598 (Ar), 1 673 cm^{-1} (Ar—CO). For $C_{15}H_{10}ClFO_2S$ (308·8) calculated: 58·35% C, 3·26% H, 11·48% Cl, 6·15% F, 10·39% S; found: 58·31% C, 3·43% H, 11·72% Cl, 6·10% F, 10·32% S.

8-Chloro-3,7-dimethoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Xc*)

Like in the preceding cases, 60·8 g acid *IXc* was cyclized with polyphosphoric acid (90 ml 85% H_3PO_4 and 180 g P_2O_5) in the presence of 600 ml boiling toluene for 8 h. A total of 40·8 g (71%) product was obtained: *Xc*, m.p. 183—184°C. Analytical sample melts at 177—178°C when a change of crystal modification takes place and the substance melts finally at 186·5—187·5°C (benzene–ethanol). UV spectrum: λ_{max} 236 nm (log ε 4·38), 261 nm (4·43), infl. 285 nm (4·10), 325 nm (3·58). IR spectrum: 798, 828, 850, 860 (2 adjacent and solitary Ar—H), 1 250, 1 264 ($ArOCH_3$), 1 490, 1 579, 1 596 (Ar), 1 665 (Ar—CO), 2 845 cm^{-1} (OCH_3). ^{1}H-NMR δ 8·20 (s, 1 H, 9-H), 7·30 (d, J = 8·0 Hz, 1 H, 1-H), 7·15 (mcs, J = 2·0 Hz, 1 H, 4-H), 7·06 (s, 1 H, 6-H), 6·88 (mcd, J = 8·0; 2·0 Hz, 1 H, 2-H), 4·25 (s, 2 H, $ArCH_2CO$) 3·97 and 3·78 (2 s, 6 H, 2 OCH_3). For $C_{16}H_{13}ClO_3S$ (320·8) calculated: 59·91% C, 4·08% H, 11·06% Cl, 10·00% S; found: 60·03% C, 4·07% H, 11·42% Cl, 9·95% S.

8-Chloro-3-fluoro-7-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Xd*)

A. Like in the preceding cases, 13·8 g pure acid *IXd* in 200 ml boiling toluene was cyclized by exposure to polyphosphoric acid (25 ml 85% H_3PO_4 and 50 g P_2O_5) for 14 h. The yield was

11·4 g (88%) product *Xd*, m.p. 195—197°C (benzene–ethanol). UV spectrum: λ_{max} 228 nm (log ε 4·27), 258·5 nm (4·40), 322 nm (3·56). IR spectrum: 837, 851, 880 (2 adjacent and solitary Ar—H), 1268 ($ArOCH_3$), 1484, 1580 (Ar), 1661 (Ar—CO), 3040, 3065 cm^{-1} (Ar). For $C_{15}H_{10}ClFO_2S$ (308·8) calculated: 58·35% C, 3·26% H, 11·48% Cl, 6·15% F, 10·39% S; found: 58·67% C, 3·28% H, 11·44% Cl, 6·63% F, 10·20% S.

B. Analogous cyclization of 20·8 g oily acid obtained from the mother liquors after crystalline acid *IXd* yielded 8·5 g ketone *Xd*, m.p. 192—195°C (benzene–ethanol).

C. On shaking the benzene solution of acid *IXd* with sulfuric acid part of the substance passed to sulfuric acid wherefrom it was liberated by dilution with water. The substance is again ketone *Xd* which crystallizes from a mixture of benzene and ethanol and melts at 195—197°C.

8-Chloro-3,7-difluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIa*)

A solution of 7·9 g ketone *Xa* in 100 ml dioxane was combined with a solution of 1·0 g $NaBH_4$ in 3 ml water with two drops 20% NaOH added dropwise. The mixture was refluxed for 5·5 h, dioxane was evaporated, the residue was diluted with water and the product was isolated by extraction with benzene. Evaporation of the extract yielded a crude product which was recrystallized from a mixture of cyclohexane and ether; 6·0 g (76%), m.p. 84—86°C. IR spectrum: 822 881 (2 adjacent and solitary Ar—H), 1059 (CHOH in a ring), 1211, 1250 (C—F), 1492, 1574, 1593, 1601 (Ar), 3170, 3250 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·54 (d, J = 8·0 Hz, 1 H, 9-H), 6·80—7·40 (m, 4 H, remaining Ar—H), 5·20 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·75 and 3·28 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·12 (s, disappears after D_2O, 1 H, OH). For $C_{14}H_9ClF_2OS$ (298·7) calculated: 56·29% C, 3·04% H, 11·87% Cl, 12·72% F, 10·73% S; found: 56·45% C, 3·23% H, 11·96% Cl, 12·72% F, 10·79% S.

8-Chloro-7-fluoro-3-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIb*)

In analogy with the preceding case, 10·0 g ketone *Xb* was reduced with 0·45 g $NaBH_4$ in 160 ml ethanol and 4·5 ml water. Processing yielded 9·3 g (92%) crude product melting at 116—119°C; analytical sample, m.p. 124—127°C (cyclohexane). IR spectrum (KBr): 795, 868, 889 (2 adjacent and solitary Ar—H), 1029, 1047, 1233, 1245, 1273 ($ArOCH_3$), 1475, 1490, 1570, 1597 (Ar), 1029, 1047 (CHOH in a ring), 3360 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·58 (d, J_{H-F} = 8·0 Hz, 1 H, 9-H), 7·48 (d, J_{H-F} = 9·0 Hz, 1 H, 6-H), 7·10 (d, J = 8·0 Hz, 1 H, 1-H), 6·90 (mcs, J = 3·0 Hz, 1 H, 4-H), 6·75 (mcd, J = 8·0; 3·0 Hz, 1 H, 2-H), 5·82 (d, J = 5·0 Hz, 1 H, OH), 5·12 (m, 1 H, Ar—CH—O), 3·69 (s, 3 H, OCH_3), 3·20 (m, 2 H, $ArCH_2$). For $C_{15}H_{12}ClFO_2S$ (310·8) calculated: 57·97% C, 3·89% H, 11·41% Cl, 6·11% F, 10·32% S; found: 58·54% C, 3·82% H, 11·34% Cl, 5·63% F, 10·09% S.

8-Chloro-3,7-dimethoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIc*)

In analogy with the preparation of *XIa*, 22·5 g ketone *Xc* was reduced to obtain 22·6 g (100%) crude product which was once crystallized from benzene and light petroleum to analytical purity; m.p. 105—107°C. IR spectrum: 805, 850, 870, 890 (2 adjacent and solitary Ar—H), 1042 (CHOH in a ring), 1250 ($ArOCH_3$), 1492, 1588, 1598 (Ar), 3370 cm^{-1} (OH). For $C_{16}H_{15}ClO_3S$ (322·8) calculated: 10·98% Cl, 9·93% S; found: 10·74% Cl, 9·52% S.

8-Chloro-3-fluoro-7-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XId*)

In analogy to the preparation of *XIa* and *XIc*, 5·6 g ketone *Xd* was reduced with the difference that the reaction mixture was stirred for 6 h at room temperature, yielding 5·45 g (98%) crude product; m.p. 140—142°C. Crystallization from benzene yielded a pure pruduct, m.p. 143—145°C. IR spectrum: (KBr): 802, 872 (2 adjacent and solitary Ar—H), 1042 (CHOH), 1258 ($ArOCH_3$), 1486, 1590 (Ar), 3330 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 7·45 (s, 1 H, 9-H), 6·80—7·30 (m, 3 H, 1,2,4-H_3), 6·90 (s, 1 H, 6-H), 5·10 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·82 (s, 3 H, OCH_3), 3·62 and 3·23 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·10 (bs, 1 H, OH). For $C_{15}H_{12}ClFO_2S$ (310·8) calculated: 57·97% C, 3·89% H, 11·41% Cl, 6·11% F, 10·32% S; found: 57·86% C, 3·91% H, 11·54% Cl, 6·29% F, 10·34% S.

8,10-Dichloro-3,7-difluoro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIa*)

Powdered $CaCl_2$ (5·0 g) was added to a solution of 7·6 g *XIa* in 100 ml dichloromethane and the mixture was saturated for 2 h with hydrogen chloride. After standing overnight, it was filtered and evaporated; 8·0 g (almost 100%), m.p. 116—118°C; analytical sample, m.p. 118·5—119·5°C (cyclohexane). ^{1}H-NMR spectrum: δ 7·52 (d, J = 8·0 Hz, 1 H, 9-H), 6·80—7·40 (m, 4 H, remaining Ar—H), 5·60 (dd, J = 4·0; 8·0 Hz, 1 H, Ar—CH—Cl), 3·92 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_8Cl_2F_2S$ (317·2) calculated: 53·01% C, 2·54%H, 22·36% Cl, 11·98% F, 10·11% S; found: 53·33% C, 2·72% H, 22·12% Cl, 12·09% F, 10·23% S.

8,10-Dichloro-7-fluoro-3-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIb*)

The preparation was done using 7·0 g alcohol *XIb* like in the preceding case but in 60 ml benzene as a medium. In view of the fact that the product already crystallized during the reaction, the mixture had to be diluted with further 60 ml benzene and warmed before filtration to remove the $CaCl_2$. A total of 7·3 g (99%) product was obtained; m.p. 136—139°C. On recrystallization from benzene the m.p. stabilized at 139—142°C but further crystallization caused it to rise suddenly to 152—154°C. We are apparently dealing here with two crystal modifications; the higher-melting one was analyzed. For $C_{15}H_{11}Cl_2FOS$ (329·2) calculated: 54·72% C, 3·37% H, 21·54% Cl, 5·77% F, 9·74% S; found: 55·17% C, 3·42% H, 21·60% Cl, 5·63% F, 9·73% S.

8,10-Dichloro-3,7-dimethoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIc*)

This was prepared like *XIIa* from 22·5 g alcohol *XIc* but without adding $CaCl_2$. The yield was 23·4 g (98%) product melting at 151—153°C. On crystallization from dichloromethane the m.p. did not change. ^{1}H-NMR spectrum: δ 7·48 (s, 1 H, 9-H), 7·20 (d, J = 8·0 Hz, 1 H, 1-H), 7·08 (mcs, J = 2·5 Hz, 1 H, 4-H), 6·90 (s, 1 H, 6-H), 6·80 (mcd, J = 8·0; 2·5 Hz, 1 H, 2-H), 5·60 (dd, J = 8·0; 4·0Hz, 1 H, Ar—CH—Cl), 3·88 and 3·76 (2 s, 8·H, $ArCH_2$ and 2 OCH_3). For $C_{16}H_{14}Cl_2O_2S$ (341·3) calculated: 56·31% C, 4·14% H, 20·78% Cl, 9·39% S; found: 56·42% C, 4·19% H, 20·26% Cl, 9·30% S.

8,10-Dichloro-3-fluoro-7-methoxy-10,11-dihydrodibenzo [*b,f*]thiepin (*XIId*)

In analogy to the preceding case, 5·6 g alcohol *XId* yielded 5·8 g (100%) compound melting at 162—163°C (dichloromethane). ^{1}H-NMR spectrum: δ 7·48 (s, 1 H, 9-H), 6·80—7·40 (m, 3 H, 1,2,4-H_3), 6·90 (s, 1 H, 6-H), 5·60 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·90 and 3·60 (2 dd,

$J = 14{\cdot}0$; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 3·90 (s, 3 H, OCH_3). For $C_{15}H_{11}Cl_2FOS$ (329·2) calculated: 54·71% C, 3·37% H, 21·54% Cl, 5·77% F, 9·74% S; found: 54·76% C, 3·42% H, 21·33 Cl, 6·00% F, 9·95% S.

8-Chloro-3,7-dimethoxy-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*IIIc*)

A solution of 3·2 g $TiCl_4$ in 10 ml benzene was added dropwise to a solution of 9·63 g ketone *Xc* and 20 ml 1-methylpiperazine in 80 ml benzene and the mixture was refluxed for 21 h, then it was cooled, decomposed with water, the precipitate was filtered and washed with benzene. The benzene layer was separated from the filtrate, dried with K_2CO_3 and shaken with a solution of 2·9 g maleic acid in 200 ml water. The precipitated crude maleate was filtered, suspended in the aqueous layer of the filtrate, the suspension was made alkaline with NH_4OH and base *IIIc* was isolated by extraction with benzene; 6·5 g (54%), m.p. 188—190°C (ethanol–benzene). UV spectrum: λ_{max} 245 nm (log ε 4·43), 272 nm (4·25), infl. 315 nm (3·86). IR spectrum: 821, 871, 894 (2 adjacent and solitary Ar—H), 1 249 ($ArOCH_3$), 1 489, 1 582, 1 609 (Ar), 2 795 cm^{-1} (N—CH_3). ^{1}H-NMR spectrum: δ 7·65 (s, 1 H, 9-H), 7·15 (d, $J = 8{\cdot}0$ Hz, 1 H, 1-H), 7·09 (s, 1 H, 6-H), 7·02 (mcs, $J = 2{\cdot}0$ Hz, 1 H, 4-H), 6·79 (mcd, $J = 8{\cdot}0$; 2·0 Hz, 1 H, 2-H), 6·25 (s, 1 H, Ar—CH═), 3·90 and 3·78 (2 s, 6 H, 2 OCH_3), 2·99 (def. t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·58 (def. t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·33 (s, 3 H, NCH_3). For $C_{21}H_{23}ClN_2O_2S$ (403·0) calculated: 62·60% C, 5·75% H, 8·80% Cl, 6·95% N, 7·96% S; found: 62·85% S, 5·81% H, 8·89% Cl, 6·62% N, 8·08% S.

Maleate, m.p. 220—221°C (ethanol). For $C_{25}H_{27}ClN_2O_6S$ (519·1) calculated: 57·85% C, 5·24% H, 6·83% Cl, 5·40% N, 6·18% S; found: 57·64% C, 5·19% H, 7·09% Cl, 5·40% N, 6·33% S.

8-Chloro-3-fluoro-7-methoxy-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*IIId*)

Like in the preceding case, a reaction of 20·3 g ketone *Xd* with 40 ml 1-methylpiperazine and 8·0 g $TiCl_4$ in 180 ml benzene yielded 19·3 g crude enamine *IIId* which is contaminated with the starting ketone (thin-layer chromatography). Crystallization from ethanol yielded a base melting at 167 to 168°C. UV spectrum: λ_{max} 250 nm (log ε 4·35), 271·5 nm (4·22), infl. 315 nm (3·83). IR spectrum: 834, 878, 892 (2 adjacent and solitary Ar—H), 1 225, 1 230, 1 260 ($ArOCH_3$), 1 488, 1 595 (Ar), 2 765, 2 790 cm^{-1} (NCH_3). ^{1}H-NMR spectrum: δ 7·62 (s, 1 H, 9-H), 7·10 (s, 1 H, 6-H), 6·80—7·40 (m, 3 H, remaining Ar—H), 6·15 (s, 1 H, Ar—CH═), 3·90 (s, 3 H, OCH_3), 3·01 and 2·58 (2 def. t, 8 H, 4 NCH_2 of piperazine), 2·38 (s, 3 H, NCH_3). For $C_{20}H_{20}ClFN_2OS$ (390·9) calculated: 61·45% C, 5·16% H, 9·07% Cl, 4·86% F, 7·17% N, 8·20% S; found: 61·55% C, 5·22% H, 9·14% Cl, 5·05% F, 7·22% N, 8·32% S.

Maleate, m.p. 204—206°C under decomposition (ethanol). For $C_{24}H_{24}ClFN_2O_5S$ (507·0) calculated: 56·85% C, 4·77% H, 6·99% Cl, 3·75% F, 5·53% N; found: 56·26% C, 4·72% H, 7·16% Cl, 4·08% F, 5·88% N.

4-(8-Chloro-3-fluoro-7-methoxydibenzo[*b,f*]thiepin-10-yl)-1-methylpiperazine Borane (*XIV*)

Sodium borohydride (4·54 g) was added to a solution of 15·64 g enamine *IIId* in 80 ml tetrahydrofuran and this was followed, in an atmosphere of nitrogen at 10—20°C, by a dropwise addition under stirring of 7·0 g acetic acid containing 2% acetic anhydride in 20 ml tetrahydrofuran (2 h). The mixture was stirred for 5 h at room temperature, left to stand overnight, then briefly refluxed in a 60°C bath and, after cooling, decomposed with 60 ml 10% NaOH. The insoluble solid was filtered and crystallized from a mixture of benzene and ethanol and then from benzene to yield

1·8 g amine-borane *XIV* melting at 195·5—197°C. Processing of the mother liquors yielded further 13·9 g, the total yield thus being 15·7 g (97%). UV spectrum λ_{max} 249 nm (log ε 4·32), 271 nm (4·21), infl. 315 nm (3·79). IR spectrum: 829, 850, 859, 901 (2 adjacent and solitary Ar—H), 1225, 1240, 1251 ($ArOCH_3$), 1488, 1588, 1612 (Ar), 2280, 2320, 2385 cm^{-1} (NH^+, B—H). ^{1}H-NMR spectrum: δ 7·52 (s, 1 H, 9-H), 6·70—7·30 (m, 3 H, 1,2,4-H_3), 7·09 (s, 1 H, 6-H), 6·26 (s, 1 H, Ar—CH=), 3·89 (s, 3 H, OCH_3), 2·50—3·40 (m, 8 H, 4 NCH_2 of piperazine), 2·70 (s, 3 H, NCH_3). For $C_{20}H_{23}BClFN_2OS$ (404·8) calculated: 59·35% C, 5·73% H, 8·76% Cl, 4·69% F, 6·92% N, 7·92% S; found: 58·88% C, 5·69% H, 8·86% Cl, 4·10% F, 6·64% N, 8·09% S.

A mixture of 5·8 g *XIV*, 100 ml ethanol and 10 ml 20% NaOH was refluxed for 8·5 h, ethanol was evaporated, the residue was diluted with water and the product was extracted with benzene; 5·56 g (nearly 100%) enamine *IIId*, m.p. 164·5—166°C; after recrystallization from ethanol m.p. 167—168°C.

8-Chloro-3,7-difluoro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ia*)

A mixture of 7·5 g chloride *XIIa*, 15 ml 1-methylpiperazine and 15 ml chloroform was refluxed for 8 h. After cooling, it was diluted with benzene and washed with water. The organic layer was shaken with excess 10% sulfuric acid. The precipitated hydrochloride was filtered, suspended in the acid aqueous layer of the filtrate and the suspension was made alkaline with NH_4OH. The base was isolated by extraction with benzene; 7·6 g (84%); it crystallizes from aqueous ethanol, m.p. 82—84°C. ^{1}H-NMR spectrum: δ 7·70 (d, J = 7·0 Hz, 1 H, 9-H), 6·70—7·30 (m, 4 H, remaining Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 and 2·40 (2 def. t, 8 H, 4 NCH_2 of piperazine), 2·20 (s, 3 H, NCH_3). For $C_{19}H_{19}ClF_2N_2S$ (380·9) calculated: 59·91% C, 5·03% H, 7·35% N; found: 59·33% C, 5·27% H, 7·29% N.

Dimethanesulfonate crystallizes as monohydrate from aqueous ethanol after addition of ether; m.p. 149—152°C. For $C_{21}H_{29}ClF_2N_2O_7S_3$ (591·1) calculated: 42·65% C, 4·95% H, 6·00% Cl, 6·43% F, 4·74% N, 16·27% S; found: 42·91% C, 4·80% H, 6·23% Cl, 6·64% F, 5·06% N, 16·20% S.

Evaporation of the original benzene solution, from which the basic product was extracted by shaking with hydrochloric acid, yielded 1·4 g of a neutral substance which was recrystallized from ethanol to melt at 126—128°C. It is 2-chloro-3,7-difluorodibenzo[*b,f*]thiepin (*XIIIa*). UV spectrum (saturated solution in CH_3OH): λ_{max} 321·5 nm. ^{1}H-NMR spectrum: δ 6·90—7·40 (m, 5 H, Ar—H), 7·00 and 6·83 (ABq, J = 12·0 Hz, 2 H, CH=CH). For $C_{14}H_7ClF_2S$ (280·7) calculated: 59·89% C, 2·51% H, 12·63% Cl, 13·54% F, 11·42% S; found: 60·03% C, 2·53% H, 12·80% Cl, 13·79% F, 11·70% S.

8-Chloro-7-fluoro-3-methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ib*)

Like in the preceding case, a reaction of 7·0 g chloride *XIIb* with 6·4 g 1-methylpiperazine in 18 ml boiling chloroform yielded 5·3 g (63%) crude base which was crystallized from benzene, m.p. 139—141°C. ^{1}H-NMR spectrum: δ 6·50—7·80 (m, 5 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·85 (s, 3 H, OCH_3), 2·68 and 2·45 (2 def. t, 8 H, 4 NCH_2 of piperazine), 2·28 (s, 3 H, NCH_3). For $C_{20}H_{22}ClFN_2OS$ (392·9) calculated: 61·13% C, 5·64% H, 9·02% Cl, 4·84% F, 7·13% N, 8·16% S; found: 61·51% C, 5·70% H, 9·00% Cl, 4·59% F, 7·33% N, 8·40% S.

Like in the preceding case, 1·4 g of 2-chloro-3-fluoro-7-methoxydibenzo[*b,f*]thiepin (*XIIIb*) was isolated; m.p. 143—146°C (cyclohexane). UV spectrum: λ_{max} 271·5 nm (log ε 4·43), infl. 301 nm (3·67), 334 nm (3·44). IR spectrum (KBr): 817, 829, 862, 892 (2 adjacent and solitary Ar—H), 1052, 1227, 1252, 1274, 1294 ($ArOCH_3$), 1478, 1493, 1504, 1596, 3015 cm^{-1} (Ar).

^{1}H-NMR spectrum: δ 6·50—7·30 (m, 7 H, Ar—H and CH=CH), 3·72 (s, 3 H, OCH_3). For $C_{15}H_{10}ClFOS$ (292·7) calculated: 61·54% C, 3·44% H, 12·11% Cl, 6·49% F, 10·95% S; found: 61·60% C, 3·65% H, 12·22% Cl, 6·18% F, 11·00% S.

8-Chloro-3,7-dimethoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Ic*)

Like in the preceding cases, a reaction of 23·0 g chloride *XIIc* with 50 ml 1-methylpiperazine in 50 ml chloroform yielded 21·8 g (80%) base melting at 147—149°C; analytical sample, m.p. 149—150°C (ethanol). IR spectrum: 815, 845, 890 (2 adjacent and solitary Ar—H), 1253 ($ArOCH_3$), 1492, 1588, 1600 (Ar), 2745, 2755 cm^{-1} ($N—CH_3$). ^{1}H-NMR spectrum: δ 7·69 (s, 1 H, 9-H), 7·20 (d, J = 8·0 Hz, 1 H, 1-H), 7·09 (mcs, J = 2·5 Hz, 1 H, 4-H), 6·93 (s, 1 H, 6-H), 6·78 (mcd, J = 8·0; 2·5 Hz, 1 H, 2-H), 3·89 and 3·75 (2 s, 6 H, 2 OCH_3), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·63 and 2·48 (2 def. t, 8 H, 4 NCH_2 of piperazine), 2·30 (s, 3 H, NCH_3). For $C_{21}H_{25}ClN_2O_2S$ (405·0) calculated: 62·28% C, 6·22% H, 8·76% Cl, 6·92% N, 7·92% S; found: 62·55% C, 6·26% H, 9·16% Cl, 6·78% N, 8·06% S.

Di(hydrogen maleate), m.p. 95—100°C and again at 120—122°C (ethanol–ether). For $C_{29}H_{33}ClN_2O_{10}S$ (637·1) calculated: 54·67% C, 5·22% H, 5·57% Cl, 4·40% N, 5·03% S; found: 54·81% C, 5·44% H, 5·56% Cl, 4·43% N, 5·13% S.

Like in the preceding cases, 3·0 g 2-chloro-3,7-dimethoxydibenzo[*b,f*]thiepin (*XIIIc*) was isolated; m.p. 138—139°C (ethanol). UV spectrum: λ_{max} 235 nm infl. (log ε 4·43), 272 nm (4·53), infl. 307·5 nm (3·69), infl. 337 nm (3·55). ^{1}H-NMR spectrum: δ 7·17 (s, 1 H, 1-H), 7·13 (d, J = = 8·0 Hz, 1 H, 9-H), 7·03 (s, 1 H, 4-H), 7·00 (mcs, J = 2·5 Hz, 1 H, 6-H), 6·81 (mcd, J = 8·0; 2·5 Hz, 1 H, 8-H), 6·94 and 6·71 (ABq, J = 12·0 Hz, 2 H, CH=CH), 3·90 and 3·80 (2 s, 6 H, 2 OCH_3). For $C_{16}H_{13}ClO_2S$ (304·8) calculated: 63·05% C, 4·30% H, 11·63% Cl, 10·52% S; found: 63·06% C, 4·38% H, 11·53% Cl, 10·39% S.

8-Chloro-3-fluoro-7-methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Id*)

A. Like in the preceding cases, a reaction of 5·7 g chloride *XIId* with 15 ml 1-methylpiperazine in 15 ml boiling chloroform yielded 5·0 g (74%) base which crystallizes from cyclohexane as a solvate with 1/3 cyclohexane molecule and which melts at 135—136°C. ^{1}H-NMR spectrum: δ 7·67 (s, 1 H, 9-H), 7·00—7·40 (m, 3 H, 1,2,4-H_3), 6·90 (s, 1 H, 6-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·88 (s, 3 H, OCH_3), 2·68 and 2·48 (2 def. t, 8 H, 4 NCH_2 of piperazine), 2·30 (s, 3 H, NCH_3). For $C_{20}H_{22}ClFN_2OS + 1/3\ C_6H_{12}$ (421·0) calculated: 62·77% C, 6·23% H, 8·42% Cl, 6·65% N, 7·62% S; found: 62·98% C, 6·48% H, 8·51% Cl, 6·37% N, 7·72% S.

Di(hydrogen maleate), m.p. 167—169°C (ethanol–ether). IR spectrum: (KBr): 809, 861 (2 adjacent and solitary, Ar—H), 1189 ($ArOCH_3$), 1210, 1250 (COOH, $ArOCH_3$), 1486 (Ar), 1582, 1619 (COO^- and Ar), 1692 (C=C—COOH), 2450 cm^{-1} (NH^+). For $C_{28}H_{30}ClFN_2O_9S$ (625·1) calculated: 53·80% C, 4·84% H, 5·67% Cl, 3·04% F, 4·48% N, 5·13% S; found: 53·88% C, 5·10% H, 5·84% Cl, 3·03% F, 4·46% N, 5·25% S.

Like in the preceding cases, 0·6 g 2-chloro-7-fluoro-3-methoxydibenzo[*b,f*]thiepin (*XIIId*) was isolated, m.p. 164—165°C (ethanol). UV spectrum: λ_{max} 231·5 nm(inflexion) (log ε 4·40), 272·5 nm (4·45), infl. 315 nm (3·52). IR spectrum (KBr): 819, 869, 886 (2 adjacent and solitary Ar—H), 1042, 1253 ($ArOCH_3$), 1488, 1589 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·18 (s, 1 H, 1-H), 7·00 (s, 1 H, 4-H), 6·90—7·30 (m, 3 H, 6,8,9-H_3), 6·85 (s, 2 H, CH=CH), 3·88 (s, 3 H, OCH_3). For $C_{15}H_{10}ClFOS$ (292·8) calculated: 61·54% C, 3·44% H, 12·11% Cl, 6·49% F, 10·95% S; found: 61·87% C, 3·62% H, 11·95% Cl, 6·78% F, 10·88% S.

B. Sodium borohydride (3·2 g) was added to a solution of 10·7 g enamine *IIId* in 50 ml tetrahydrofuran, the solution was then stirred without cooling in nitrogen atmosphere while 18 ml acetic acid containing 3% acetic anhydride was added dropwise over a period of 1·5 h (25—40°C). The mixture was stirred for 30 min without heating, then refluxed for 4·5 h and, after standing overnight, diluted with ether and decomposed with 50 ml 10% NaOH. The organic layer was washed with water and shaken with 10% hydrochloric acid. The precipitated hydrochloride was filtered, suspended in the acid aqueous phase of the filtrate, the suspension was made alkaline with NH_4OH and extracted with benzene. Processing of the extract yielded 6·7 g nonhomogeneous product which crystallized from a mixture of ethanol and benzene to yield 3·0 g substance melting at 183—185°C which was analyzed and run on TLC and identified as ketone *Xd* (m.p. of pure compound 195—197°C). The mother liquor was neutralized with 3·0 g maleic acid in a mixture of ethanol and ether to yield 4·2 g (25%) di(hydrogen maleate) of base *Id*, m.p. 165—168°C. The base released from this salt crystallized from cyclohexane as the above mentioned solvate and melted at 135—136°C. The ether layer from which bases had been removed by shaking with hydrochloric acid, was evaporated and crystallized from a mixture of ethanol and benzene to yield further 0·8 g ketone *Xd*, m.p. 189—193°C. The residue of the mother liquors was chromatographed on a column of Al_2O_3 (activity II). Elution with a mixture of benzene and light petroleum led to a small quantity of olefin *XIIId* (m.p. 164—165°C) and of alcohol *XId*, m.p. 141—143°C(benzene).

2-Chloro-7-fluoro-3-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XV*)

Acetic anhydride (2 ml) was added to a boiling solution of 5·0 g maleate of enamine *IIId* in 100 ml acetic acid which was followed over a period of 30 min with 12·5 g Zn. The mixture was refluxed for 3·5 h, filtered and evaporated *in vacuo*. The residue was made alkaline with NH_4OH and extracted with benzene. The extract was washed with 5% hydrochloric acid (no base was obtained by alkalification of the acid solution) and with water, dried and evaporated. A total of 2·9 g oily mixture of neutral compounds was obtained and chromatographed on a column of 100 g alumina (activity II). Elution with a mixture of benzene and light petroleum yielded 0·30 g of the least polar substance which crystallized from ethanol to melt at 91—92°C. It was identified by analyses and spectra as *XV*. UV spectrum: λ_{max} 230 nm infl. (log ε 4·24), 253 nm (3·80), 280·5 nm (3·98). IR spectrum: 800, 853, 869 (2 adjacent and solitary Ar—H), 1036, 1250, 1267 ($ArOCH_3$), 1484, 1590 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·10 (s, 1 H, 1-H), 6·98 (s, 1 H, 4-H), 6·70—7·20 (m, 3 H, 6,8,9-H_3), 4·82 (s, 3 H, OCH_3), 3·15 (s, 4 H, CH_2CH_2). For $C_{15}H_{12}ClFOS$ (294·8) calculated: 61·12% C, 4·10% H, 12·03% Cl, 6·45% F, 10·88% S; found: 61·48% C, 4·26% H, 12·34% Cl, 6·98% F, 11·28% S.

On continuing with the chromatography, 0·70 g substance was eluted which after recrystallization, from cyclohexane, melted at 150—154°C. The analysis is in agreement with the theoretical assumption of $C_{15}H_{10}ClFOS$, *i.e.* of *XIIId* which, however, in the pure state will melt some 10°C higher. According to the NMR spectrum it is *XIIId* containing about 25% dihydro derivative *XV*. Further substance to be washed out was 0·25 g ketone *Xd*, m.p. 193—195°C (ethanol) and finally 0·20 g alcohol *XId*, m.p. 141—143°C (benzene).

8-Chloro-7-fluoro-3-hydroxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*IV*)

A solution of 8·0 g BBr_3 in 10 ml dichloromethane was added dropwise under stirring and cooling to a solution of 3·93 g base *Ib* in 20 ml dichloromethane. The mixture was stirred for 7 h at room temperature, left to stand overnight, then 25 ml of a 20% solution of Na_2CO_3 was added dropwise and stirring continued for 3 h. After separation the dichloromethane layer was combined with the solid precipitated on the walls of the reaction vessel and dichloromethane was evaporated.

The residue was dissolved in ethanol, 5 ml 20% NaOH was added and the mixture was refluxed for 4 h. Ethanol was then evaporated in vacuo, the residue was dissolved in water and the crude product was precipitated by neutralization with acetic acid. This was filtered, dissolved in benzene and the solution was shaken with excess 10% hydrochloric acid. The precipitated hydrochloride was added to the acid aqueous layer of the filtrate and the mixture was neutralized with 20% K_2CO_3. The amorphous base (0·9 g) was precipitated and could not be recrystallized. It was dissolved in ethanol and the solution was neutralized with 0·7 g maleic acid; after adding ether, 0·8 g maleate separated which was recrystallized from ethanol–ether to melt at 214—216°C. For $C_{23}H_{24}ClFN_2O_5S$ (495·0) calculated: 55·81% C, 4·89% H, 7·16% Cl, 3·84% F, 5·66% N, 6·48% S; found: 55·90% C, 5·25% H, 7·35% Cl, 3·63% F, 5·76% N, 6·72% S.

Decomposition of a sample of the maleate with 5% $NaHCO_3$ released the amorphous phenolic base; after softening at 120—125°C it melts under decomposition at 220—225°C. It was used for obtaining the ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·62 (d, J_{H-F} = 8·0 Hz, 1 H, 9-H), 7·20 (d, J_{H-F} = 10·0 Hz, 1 H, 6-H), 7·00 (d, J = 8·0 Hz, 1 H, 1-H), 6·75 (mcs, J = 2·0 Hz, 1 H, 4-H), 6·55 (mcd, J = 8·0; 2·0 Hz, 1 H, 2-H), 2·80—3·80 (m, 3 H, $ArCH_2CHAr$), 2·42 and 2·18 (2 m, 8 H, 4 NCH_2 of piperazine), 2·05 (bs, 3 H, NCH_3).

2-Chloro-7-fluoro-3-hydroxydibenzo[*b,f*]thiepin (*XVI*)

A solution of 10·6 g BBr_3 in 5 ml chloroform was added dropwise over a period of 15 min under stirring at 20—25°C to a solution of 5·90 g base *Id* in 25 ml chloroform. The mixture was stirred for 6·5 h at room temperature, left to stand overnight, cooled while 25 ml ethanol was being added, stirred for 8 h, 40 ml ether was added and the precipitated product was filtered. It was suspended in 5% $NaHCO_3$ and extracted with dichloromethane. Evaporation of the extract yielded 5·7 g oil which was dissolved in acetone and the solution was neutralized with maleic acid. Crystallization of the precipitated salt from ethanol yielded 0·8 g di(hydrogen maleate) of 1-methylpiperazine, m.p. 172—173°C. For $C_{13}H_{20}N_2O_8$ (332·3) calculated: 46·98% C, 6·07% H, 8·43% N; found: 47·32% C, 6·25% H, 8·32% N.

The mother liquor was processed to obtain maleate melting at 143—145°C (ethanol–ether), or 145—148°C (water) which could not be identified. Further mother liquors were evaporated and decomposed with 5% $NaHCO_3$ to release a base which was isolated by extraction with dichloromethane (3·0 g red oil). Treatment with an ether solution of hydrogen chloride led to a hydrochloride melting at 188—190°C (aqueous ethanol–ether) which could not be identified. The ether mother liquor was washed with water and evaporated to yield 1·0 g olefin *XVI*, m.p. 136—137°C (benzene–light petroleum). UVspectrum: λ_{max} 232 nm (log ε 4·43), 268 nm (4·49), infl. 315 nm (3·73). IR spectrum: 814, 838, 868, 890 (2 adjacent and solitary Ar—H), 1 170, 1 205, 1 270 (Ar—OH), 1 480, 1 549, 1 569, 1 589 (Ar), 3 465, 3 515 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·80—7·40 (m, 7 H, 5 Ar—H and CH=CH), 5·60 (bs, 1 H, OH). For $C_{14}H_8ClFOS$ (279·7) calculated: 60·11% C, 3·24% H, 12·68% Cl, 6·79% F, 11·46% S; found: 60·14% C, 2·92% H, 12·80% Cl, 7·11% F, 11·63% S.

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