# NONCATALEPTIC POTENTIAL NEUROLEPTICS: 2-ACETAMIDO-, 2-AMINO- AND 2-ACETYL DERIVATIVES OF 10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN*

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5-Amino-2-(phenylthio)phenylacetic acid (*VIc*) prepared in seven steps from 2-chloro-5-nitrobenzoic acid was cyclized to the amino ketone *IXc* which yielded in further four steps the 2-acetamido derivative of perathiepin (*Ib*). Its alkaline hydrolysis gave rise to amine *Ic*. The amino alcohol *Xc* obtained by reduction of amino ketone *IXc* was diazotized, exposed to acetaldehyde semicarbazone and hydrolyzed to 2-acetyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*Xd*) which, in two further steps, yielded the 2-acetyl derivative of perathiepin (*Id*). Attempts at nitration of ketones *IX* (R = H) and *XVII*, as well as of enol acetate *XXI*, resulted (*a*) in the introduction of one or two nitro groups into position 11, (*b*) in the oxidation of sulfide to sulfoxide and (*c*) in an oxidative cleavage of the 10,11-bridge to dicarboxylic acids but in no case to the expected introduction of the nitro group into the ring. Acetamide *Ib* and amine *Ic* are highly effective central depressants but are almost inactive as cataleptics; they can thus be considered as potential antipsychotics of the clozapine type.

In a previous communication of this series[1] we mentioned one of the present trends in the research of new tricyclic neuroleptics which consists in attempts at finding antipsychotically effective agents free of the undesirable side effects of extrapyramidal type. The attempts were stimulated by the discovery of the dibenzo[*b*,*e*]-1,4-diazepine derivative clozapine[2,3] which, in experiments with animals, retains its typical central depressant activity but lacks the cataleptic and antiapomorphine activities; clinical tests suggest an antipsychotic activity with practically complete absence of the mentioned side effects[4]. An important feature of the clozapine molecule is the atypical position of the substituent (chlorine atom) in the ring. Proceeding from this structural feature, we took up the synthesis and pharmacology[1] of 2-methoxy, 2-methylthio, 2-(dimethylsulfamoyl) and 2-trifluoromethyl derivatives of perathiepin and of some related compounds which lacked the unwanted cataleptic activity but which are weaker sedatives than clozapine. The present study is a continuation of systematic attempts at finding a potential antipsychotic of clozapine type in the series of 10-pipe-

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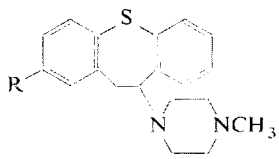
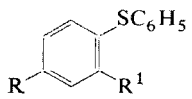
razinodibenzo[*b,f*]thiepin derivatives, and deals with 2-acetamido, 2-amino and 2-acetyl derivatives of perathiepin (*Ib–Id*). The corresponding 8-substitution isomers of these compounds were described earlier[5–7] and, particularly with the 8-acetyl derivative of perathiepin, we observed a high degree of neuroleptic activity in the classical sense of the word (in animal experiments there were both a depressant and a cataleptic activity present)[7].



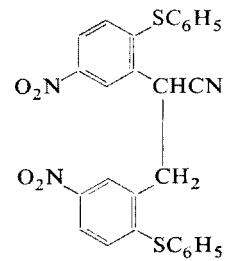

*I*

In all formulas *a*, R = $NO_2$; *b*, R = $NHCOCH_3$; *c*, R = $NH_2$; *d*, R = $COCH_3$

In view of the chemical reactivity of substituents in *Ib–Id* it was necessary to use for their synthesis somewhat different procedures when compared with the mentioned compounds (*e.g.*[1]); in most cases, methods analogous to those for the synthesis of 8-substitution isomers were employed[5–7]. The common starting compound was 2-chloro-5-nitrobenzoic acid[8] obtained by nitration of 2-chlorobenzoic acid. Its reaction with thiophenol in an aqueous solution of potassium hydroxide and in the presence of copper led to 5-nitro-2-(phenylthio)benzoic acid (*IIa*) which was reduced with diborane *in situ* (ref.[1]) to nitro alcohol *IIIa*. The attempt at using this compound for the synthesis of the 2-nitro derivative of perathiepin (*Ia*) was left incomplete. Nitroalcohol *IIIa* when exposed to thionyl chloride, yielded the corresponding nitrobenzyl chloride *IVa* but in the subsequent step (reaction of *IVa* with alkaline cyanides) carried out under various conditions, no characterized nitrile *Va* could be obtained. Nonhomogeneous products resulted, from which conducting the reaction in acetone, a substantial amount of a compound $C_{27}H_{19}N_3O_4S_2$ was isolated (according to analysis and mass spectrum) which has the structure of *VIII*, *i.e.* the product of alkylation of nitrile *Va* with chloride *IVa* (for analogy see ref.[1,9]). The crude products evidently contain nitrile *Va* since upon hydrolysis they gave rise to a small



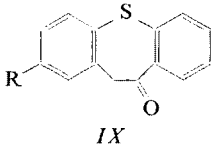

*II*, $R^1$ = COOH
*III*, $R^1$ = $CH_2OH$
*IV*, $R^1$ = $CH_2Cl$
*V*, $R^1$ = $CH_2CN$
*VI*, $R^1$ = $CH_2COOH$
*VII*, $R^1$ = $CH_2CONH_2$



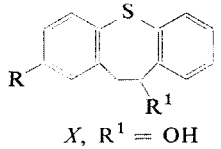

*VIII*

amount of the desired acid *VIa*. However, because of the insufficient amount of material the attempts aiming at the synthesis of *Ia* were interrupted at this stage.

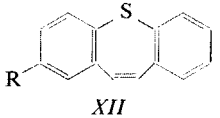
Reduction of nitro alcohol *IIIa* with stannous chloride led to amino alcohol *IIIc* which was selectively N-acetylated with isopropenyl acetate[10] to acetamido alcohol *IIIb*. Subsequent treatment with thionyl chloride in the presence of pyridine yielded chloride *IVb* which was converted with sodium cyanide in dimethylformamide to nitrile *Vb* which was then hydrolyzed under alkaline conditions to amino acid *VIc*; a by-product of this reaction was amide *VIIc*. The free amino acid *VIc* is readily cyclized through the action of polyphosphoric acid at 125°C to 2-aminodibenzo[*b*,*f*]-thiepin-10(11*H*)-one (*IXc*) (for analogy see ref.[6]). The acetamido ketone *IXb* obtained by acetylation was reduced with sodium borohydride to alcohol *Xb* which was converted by treatment with hydrogen chloride in chloroform to chloride *XIb*. Substitution reaction with 1-methylpiperazine in boiling chloroform yielded the 2-acetamido derivative of perathiepin (*Ib*), together with the usual elimination product, *viz.* 2-acetamidodibenzo[*b*,*f*]thiepin[5] (*XIIb*). Hydrolysis of *Ib* with ethanolic potassium hydroxide yielded triamine *Ic*.




*IX*




*X*, $R^1$ = OH
*XI*, $R^1$ = Cl

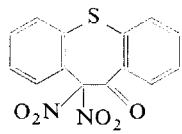



*XII*

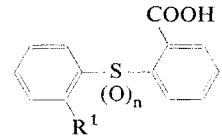
Reduction of amino ketone *IXc* with sodium borohydride led to amino alcohol *Xc* which was converted by Beach's method[11] to 2-acetyl-10,11-dihydrodibenzo[*b*,*f*]-thiepin-10-ol (*Xd*) (for analogy see ref.[7]); the reaction sequence used started with diazotization of amino alcohol *Xc*, the diazonium salt reacting then with acetaldehyde semicarbazone, the product being finally hydrolyzed with a solution of oxalic acid. A minor product separated by chromatography of the crude reaction product was a less polar substance which appears to be *IXd* according to analysis and spectra (for an analogous by-product see ref.[7]). Alcohol *Xd* was treated with hydrogen chloride and converted to chloride *XId* which underwent a substitution reaction with 1-methylpiperazine to the piperazine derivative *Id*; a product of elimination proceeding in parallel was the previously known[7] 2-acetyldibenzo[*b*,*f*]thiepin (*XIId*).

In view of the unsuccessful attempt at synthesizing compound *Ia* by a systematic build-up from the aromatic fragment containing the nitro group, an orientation

study was carried out as to the possibilities of introducing the nitro group only at the stage of an intermediate product containing the dibenzo[*b*,*f*]thiepin skeleton. The first compound chosen was dibenzo[*b*,*f*]thiepin-10(11*H*)-one[12,13] (*IX*, R = H) which was nitrated by a nitration mixture in acetic acid at 15°C. The reaction did not take place at a lower temperature when the starting compound was fully recovered. Under these conditions a relatively high yield of a neutral product was obtained which, according to analysis, appears to be the dinitro derivative of the starting compound. Its IR spectrum shows a preserved conjugated keto group $\nu$(CO) 1685 $cm^{-1}$), the NMR spectrum containing only a multiplet corresponding to aromatic protons. Thus the NMR spectrum excludes the presence of a $ArCH_2$ or ArCH fragment. The UV spectrum does not correspond to an aromatic nitro or dinitro derivative. These and some other observations suggest that the product is geminally dinitrated in the only aliphatic position present, *i.e.* 11, and that hence it has the structure of *XIII*. The literature contains data on geminal dinitration in the α-position with respect to the keto group. During oxidation of ethyl isopropyl ketone with nitric acid one of the products is 2-methyl-4,4-dinitro-3-pentanone[14] while in a similar oxidation of cyclododecanone a 25% yield of 2,2-dinitrocyclododecanone was obtained[15]. The present case resembles most the reaction of 2-(3-oxo-1-indanylidene)-1,3-indanedione (bindone) with fuming nitric acid in acetic acid when the 2,2-dinitro derivative is formed[16]; here, too, a geminal dinitration in the only aliphatic position present takes place although aromatic rings capable of nitration are present. In the case described here, a high-melting carboxylic acid was isolated as a by-product and identified by analysis and spectra as well as by comparison with an authentic product[17] as diphenylsulfoxide-2,2'-dicarboxylic acid (*XIV*).




*XIII*



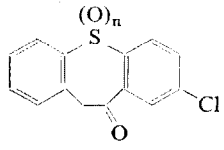

*XIV*, $R^1$ = COOH, $n = 1$
*XV*, $R^1$ = $CH(NO_2)_2$, n = 0
*XVI*, $R^1$ = CHO, n = O

The identity of the present product *XIII* is supported by the results of solvolytic reactions. Thus on heating *XIII* with dilute aqueous–ethanolic solution of sodium hydroxide an orange carboxylic acid is formed which still contains both nitro groups; on the basis of analysis and NMR spectra it is supposed to have structure *XV*. The cleavage of the C—C bonds which takes place is apparently of the type found during hydrolysis of aliphatic α,α-dinitro ketones[18] and further during alcoholysis[19] or

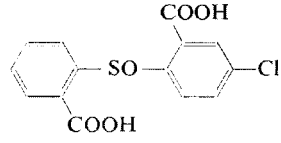
hydrolysis[20] of α-phenyl-α-nitroacetophenone; in both cases the product is phenylnitromethane, the by-product being in the first case ethyl benzoate, in the second case benzoic acid. When heating *XIII* with a mixture of acetic acid and hydrochloric acid the formation of neutral and acid products was observed. The neutral compound was identified as thioxanthone[21,22]; during its formation one must assume the occurrence of the corresponding diketone as the intermediate product which might yield thioxanthone either directly by decarbonylation or after previous transformation to an α-hydroxy acid of the type of benzylic acid (ref.[12,22]). The acid product is assumed to have the structure of aldehydo acid *XVI* and it is assumed to be genetically related to the dinitro acid *XV*. The spectra of the present "aldehydo acid" are not very convincing and literature data on the possibility of hydrolysis of geminal dinitro compounds to aldehydes or ketones are rather contradictory: hydrolysis of tetranitromethane to carbonic acid has been reported[23] as well as hydrolysis of trinitromethyl derivatives to carboxylic acids[24], an analogous hydrolysis of geminal dinitro compounds (tested on the case of 4,4-dinitropimelic acid) has not been found feasible[24]. On the other hand, phenyldinitromethane has been reported[25] to be stable to the action of dilute acids but to be decomposed by sulfuric acid, giving rise to benzaldehyde (ref.[26]). This observation represents a close analogy to the present case.

We attempted further to nitrate 8-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one[27,28] (*XVII*). In the reaction of ketone *XVII* with the nitration mixture in acetic anhydride in the presence of chloroform at −10°C no nitration took place but only an oxidation, giving rise to a fine yield of sulfoxide *XVIII*. In a similar reaction in a mixture of acetic acid and acetic anhydride at 0−5°C, a mixture of products is formed from which the two principal ones were isolated. First of all, it is the nitrogen-free aromatic acid ($\nu$(COOH) 1692 $cm^{-1}$) containing the sulfoxide group ($\nu$(SO) 1050 $cm^{-1}$) which apparently corresponds to *XIV* with structure *XIX*. The similarity of acid *XIV* and *XIX* is manifested among other things by the fact that they both crystallize from ethanol in the form of ethanol solvates. The other product of this nitration attempt is neutral, containing one nitro group ($\nu(NO_2)$ 1378 and 1570 $cm^{-1}$) and further a vinyl ester fragment ($\nu$(C=C—O—CO) 1785 $cm^{-1}$); its NMR spectrum displays only a multiplet of seven aromatic protons and a singlet of protons of the methyl group. On the basis of these facts and of analysis it is assumed to have the structure of the nitroenol acetate *XX*. On heating with a dilute solution of hydrochloric acid in ethanol it yields the deacetylation product, the NMR spectrum of which displays signals only in the region of aromatic protons. The IR spectrum suggests a preserved nitro group, has a band at 1670 $cm^{-1}$ (it may belong to a conjugated keto group but possibly also only to a C=C bond) and finally a band of the hydroxyl group (3200 $cm^{-1}$). The compound is formulated as nitro-enol *XXI* which is apparently in equilibrium with a smaller amount of the tautomeric ketone. Keto-enol tautomerism is suggested also for the above mentioned α-phenyl-α-nitroacetophenone,

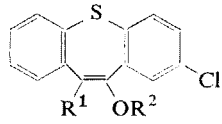
the IR spectrum of which displays the band of a conjugated keto group[29] ($\nu$(CO) 1 694 $cm^{-1}$) but the compound is soluble in alkaline solutions and in aqueous ammonia[19]. To complete the study, ketone *XVII* was left to react with acetic anhydride under acid catalysis to yield enol acetate *XXII* which was nitrated in acetic anhydride at $-10°C$. A low yield of an acid product was obtained, the NMR spectrum of which contains signals only in the region of aromatic protons and the IR spectrum of which suggests the presence of a nitro and a sulfoxide group. According to its mass spectrum, the product is not homogeneous and attempts at its purification and identification were unsuccessful.




*XVII*, n = 0
*XVIII*, n = 1




*XIX*




*XX*, $R^1 = NO_2$, $R^2 = COCH_3$
*XXI*, $R^1 = NO_2$, $R^2 = H$
*XXII*, $R^1 = H$, $R^2 = COCH_3$

TABLE I

Pharmacological Properties (mg/kg) of Compounds Prepared

| Compound | Application | Acute toxicity $LD_{50}$ | Rotating rod $ED_{50}$ | Catalepsy $ED_{50}$ |
|---|---|---|---|---|
| *Ib* | *p.o.* | 125 | 1·8 | $>50^a$ |
| *Ic* | *p.o.* | 84 | 1·25 | $>50^a$ |
| *Id* | *i.v.* | 38 | $11·5^d$ | $>30^{b,c}$ |
| Clozapine[3] | *p.o.* | 210 | 3·8 | $>50^c$ |
| *I* (R = Cl)[32] | *p.o.* | 70 | 1·2 | $>100^a$ |
| | *i.v.* | 36 | 0·23 | |
| Clorotepin[31] | *p.o.* | 78 | 2·2 | 4·3 |
| | *i.v.* | 46·3 | 0·06 | $2·4^b$ |

[a] The dose shown brings about "pseudocatalepsy" with at most 30% animals; at half the dose no effect is observed. [b] Intraperitoneally. [c] At the dose shown, no catalepsy was observed in any of ten animals. [b] On oral administration, $ED_{50}$ = 80 mg/kg.

After these very unpromising attempts further work on the synthesis of *Ia* was stopped. Only after termination of the work a patent application[30] described the continuation of our synthesis: the uncharacterized nitrile *Va* was hydrolyzed under acid conditions to acid *VIa* from which *IXa*, *X*a and *XIa* were consecutively synthesized, *i.e.* up to the immediate precursor of *Ia*. The patent application[30] further describes the preparation of several other intermediates without data on yields and without analytical and spectral data; the corresponding references are mentioned in the experimental section.

In the form of salts, compounds *Ib*–*Id* were evaluated pharmacologically by using methods employed before[1]. The acute toxicity for mice was estimated, the mean effective doses ($ED_{50}$) were assessed in the rotating-rod test on mice (incoordinating effect corresponding to central inhibition) and attempts were made to detect a cataleptic effect on rats. The numerical data on toxicity and activity (in mg/kg) are collected in Table I and refer to the corresponding bases. For the sake of comparison, the table includes clozapine[3], clorotepin (octoclothepin)[31] and its 2-chloro isomer[32] (*I*, R = Cl). The results indicate that *Ib* and *Ic* have a similar pharmacological profile as the 2-chloro isomer of clorotepin (*I*, *R* = Cl). They are highly effective as central depressants, approximately 2–3 times more than clozapine and almost twice more than clorotepin, while displaying practically no cataleptic activity. Suggestions of a cataleptic effect as they appear with some animals after high doses may be designated as pseudocatalepsy which is simulated by a deep depression of the animals. Compound *Id* is also inactive cataleptically but, at the same time, it is much weaker even in the rotating-rod test. *Ib* and *Ic* may be designated as very promising from the point of view of the attempt at finding a noncataleptic antipsychotic of clozapine type in the series of 10-piperazinodibenzo[*b*,*f*] thiepin derivatives.

All the compounds were also tested for antimicrobial activity *in vitro* (Dr J. Turinová, Dr A. Čapek); they were inhibitory only toward several microorganisms (the minimum inhibitory concentrations in μg/ml are shown): *Streptococcus β-haemolyticus*, *Id*, 50; *Streptococcus faecalis*, *Id*, 50; *Staphylococcus pyogenes aureus*, *Id*, 50; *Mycobacterium tuberculosis* H37Rv, *Ib*, 100; *Ic* 50; *Id*, 50; *Trichophyton mentagrophytes*, *Ib*, 25; *Ic*, 25; *Aspergillus niger*, *Ib*, 100; *Ic*, 100.

## EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at about 0·5 Torr over $P_2O_5$ at room temperature or at a temperature suitably raised (100°C at most). 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 200G or an Infrascan (Hilger and Watts) spectrophotometer, the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR-60 (Zeiss, Jena) spectrometer and the mass spectra in a MS 902 (AEI) mass spectrometer. The homogeneity of the compounds was checked by thin-layer chromatography on silica gel. Preparative chromatography was done on alumina of activity II.

5-Nitro-2-(phenylthio)benzoic Acid (*IIa*)

A solution of 24·3 g 85% KOH in 250 ml water was combined with 11·0 g thiophenol, 20·1 g 2-chloro-5-nitrobenzoic acid[8] (m.p. 163—165°C) and 1 g Cu paste and the mixture was refluxed under stirring for 8 h. Then it was combined with 350 ml dimethylformamide and refluxed for further 12 h. After cooling, it was filtered and the filtrate was diluted with 500 ml water. A small amount of precipitate was filtered and the filtrate was acidified with hydrochloric acid. On the following day the product was filtered; 21·0 g (78%), m.p. 232—235°C (ethanol). UV spectrum: $\lambda_{max}$ 241 nm (log $\varepsilon$ 4·19), 252 nm (3·89). IR spectrum (KBr): 692, 710, 723, 742, 758, 817, 840, 890 (5 and 2 adjacent and solitary Ar—H), 913, 1255 (COOH), 1345, 1510, 1520 ($NO_2$), 1570, 1599 (Ar), 1698 (Ar—COOH), 2515, 2580 $cm^{-1}$ (COOH). For $C_{13}H_9NO_4S$ (275·3) calculated: 56·72% C, 3·29% H, 5·09% N, 11·65% S; found: 56·52% C, 3·25% H, 5·08% N, 11·66% S.

5-Nitro-2-(phenylthio)benzyl Alcohol (*IIIa*)

To a suspension of 27·5 g *IIa* in 60 ml tetrahydrofuran 3·8 g $NaBH_4$ was added under stirring over a period of 20 min at 10—20°C, the solution was stirred for 30 min at the same temperature and, over 45 min, a solution of 13 ml boron trifluoride etherate in 10 ml tetrahydrofuran was added dropwise. The mixture was stirred for 3 h at 10—20°C; after cooling below 10°C, a total of 15 ml 5% hydrochloric acid was added dropwise over a period of 15 min, the solution was diluted with benzene and washed with water, 3% NaOH, water, dried with $Na_2SO_4$ and evaporated: 23·9 g (91%) crude product melting at 110—113°C; the analytical product melts at 115 to 117°C (ethanol). IR spectrum (KBr): 690, 707, 746, 757, 818, 841, 852 (5 and 2 adjacent and solitary Ar—H), 1040 ($CH_2OH$), 1337, 1523 ($NO_2$), 1605 (Ar), 3345 $cm^{-1}$ (OH). For $C_{13}H_{11}NO_3S$ (261·3) calculated: 59·75% C, 4·24% H, 5·36% N, 12·27% S; found: 59·64% C, 4·40% H, 5·42% N, 12·27% S. Patent application[30] describes the preparation of the compound by reduction of 5-nitro-2-(phenylthio)-benzaldehyde with $NaBH_4$ and reports a melting point for the product of 104—107°C.

5-Nitro-2-(phenylthio)benzyl Chloride (*IVa*)

To a solution of 26·1 g *IIIa* in 80 ml benzene, 8 ml $SOCl_2$ was added dropwise over 15 min at 70°C. The mixture was refluxed for 1 h, the volatile fractions were evaporated at reduced pressure in a water bath; the residue (24 g, 86%) is a crude product which was used in this state for further work. A small sample was distilled; b.p. 190°C/3 Torr, m.p. 62—64°C (cyclohexane). Even the crude product crystallizes on standing and melts at 60—63°C. NMR spectrum: $\delta$ 8·21 (d, $J$ = 2·0 Hz, 1 H, 6-H of benzyl chloride), 7·86 (q, $J$ = 9·0; 2·0 Hz, 1 H, 4-H of benzyl chloride), 7·44 (s, 5 H, $C_6H_5$), 6·88 (d, $J$ = 9·0 Hz, 1 H, 3-H of benzyl chloride), 4·71 (s, 2 H, $CH_2Cl$). For $C_{13}H_{10}ClNO_2S$ (279·7) calculated: 55·81% C, 3·60% H, 12·68% Cl, 5·01% N, 11·46% S; found: 56·00% C, 3·61% H, 12·56% Cl, 4·97% N, 11·64% S. Patent application[30] describes the preparation of the compound from *IIIa* and $SOCl_2$ in chloroform in the presence of pyridine; a m.p. of 58—60°C is reported.

2,3-Bis(5-nitro-2-phenylthiophenyl)propionitrile (*VIII*)

Sodium cyanide (0·74 g) and 0·1 g NaI were added to a solution of 2·80 g *IVa* in 50 ml acetone and the mixture was refluxed for 13 h. After cooling, it was diluted with 200 ml benzene, washed with water, dried with $MgSO_4$ and evaporated. Crystallization of the residue from a mixture of ethanol and benzene yielded 2·35 g (91%) compound melting at 161—163·5°C. Mass spectrum:

molecular ion at *m/e* 513. IR spectrum (KBr): 700, 750, 810, 855 (5 and 2 adjacent and solitary Ar—H), 1350, 1525 ($ArNO_2$), 1570 (Ar), 2260 $cm^{-1}$ (R—CN). NMR spectrum: $\delta$ 8·46 (d, $J = 2{\cdot}5$ Hz, 1 H, 6-H of diphenylpropionitrile), 7·80—8·20 (m, 3 H, 4,4',6'-$H_3$ of diphenylpropionitrile), 7·44 and 7·46 (2 s, 10 H, 2 $C_6H_5$), 7·04 and 6·95 (2 d, $J = 9{\cdot}0$ Hz, 2 H, 3,3'-$H_2$ of diphenylpropionitrile), 4·95 (t, $J = 8{\cdot}0$ Hz, 1 H, CHCN), 3·50 (d, $J = 8{\cdot}0$ Hz, 2 H, $ArCH_2$). For $C_{27}H_{19}N_3O_4S_2$ (513·6) calculated: 63·14% C, 3·73% H, 8·18% N, 12·49% S; found: 63·86% C, 4·06% H, 7·85% N, 12·01% S.

5-Nitro-2-(phenylthio)phenylacetic Acid (*VIa*)

Sodium cyanide (14·7 g) was added to a solution of 55·9 g *IVa* in 200 ml dimethylformamide and the mixture was stirred for 10 h at room temperature. After 48 h of standing it was diluted with 1 l of water and extracted with benzene. Treatment of the extract yielded 34·3 g oil (crude *Va*) which was refluxed for 3 h with a mixture of 35 ml acetic acid, 35 ml $H_2SO_4$ and 35 ml water. After cooling, it was diluted with water and extracted with benzene. The acid product was removed from the extract by shaking with 5% $Na_2CO_3$ and the sodium salt solution obtained was acidified with hydrochloric acid, yielding 2·10 g *VIa*, m.p. 143—145°C (benzene–light petroleum). IR spectrum: 690, 742, 755, 822, 836 (Ar—H), 930, 1231, 1271 (COOH), 1335, 1502 ($NO_2$), 1571 (Ar), 1689 $cm^{-1}$ (COOH). NMR spectrum: $\delta$ 10·75 (bs, disappears after $D_2O$, 1 H, COOH), 8·15 (d, $J = 2{\cdot}5$ Hz, 1 H, 6-H of phenylacetic acid), 7·95 (q, $J = 9{\cdot}0$; 2·5 Hz, 1 H, 4-H of phenylacetic acid), 7·44 (s, 5 H, $C_6H_5$), 7·05 (d, $J = 9{\cdot}0$ Hz, 1 H, 3-H of phenylacetic acid), 3·90 (s, 2 H, $ArCH_2COO$). For $C_{14}H_{11}NO_4S$ (289·2) calculated: 58·13% C, 3·83% H, 4·84% N, 11·08% S; found: 57·83% C, 4·02% H, 4·47% N, 11·00% S. Patent application[30] describes a similar preparation of the compound without data on the yield, reporting a m.p. of 138—140°C.

5-Amino-2-(phenylthio)benzyl Alcohol (*IIIc*)

A solution of 165 g *IIIa* in 1800 ml ether was combined with 572 g $SnCl_2.2\,H_2O$ and, during refluxing, 250 ml hydrochloric acid was added to the mixture dropwise over a period of 2 h. The mixture was refluxed for 5 h and then, under external cooling, 1600ml 20% NaOH were slowly added, the ether layer was separated and the aqueous one was extracted with benzene. The combined organic phases were dried with $MgSO_4$ and evaporated. The residue crystallized from a mixture of benzene and light petroleum and yielded 131 g (90%) product melting at 63—65°C; the analytical product melted at 65—66°C. IR spectrum: 696, 735, 748, 831, 878 (5 and 2 adjacent and solitary Ar—H), 770 ($ArNH_2$), 1032, 1062 ($CH_2OH$), 1580, 1594, 1630 (Ar), 3300, 3385 and 3460 $cm^{-1}$ (OH, $NH_2$). NMR spectrum: $\delta$ 7·26 (d, $J = 9{\cdot}0$ Hz, 1 H, 3-H), *c.* 7·05 (m, 5 H, $C_6H_5$), 6·79 (d, $J = 2{\cdot}5$ Hz, 1 H, 6-H), 6·51 (q, $J = 9{\cdot}0$; 2·5 Hz, 1 H, 4-H), 4·55 (s, 2 H, $ArCH_2O$), 3·41 (s, disappears after $D_2O$, 3 H, $NH_2$ and OH). For $C_{13}H_{13}NOS$ (231·2) calculated: 67·52% C, 5·67% H, 6·06% N, 13·84% S; found: 67·53% C, 5·99% H, 5·80% N, 13·77% S.

5-(Acetamido)-2-(phenylthio)benzyl Alcohol (*IIIb*)

A solution of 127 g *IIIc* in 250 ml isopropenyl acetate was refluxed for 12 h. The volatile fractions were then evaporated at normal pressure up to the boiling point of 95°C and the residue was refluxed for 7 h. The mixture was diluted with 250 ml benzene and left to stand overnight. A total of 145 g (96%) product crystallized; m.p. 118—121°C; analytical product, m.p. 120·5—121·5°C (benzene–ethanol). IR spectrum: 700, 745, 800, 850 (5 and 2 adjacent and solitary Ar—H), 1029 ($CH_2OH$), 1540, 1580, 1666 (CONH), 1608 (Ar), 3100, 3170, 3240, 3285 $cm^{-1}$ (OH, NH). NMR spectrum ($C_5D_5N$): $\delta$ 8·05 (q, $J = 9{\cdot}0$; 2·5; Hz, 1 H, 4-H), 7·50 (d, $J = 9{\cdot}0$ Hz, 1 H, 3-H),

7·12 (s, $C_6H_5$, NH and 6-H), 5·90 (bs, 1 H, OH), 5·07 (s, 2 H, $ArCH_2O$), 2·10 (s, 3 H, $COCH_3$). For $C_{15}H_{15}NO_2S$ (273·4) calculated: 65·91% C, 5·53% H, 5·12% N, 11·73% S; found: 66·04% C, 5·81% H, 4·94% N, 11·54% S.

5-(Acetamido)-2-(phenylthio)benzyl Chloride (*IVb*)

A solution of 145 g *IIIb* in 200 ml chloroform was combined with 55 ml pyridine and than, over a period of 2 h, 76 g $SOCl_2$ was added dropwise at 15°C. The mixture was stirred for 1 h, left to stand for 48 h, was washed with water, 5% NaOH, 5% hydrochloric acid and water. The precipitated crystalline product was filtered, the chloroform solution was evaporated and the residue after washing with benzene was combined with the previously filtered product; 137 g (89%), m.p. 137—138°C, remaining unchanged after crystallization from benzene. NMR spectrum: $\delta$ 8·15 (bs, 1 H, NH), 7·74 (d, $J$ = 2·5 Hz, 1 H, 6-H), 7·52 (q, $J$ = 9·0; 2·5 Hz, 1 H, 4-H), 7·30 (d, $J$ = 9·0 Hz, 1 H, 3-H), 7·20 (s, 5 H, $C_6H_5$), 4·66 (s, 2 H, $ArCH_2Cl$), 2·12 (s, 3 H, $COCH_3$). For $C_{15}H_{14}ClNOS$ (291·8) calculated: 61·74% C, 4·84% H, 12·15% Cl, 4·80% N, 10·99% S; found: 62·15% C, 5·00% H, 12·22% Cl, 4·71% N, 10·85% S.

5-(Acetamido)-2-(phenylthio)phenylacetonitrile (*Vb*)

Sodium cyanide (37·5 g) was added to a solution of 137 g *IVb* in 500 ml dimethylformamide and the mixture was heated under stirring for 4 h on a boiling-water bath. The solvent was then distilled off at reduced pressure, the residue was diluted with 300 ml chloroform, the solution washed with water, dried with $MgSO_4$ and evaporated. The crystalline residue was mixed with some benzene and evaporated; 80 g crude product, a sample of which was recrystallized for analysis from a mixture of benzene and light petroleum, m.p. 100—102°C. Evaporation of the mother liquor yielded 66 g oil which, according to thin-layer chromatography, consists of nitrile *Vb* and of a more polar compound (its processing is described below). IR spectrum (KBr) of *Vb*: 700, 750, 843, 870 (5 and 2 adjacent and solitary Ar—H), 1545, 1675 (CONH), 1605 (Ar), 2260 (CN), 3265 and 3310 $cm^{-1}$ (NH). For $C_{16}H_{14}N_2OS$ (282·4) calculated: 68·06% C, 5·00% H 9·92% N, 11·35% S; found: 67·93% C, 5·28% H, 9·94% N, 11·58% S.

5-Amino-2-(phenylthio)phenylacetic Acid (*VIc*)

A solution of 55 g KOH in 110 ml water was added to a solution of 80 g *Vb* in 250 ml ethanol and the mixture was refluxed for 4 h. It was diluted with 500 ml hot water, the ethanol was distilled at normal pressure and the warm residue was acidified with acetic acid. On standing in a refrigerator, 70·6 g (96%) compound melting at 153—159°C (decomp.) crystallized. The melting point did not change on crystallization from a mixture of chloroform and benzene. The compound retains persistently a small amount of benzene which affects the analysis. IR spectrum (KBr): 700, 760, 830, 872 (5 and 2 adjacent and solitary Ar—H), 963, 1248, 1705 (COOH), 1489, 1580, 1590, 1605 (Ar), 1630 ($ArNH_2$), 2570—3200 (COOH), 3405 and 3500 $cm^{-1}$ ($NH_2$). For $C_{14}H_{13}NO_2S$ (259·3) calculated: 64·85% C, 5·05% H, 5·40% N, 12·36% S; found: 65·64% C, 5·58% H, 5·93% N, 12·03% S. Patent application[30] describes the preparation of acid *VIc* by hydrogenation of nitro acid *VIa* on palladium and reports a m.p. of 160—162°C for a product crystallizing from acetone–hexane.

5-Amino-2-(phenylthio)phenylacetamide (*VIIc*)

The oily substance (66 g) obtained from the mother liquor after *Vb* was hydrolyzed for 4 h by refluxing with 44 g KOH in 90 ml water and 200 ml ethanol. The ethanol was distilled off,

the residue was diluted with 400 ml water and the undissolved oil was isolated by extraction with a mixture of benzene and chloroform. Acidification of the aqueous layer with acetic acid and standing resulted in 17 g acid *VIc* melting at 152—156°C. Evaporation of the benzene–chloroform extract yielded 13·8 g amide *VIIc*, m.p. 137—139°C (chloroform–ethanol). IR spectrum: 705, 760, 825, 860, (5 and 2 adjacent and solitary Ar—H), 1486, 1600, 1616 (Ar), 1648 ($CONH_2$), 3190, 3371, 3410, 3465 $cm^{-1}$ ($NH_2$). NMR spectrum ($CD_3SOCD_3$): $\delta$ 6·80—7·40 (m, 5 H, $C_6H_5$), 7·13 (d, $J$ = 9·0 Hz, 1 H, 3-H), 6·62 (d, $J$ = 2·5 Hz, 1 H, 6-H), 6·52 (q, $J$ = 9·0; 2·5 Hz, 1 H, 4-H), 5·45 (bs, 2 H, $CONH_2$), 3·41 (bs, 4 H, $H_2N—Ar—CH_2$). For $C_{14}H_{14}N_2OS$ (258·3) calculated: 65·09% C, 5·46% H, 10·85% N, 12·41% S; found: 64·87% C, 5·69% H, 11·06% N, 12·53% S.

2-Aminodibenzo[*b,f*]thiepin-10(11*H*)-one (*IXc*)

Polyphosphoric acid was prepared from 300 ml 85% $H_3PO_4$ and 600 g $P_2O_5$. A total of 77 g *VIc* was added and the mixture was stirred for 1·5 h at 125°C. After pouring into water, the precipitated product was filtered, suspended in 10% $Na_2CO_3$, left to stand for 1 h, again filtered, washed with water and dried: 65 g (91%), m.p. 189—193°C. The analytical sample melts at 193 to 195°C (ethanol–benzene). UV spectrum: $\lambda_{max}$ 258·8 nm (log $\varepsilon$ 4·27), 346 nm (3·54). IR spectrum: 767, 821, 871 (4 and 2 adjacent and solitary Ar—H), 1490, 1595 (Ar), 1635 ($ArNH_2$), 1670 (ArCO), 3202, 3315, 3420 $cm^{-1}$ ($NH_2$). NMR spectrum ($CD_3SOCD_3$): $\delta$ 8·09 (m, 1 H, 9-H), 7·30—7·70 (m, 3 H, 6,7,8-$H_3$), 7·33 (d, $J$ = 9·0 Hz, 1 H, 4-H), 6·70 (d, $J$ = 2·5 Hz, 1 H, 1-H), 6·45 (q, $J$ = 9·0; 2·5 Hz, 1 H, 3-H), 5·45 (bs, disappears after $D_2O$, 2 H, $NH_2$), 4·10 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{11}NOS$ (241·3) calculated: 69·68% C, 4·60% H, 5·80% N, 13·29% S; found: 69·47% C, 4·69% H, 5·96% N, 13·25% S. Patent application[30] describes the preparation of the compound by a similar cyclization at 140°C (reaction time 10 min) and reports a m.p. of 191—193°C for the product.

2-Acetamidodibenzo[*b,f*]thiepin-10(11*H*)-one (*IXb*)

Acetic anhydride (5·1 g) was added dropwise under stirring at 20°C to a solution of 12·1 g *IXc* in 100 ml pyridine and the mixture was left to stand overnight. Then it was poured into 1 litre of water, the precipitated product was filtered and recrystallized from ethanol; 10·4 g (78%), m.p. 208—210°C. UV spectrum: $\lambda_{max}$ 239·5 nm (log $\varepsilon$ 4·47), 260 nm (4·26), 274·5 nm (4·28), 332 nm (3·59). IR spectrum (KBr): 765, 835, 885 (4 and 2 adjacent and solitary Ar-H), 1290, 1555 (CONH), 1485, 1600 (Ar), 1670 (ArCO), 1685 (CONH), 3190, 3260, 3310 $cm^{-1}$ (NH). NMR spectrum ($CD_3SOCD_3$): $\delta$ 10·21 (s, 1 H, NH), 8·02 (m, 1 H, 9-H), 7·15—7·85 (m, 6 H, remaining aromatic protons), 4·20 (s, 2 H, $ArCH_2CO$), 2·06 (s, 3 H, $COCH_3$). For $C_{16}H_{13}NO_2S$ (283·3) calculated: 67·84% C, 4·63% H, 4·95% N, 11·30% S; found: 67·63% C, 4·74% H, 4·65% N, 11·14% S.

2-Acetamido-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*Xb*)

A solution of 1·9 g $NaBH_4$ in 5 ml water with a drop of 20% NaOH was added dropwise under stirring to a solution of 10·1 g *IXb* in 120 ml dioxane. The mixture was stirred for 6 h at room temperature, diluted with 600 ml water, acidified with 5 ml concentrated hydrochloric acid and the precipitated product was filtered; 9·5 g (94%), m.p. 203—206°C. Analytical product melted at 207 to 209°C (ethanol). For $C_{16}H_{15}NO_2S$ (285·3) calculated: 67·36% C, 5·30% H, 4·91% N, 11·22% S; found: 67·00% C, 5·19% H, 4·73% N, 10·97% S.

2-Acetamido-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIb*)

A solution of 9·2 g *Xb* in 300 ml chloroform was combined with 3 g powdery $CaCl_2$ and the suspension was saturated for 2 h with anhydrous hydrogen chloride. After standing overnight, it was heated to 50°C, filtered and washed with warm chloroform. Evaporation of the filtrate yielded the product in theoretical yield (9·7 g), m.p. 160—162°C; it solidifies on further heating to melt again at 198—202°C (the higher melting point apparently corresponds to *XIIb* being formed) (crystallized from chloroform or trichloroethylene). NMR spectrum ($CD_3SOCD_3$): $\delta$ 10·08 (s, 1 H, NH), 7·00—7·70 (m, 7 H, aromatic protons), 5·90 (dd, $J$ = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·87 and 3·45 (2 dd, $J$ = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). 2·02 (s, 3 H, $COCH_3$). For $C_{16}H_{14}ClNOS$ (303·8) calculated: 63·25% C, 4·65% H, 11·67% Cl, 4·61% N, 10·55% S; found: 63·31% C, 4·80% H, 11·92% Cl, 4·62% N, 10·37% S.

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

A mixture of 9·7 g *XI*, 25 ml chloroform and 25 ml 1-methylpiperazine was refluxed for 8 h. After cooling, it was diluted with 150 ml benzene and washed several times with water and 300 ml 5% hydrochloric acid. Evaporation of the benzene solution yielded 2·0 g of the elimination product, *i.e.* 2-acetamidodibenzo[*b,f*]thiepin (*XIIb*), melting at 197—200°C (benzene–light petroleum). The compound was previously reported[5] to melt at 201—202°C.

The acid aqueous solution was made alkaline with a 20% solution of NaOH and the released base *Ib* was isolated by extraction with benzene; 8·8 g (72%) oil which crystallizes from wet benzene as monohydrate, m.p. 103—105°C. IR spectrum (KBr): 770, 830, 900 (4 and 2 adjacent and solitary Ar—H), 1480, 1590, 1620 (Ar), 1550, 1680 (CONH), 2820 (N—$CH_3$), 3440 (NH, $H_2O$) $cm^{-1}$. NMR spectrum: $\delta$ 8·05 (bs, 1 H, NH), 6·80—7·60 (m, 7 H, aromatic protons), 2·90—4·00 (m, 3 H, $ArCH_2CHAr$), 2·80 (s, disappears after $D_2O$, $H_2O$), 2·50 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·38 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, $NCH_3$), 2·06 (s, 3 H, $COCH_3$). For $C_{21}H_{27}N_3O_2S$ (385·5) calculated: 65·42% C, 7·06% H, 10·90% N, 8·32% S; found: 65·87% C, 6·89% H, 10·64% N, 8·40% S.

*Bis(methanesulfonate)*, m.p. 201—203°C with decomposition (aqueous ethanol–ether). For $C_{23}H_{33}N_3O_7S_3$ (559·7) calculated: 49·35% C, 5·94% H, 7·51% N, 17·19% S; found: 49·10% C, 6·09% H, 7·56% N, 16·94% S.

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

A mixture of 3·84 g *Ib*, 4 g KOH and 5 ml ethanol was refluxed for 2 h in a 125—130°C bath. The mixture was then diluted with water, the precipitated product was filtered and dried; 3·10 g (96%), m.p. 202—205°C. Analytical product, m.p. 203—205°C (benzene–ethanol). IR spectrum (KBr): 760, 830, 870 (4 and 2 adjacent and solitary Ar—H), 1480, 1600 (Ar), 1650 ($ArNH_2$), 2810, 2830 (N—$CH_3$), 3185, 3320 and 3440 $cm^{-1}$ ($NH_2$). For $C_{19}H_{23}N_3S$ (325·5) calculated: 70·12% C, 7·12% H, 12·91% N, 9·85% S; found: 70·33% C, 7·16% H, 12·80% N, 9·69% S.

*Tris(methanesulfonate)* (solvate with one molecule of water and one of ethanol), m.p. 157 to 162°C (ethanol–ether). For $C_{24}H_{43}N_3O_{11}S_4$ (677·9) calculated: 42·52% C, 6·39% H, 6·20% N, 18·92% S; found: 42·32% C, 6·32% H, 6·16% N, 19·03% S.

2-Amino-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*Xc*)

A solution of 7·0 g *IXc* in 80 ml dioxane was reduced with a solution of 1·1 g $NaBH_4$ in 3 ml water similarly to the preparation of *Xb* at an initial temperature of 35°C. After evaporation

of dioxane it was diluted with water and the product was isolated by extraction with benzene; 7·0 g (almost theoretical yield) oily product which crystallizes from a mixture of benzene and cyclohexane, m.p. 102—103°C. UV spectrum: $\lambda$ 266 nm (log $\varepsilon$ 4·20). IR spectrum: 775, 830, 881 (4 and 2 adjacent and solitary Ar—H), 1040, 1050 (CHOH in a ring), 1490, 1600 (Ar), 1630 ($ArNH_2$), 3205, 3328, 3408 $cm^{-1}$ ($NH_2$ and OH). NMR spectrum: $\delta$ 7·00—7·60 (m, 4 H, 6,7,8,9-$H_4$), 7·28 (d, $J$ = 9·0 Hz, 1 H, 4-H), 6·54 (d, $J$ = 2·5 Hz, 1 H, 1-H), 6·35 (q, $J$ = 9·0; 2·5 Hz, 1 H, 3-H), 5·11 (dd, $J$ = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·62 and 3·04 (2 dd, $J$ = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 3·22 (s, disappears after $D_2O$, 3 H, $NH_2$ and OH). For $C_{14}H_{13}NOS$ (243·3) calculated: 69·12% C, 5·39% H, 5·76% N, 13·16% S; found: 69·10% C, 5·63% H, 5·73% N, 12·87% S.

*Hydrochloride*, m.p. 190—195°C (remainder at 235°C) (aqueous ethanol–ether). For $C_{14}H_{14}$·.ClNOS (279·8) calculated: 12·67% Cl, 5·01% N, 11·46% S; found: 12·56% Cl, 4·77% N, 11·36% S.

2-Acetyl-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*Xd*)

A suspension of 23·1 g hydrochloride of amine *Xc* in a mixture of 300 ml water and 75 ml concentrated hydrochloric acid was diazotized at 0—5°C with a solution of 6·5 g $NaNO_2$ in 15 ml water. The mixture was stirred for 1 h at 0—5°C, combined with 1·0 g urea, filtered and the filtrate mixed with a cold solution of 90 g sodium acetate trihydrate in 90 ml water. The solution formed was added all at once at 10°C to a mixture prepared from 40·0 g acetaldehyde semicarbazone[33], 40 g sodium acetate trihydrate, 2·4 g $CuSO_4.5\,H_2O$ and 0·3 g $Na_2SO_3$ in 235 ml water. The mixture was stirred for 5 h at room temperature, left to stand overnight, acidified with 50 ml concentrated hydrochloric acid, the product was filtered and washed with water. It was then refluxed for 3 h with a solution of 60 g oxalic acid dihydrate in 300 ml water. After cooling, it was extracted with chloroform, the extract was dried with $MgSO_4$ and evaporated. The residue was dissolved in 300 ml benzene and chromatographed on a column of 500 g alumina. After elution of the least polar components of the mixture with benzene, it was eluted with a mixture of benzene and chloroform. The first to be eluted was 0·21 g compound melting at 158—160°C (cyclohexane) which was identified as 2-acetyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*IXd*). UV spectrum: $\lambda_{max}$ 239 nm (log $\varepsilon$ 4·49) 291 nm (3·95), 319·5 nm infl. (3·81). IR spectrum (KBr): 772, 782, 847 (Ar—H), 1573, 1593 (Ar), 1675 (ArCO in a ring), 1688 $cm^{-1}$ ($ArCOCH_3$). NMR spectrum: $\delta$ 8·20 (m, 1 H, 9-H), 8·01 (bs, 1 H, 1-H), 7·20—7·80 (m, 5 H, remaining aromatic protons), 4·35 (s, 2 H, $ArCH_2CO$), 2·54 (s, 3 H, $COCH_3$). For $C_{16}H_{12}O_2S$ (268·3) calculated: 71·62% C, 4·51% H, 11·95% S; found: 71·98% C, 4·63% H, 11·92% S.

On continuing with the chromatography, elution was done with chloroform alone. A total of 5·43 g (24%) homogeneous compound was eluted which was identified as *Xd*; m.p. 86—88°C (benzene–light petroleum). UV spectrum: $\lambda_{max}$ 239 nm (log $\varepsilon$ 4·17), infl. 253 nm (4·03), 305 nm (4·01). IR spectrum (KBr): 770, 840, 880 (4 and 2 adjacent and solitary Ar—H), 1040 (CHOH in a ring), 1599 (Ar), 1688 ($ArCOCH_3$), 3410 $cm^{-1}$ (OH). NMR spectrum: $\delta$ 7·82 (bs, 1 H, 1—H), 7·10—7·70 (m, 6 H, remaining aromatic protons), 5·44 (dd, $J$ = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·68 and 3·30 (2 dd, $J$ = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·65 (s, disappears after $D_2O$, 1 H, OH), 2·52 (s, 3 H, $CH_3$). For $C_{16}H_{14}O_2S$ (270·4) calculated: 71·08% C, 5·22% H, 11·86% S; found: 71·16% C, 5·44% H, 11·92% S.

2-Acetyl-10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XId*)

A solution of 3·65 g *Xd* in 100 ml chloroform was combined with 3 g powdery $CaCl_2$ and the suspension was saturated for 1 h with anhydrous hydrogen chloride. After 48 h of standing,

it was filtered and the filtrate evaporated, yielding 3·80 g (97%) product which melts at 90—93°C; the analytical product melted at 93—94°C (cyclohexane). UV spectrum: $\lambda_{max}$ 238 nm (log $\varepsilon$ 4·22), infl. 254 nm (4·04), 307 nm (3·93). IR spectrum (KBr): 743, 760, 838, 895 (4 and 2 adjacent and solitary Ar—H), 1272 (C—O), 1575, 1600 (Ar), 1688 $cm^{-1}$ ($ArCOCH_3$). NMR spectrum: $\delta$ 7·86 (bs, 1 H, 1-H), 7·00—7·75 (m, 6 H, remaining aromatic protons), 5·80 (dd, $J$ = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 4·00 and 3·60 (2 dd, $J$ = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·52 (s, 3 H, $CH_3$). For $C_{16}H_{13}ClOS$ (288·8) calculated: 66·54% C, 4·54% H, 12·28% Cl, 11·10% S; found: 66·59% C, 4·72% H, 12·15% Cl, 11·12% S.

2-Acetyl-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*Id*)

A mixture of 3·65 g *XId*, 10 ml chloroform and 10 ml 1-methylpiperazine was refluxed for 6 h. After cooling, it was diluted with benzene and washed with water. The basic product was transferred into the aqueous phase by shaking with excess 5% hydrochloric acid. The benzene solution was washed with water, dried and evaporated. Crystallization of the residue from cyclohexane yielded 0·27 g elimination product, *i.e.* 2-acetyldibenzo[*b,f*]thiepin (*XIId*), m.p. 113 to 115°C. A previously reported[7] melting point for this compound was 112—114·5°C.

Treatment of the acid aqueous solution with 20% NaOH released the base *Id* which was isolated by extraction with benzene; 3·68 g (83%). The oily base was neutralized with 2·5 g maleic acid in ethanol and thus converted to bis(hydrogen maleate) which was precipitated by adding ether; 5·3 g (72% per starting *XId*), m.p. 106—108°C (ethanol–ether). For $C_{29}H_{32}N_2O_9S$ (584·7) calculated: 59·58% C, 5·52% H, 4·79% N, 5·48% S; found: 59·55% C, 5·72% H, 4·82% N, 5·57% S.

Decomposition of a sample of the pure salt with 20% NaOH released the base for measurement of spectra; m.p. 167—172°C (cyclohexane). UV spectrum: $\lambda_{max}$ 241 nm (log $\varepsilon$ 4·26), 317·5 nm (3·89). IR spectrum: 771, 831, 891 (4 and 2 adjacent and solitary Ar—H), 1569, 1592 (Ar), 1685 ($ArCOCH_3$) $cm^{-1}$. NMR spectrum: $\delta$ 7·00—8·00 (m, 7 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·55 (s, 3 H, $COCH_3$), 2·55 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, $NCH_3$).

11,11-Dinitrodibenzo[*b,f*]thiepin-10(11*H*)-one (*XIII*)

A mixture of 10 ml concentrated $H_2SO_4$ and 10 ml $HNO_3$ ($d$ = 1·42) was combined with 20 ml acetic acid and, over a period of 10 min at 10°C, with a solution of 9·0 g dibenzo[*b,f*]thiepin-10(11*H*)-one[12,13] in 50 ml acetic acid. The mixture was stirred for 50 min at 15°C, diluted with water, the precipitated product was filtered, dissolved in benzene, the solution was washed with 5% $NaHCO_3$, dried with $MgSO_4$ and evaporated. The oily residue crystallized from a mixture of benzene and light petroleum to 5·80 g (46%) product melting at 112—115°C; analytical sample melts at 115—117°C. UV spectrum: $\lambda_{max}$ 239 nm (log $\varepsilon$ 4·15), infl. 279 nm (3·79), 350 nm (3·24). IR spectrum (6% solution in $CHCl_3$): 895, 1306, 1355 ($NO_2$), 1585 (Ar), 1685 $cm^{-1}$ (COAr). NMR spectrum: $\delta$ 7·40—8·30 (m, aromatic protons). For $C_{14}H_8N_2O_5S$ (316·3) calculated: 53·16% C, 2·55% H, 8·85%N, 10·14% S; found: 53·27% C, 2·55% H, 8·29% N, 10·25% S.

On standing of the acid aqueous mother liquor, a total of 2·30 g acid precipitated and was crystallized from ethanol; m.p. 318—322°C with decomposition. It was identified as an ethanol solvate of diphenylsulfoxide-2,2′-dicarboxylic acid (*XIV*). IR spectrum: 768 (4 adjacent Ar—H), 977, 1290 (COOH), 1710 (ArCOOH), 3380 $cm^{-1}$ (OH). NMR spectrum ($C_5D_5N$): $\delta$ 10·95 (bs, COOH), 8·25 (m, 4 H, 3,6,3′,6′-$H_4$), 7·46 (m, remaining aromatic protons). For $C_{16}H_{16}O_6S$ (336·3) calculated: 57·14% C, 4·80% H, 9·51% S; found: 56·91% C, 5·00% H, 9·41% S. For comparison, acid *XIV* was prepared according to ref.[17] by oxidation of diphenylsulfide-2,2′-di-

carboxylic acid (m.p. 232—234°C; obtained by a reaction of 2-iodobenzoic acid with thiosalicylic acid in boiling aqueous solution of KOH in the presence of Cu; for other methods see *e.g.*[17,34,35]) with hydrogen peroxide in ethanol; m.p. 315—318°C with decomposition (aqueous ethanol). Ref.[17,34] report m.p. of 310—311°C and 312°C, respectively. No ethanol solvate has been described; in the present case it was apparently detected because the analytical sample was dried at room temperature.

2-[2-(Dinitromethyl)phenylthio]benzoic Acid (*XV*)

A mixture of 0·85 g *XIII*, 20 ml ethanol and 3 ml 20% NaOH was refluxed for 3 h. After evaporation of ethanol in vacuo the residue was diluted with water, the solution was filtered and the filtrate acidified with hydrochloric acid. The precipitated product was filtered and recrystallized from aqueous ethanol; 0·37 g (41%) orange crystals melting at 133—135°C. NMR spectrum: $\delta$ 9·80 (bs, disappears after $D_2O$, 1 H, COOH), 8·25 (m, 1 H, 6-H), 8·05 (s, 1 H, $ArCH(NO_2)_2$), 7·80 (m, 4 H, aromatic protons of dinitromethylphenyl), 7·31 (m, 2 H, 4,5-$H_2$), 6·55 (m, 1 H, 3-H). For $C_{14}H_{10}N_2O_6S$ (334·3) calculated: 50·30% C, 3·02% H, 8·38% N, 9·59% S; found: 50·32% C, 3·16% H, 8·37% N, 9·47% S.

Acid Hydrolysis of *XIII*

A mixture of 3·0 g *XIII*, 30 ml acetic acid and 6 ml concentrated hydrochloric acid was refluxed for 7 h. After dilution with water, a total of 1·9 g nonhomogeneous crystalline product precipitated and was separated into a neutral and an acid fraction with the aid of 10% soda solution. The undissolved neutral fraction was purified by repeated crystallization from acetic acid, m.p. 206—214°C. We are dealing here with thioxanthone (ref.[21,22] report a m.p. of 207°C, and of 210 to 215 and 212—214°C, repectively) which could not be fully freed of an unidentified admixture. UV spectrum: $\lambda_{max}$ 254 nm (log $\varepsilon$ 4·70) infl. 283 nm (3·70), infl. 296 nm (3·54), 375 nm (3·80). IR spectrum (KBr): 740 (4 adjacent Ar—H), 1595 (Ar), 1650 $cm^{-1}$ ($Ar_2CO$). NMR spectrum: $\delta$ 8·64 (m, 2 H, 1,8-$H_2$), 7·55 (m, 6 H, remaining aromatic protons). For $C_{13}H_8OS$ (212·2) calculated: 73·56% C, 3·80% H, 15·10% S; found: 72·58% C, 3·89% H, 14·81% S.

Acidification of the alkaline aqueous solution with hydrochloric acid led to the precipitation of a small amount of a yellow substance of acid character which was recrystallized from aqueous ethanol: m.p. 90—94°C. It is probably a monohydrate of 2-(2-formylphenylthio)benzoic acid (*XVI*). UV spectrum: $\lambda_{max}$ 255 nm (log $\varepsilon$ 4·10), 265 nm (4·07), infl. 289·5 nm (3·79), 375 nm (3·34). IR spectrum: 739 and 761 (4 adjacent Ar—H), 990, 1273 (COOH), 1670 (ArCOOH, ArCHO ?), 3425 and 3480 $cm^{-1}$ (OH and $H_2O$). NMR spectrum ($CD_3SOCD_3$): $\delta$ 7·15—8·00 (aromatic protons and others?). For $C_{14}H_{12}O_4S$ (276·2) calculated: 60·85% C, 4·38% H, 11·61% S; found: 61·53% C, 4·31% H, 11·83% S.

8-Chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one 5-Oxide (*XVIII*)

A solution of 5·24 g 8-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one[27,28] (*XVII*) in a mixture of 20 ml chloroform and 20 ml acetic anhydride was slowly added dropwise at —10°C and under stirring to a mixture of 1·25 ml $H_2SO_4$ and 1·25 ml fuming $HNO_3$. The mixture was stirred for 2 h at —10°C, poured into water and extracted with chloroform. The extract was washed with 5% $Na_2CO_3$ and water, dried with $MgSO_4$ and evaporated. The crystalline product was filtered after mixing with some ethanol; 4·4 g (80%) m.p. 175—177°C (benzene–ethanol). UV spectrum: $\lambda_{max}$ 250 nm (log $\varepsilon$ 4·11) (infl.), 303 nm (3·64). IR spectrum: 740, 820, 840, 901 (4 and 2 adjacent and solitary Ar—H), 1049 (S—O), 1558, 1579 (Ar), 1680 $cm^{-1}$ ($ArCOCH_2$). NMR spectrum

$\delta$ 8·18 (d, $J$ = 2·5 Hz, 1 H, 9-H), 8·10 (d, $J$ = 9·0 Hz, 1 H, 6-H), 7·30—8·00 (m, 5 H, remaining aromatic protons), 4·50 and 4·12 (ABq, $J$ = 15·0 Hz, 2 H, $ArCH_2CO$). For $C_{14}H_9ClO_2S$ (276·7) calculated: 60·76% C, 3·27% H, 12·81% Cl, 11·59% S; found: 60·56% C, 3·47% H, 12·41% Cl, 11·55% S.

11-Acetoxy-2-chloro-10-nitrodibenzo[*b*,*f*]thiepin (*XX*)

10·45 g of *XVII* (ref.[28]) in 160 ml acetic anhydride was added over a period of 10 min at —5°C to a mixture of 7 ml $HNO_3$ ($d$ = 1·42) and 20 ml acetic acid. The mixture was stirred for 1 h at 0—5°C, diluted with 1 litre water and, after 30 min of standing, shaken with chloroform and then filtered. The filtered substance of acid character was recrystallized from a mixture of benzene and ethanol; 2·56 g, m.p. 150—160°C; after solidification again at 250—254°C. The compound was characterized as an ethanol solvate of 4-chlorodiphenylsulfoxide-2,2'-dicarboxylic acid (*XIX*). UV spectrum: $\lambda_{max}$ 237 nm (log $\varepsilon$ 4·29), 280 nm (3·57). IR spectrum: 767, 802, 861 (4 and 2 adjacent and solitary Ar—H), 960, 1280, 1310 (COOH), 1050 (S—O), 1568, 1587 (Ar), 1692 (ArCOOH), 3250 and 3370 $cm^{-1}$ (OH). NMR spectrum ($CD_3SOCD_3$): $\delta$ 7·50—8·10 (m, aromatic protons), 3·45 (q, $CH_2$ of ethanol), 1·05 (t, $CH_3$ of ethanol). For $C_{16}H_{15}ClO_6S$ (370·8) calculated: 51·83% C, 4·08% H, 9·56% Cl, 8·65% S; found: 51·46% C, 4·42% H, 9·44% Cl, 8·65% S.

The chloroform solution was separated, washed with 5% $Na_2CO_3$ and water, dried and evaporated. On diluting the residue (7·8 g oil) with benzene, 0·75 g insoluble fraction was removed. Evaporation of the clear solution and crystallization of the residue from ethanol led to 1·5 g substance, characterized as *XX*, m.p. 174—175°C with decomposition (ethanol–benzene). UV spectrum: $\lambda_{max}$ 285 nm (log $\varepsilon$ 3·61). IR spectrum: 795, 871 (Ar—H), 1210 ($OCOCH_3$), 1378 and 1570 ($NO_2$) 1688 (C=C), 1785 $cm^{-1}$ (C=C—O—CO). NMR spectrum: $\delta$ 7·30—8·30 (m, 7 H, aromatic protons), 2·21 (s, 3 H, $OCOCH_3$). For $C_{16}H_{10}ClNO_4S$ (347·8) calculated: 55·26% C, 2·90% H, 10·19% Cl, 4·03% N, 9·22% S; found: 55·14% C, 3·04% H, 10·13% Cl, 4·18% N, 9·14% S.

2-Chloro-11-hydroxy-10-nitrodibenzo[*b*,*f*]thiepin (*XXI*)

A mixture of 235 mg *XX*, 10 ml ethanol and 3 drops of concentrated hydrochloric acid was refluxed for 3 h. It was then combined with 5 ml benzene and refluxing continued for 30 min. After partial evaporation it was cooled; 200 mg (97%) m.p. 246—248°C with decomposition (benzene–ethanol). UV spectrum: $\lambda_{max}$ 232·5 nm (log $\varepsilon$ 4·43), infl. 260·5 nm (4·01). IR spectrum: 747, 839, 859 (4 and 2 adjacent and solitary Ar—H), 1300, 1552 ($NO_2$), 1670 (C=C or ArCO), 3200 $cm^{-1}$ (OH). NMR spectrum ($CD_3SOCD_3$): $\delta$ 7·50—8·00 (m, aromatic protons). For $C_{14}H_8ClNO_3S$ (305·7) calculated: 55·00% C, 2·64% H, 11·60% Cl, 4·58% N, 10·49% S; found; 54·81% C, 2·75% H, 11·70% Cl, 4·36% N, 10·34% S.

10-Acetoxy-8-chlorodibenzo[*b*,*f*]thiepin (*XXII*)

Three drops of $H_2SO_4$ were added to a solution of 34·0 g ketone[28] *XVII* in 120 ml acetic anhydride and the mixture was refluxed for 2 h. After 1 h of standing, it was poured into water and the product was isolated by extraction with ether; 35·0 g (89%), b.p. 205—207°C/1·2 Torr, m.p. 107—109°C (benzene–light petroleum). UV spectrum: $\lambda_{max}$ 263 nm (log $\varepsilon$ 4·30), 294 nm (3·74). IR spectrum: 749, 823, 889 (4 and 2 adjacent and solitary Ar—H), 1203 (C—O), 1548, 1576 (Ar), 1639 (C=C), 1765 $cm^{-1}$ (C=C—O—CO). NMR spectrum: $\delta$ 7·10—7·60 (m, 7 H, aromatic protons), 6·98 (s, 1 H, Ar—CH=), 2·25 (s, 3 H, $CH_3$). For $C_{16}H_{11}ClO_2S$ (302·8)

calculated: 53·47% C, 3·66% H, 11·71% Cl, 10·59% S; found: 63·74% C, 3·82% H, 11·51% Cl, 10·46% S.

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