8-ACYL DERIVATIVES OF 10-(4-METHYLPIPERAZINO)-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN* **

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Received August 7th, 1973

Diazotization of 8-amino-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*X*), reaction of the diazonium salt with the semicarbazones of acetaldehyde and propionaldehyde, and subsequent hydrolysis were employed to prepare 8-acetyl- (*XI*) and 8-propionyl-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIII*) which were then converted to the methylpiperazine derivatives *I* and *II*. Reduction of the 8-cyano derivative *IV* with lithium aluminium triethoxyhydride led besides the 8-aminomethyl derivative *V* to the 8-formyl derivative *III*. The 8-aminocarbonyl derivative *VII* resulted as a by-product of the conversion of the 8-bromo derivative *VI* to the nitrile *IV* with the aid of cuprous cyanide in hexamethylphosphorphamide. Deamination of *V* with nitrous acid in acetic acid led to the alcohol *VIII* and to its acetate *IX*. The acyl derivatives *I*—*III*, alcohol *VIII* and ester *IX* are highly effective neuroleptics, particularly the 8-acetyl derivative *I*, displaying both a central depressant and a cataleptic activity.

It followed from the previous studies of the relationship between structure and neuroleptic activity in the series of 10-piperazinodibenzo[*b,f*]thiepin derivatives that there is a far-reaching analogy in the effects of the various substituents in the corresponding critical position of the aromatic ring in the present series and the series of phenothiazine derivatives[1,2]; in the present case it is position 8, in the case of phenothiazine derivatives position 2. In both series the substitution of the hydrogen atom in that position with halogen[3], a lower alkyl[4,5], alkoxyl[4,6], alkylthio group[4], trifluoromethyl[7], cyano group[8], nitro group[9] and dimethylsulfamoyl group[10] results in highly neuroleptically active compounds; it may be seen that the substituents belong to both the Ist and the IInd class, *i.e.* they possess either a positive or a negative inductive effect.

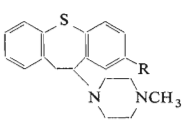
So far no information was available on the effect of the acyl group in position 8 on neuroleptic activity in our series. In the phenothiazine series the effect of the acyl group in position 2 is well known and, from the point of view of central activity, it is highly positive[1,2]. Practical application as major or minor tranquilizers, or as antipsychotic neuroleptics, is known for the 2-acyl derivatives, in particular acetyl-propionyl and butyryl derivatives, in all the series of phenothiazine agents, classified according to the side chain structure. Thus, in the promethazine series there

* Part LXXIII in the series Neurotropic and Psychotropic Agents; Part LXXII: This Journal *39*, 1596 (1974).

** Preliminary Communication appeared in Activitas Nervosa Super. *15*, 97 (1973).

are acepromethazine and propiomazine, in the promazine series acepromazine and propionylpromazine[11,12], in the perazine series butaperazine and valerylperazine[13–15], in the phenazine series acetophenazine and carphenazine[16,17] and finally in the series of piperidine derivatives it is piperacetazine[18]. It was the aim of the present communication to fill in the above-indicated gap in our knowledge and to describe the synthesis and pharmacology of the 8-acyl derivatives of perathiepin[19].

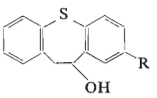
First of all, the synthesis of the 8-acetyl derivative (*I*) and of the 8-propionyl derivative (*II*) of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin was tackled. For their preparation the reaction of the known 8-cyano derivative[8] *IV* with the corresponding alkylmagnesium halogenides came into consideration but the poor availability of *IV* discouraged us from using this approach. For this reason, a synthesis from the relatively readily available 8-amino-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin[9,20] (*X*) was developed. This compound was diazotized in the usual way and the solution of the diazonium chloride, after cutting down the acidity with sodium acetate, was exposed to the semicarbazones of acetaldehyde[21] or propionaldehyde[22], under the catalysis of a mixture of cupric sulfate and sodium sulfite in the sense of the Beech method[23] of preparation of aromatic ketones. The crude reaction products were hydrolyzed by boiling with an aqueous solution of oxalic acid and then separated by chromatography on a column of alumina. An approximately 25% yield of 8-acyl alcohols *XI* and *XIII* was obtained, their identity being supported by analyses and spectra. In the case of the acetyl derivative chromatography yielded a very small amount of 10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin[24] (*XII*), formed ap-



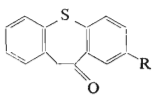
I, R = $COCH_3$
II, R = $COCH_2CH_3$
III, R = CHO

IV, R = CN
V, R = CH_2NH_2
VI, R = Br

VII, R = $CONH_2$
VIII, R = CH_2OH
IX, R = CH_2OCOCH_3



X, R = NH_2
XI, R = $COCH_3$
XII, R = H
XIII, R = $COCH_2CH_3$
XIV, R = CN
XV, R = $CONH_2$

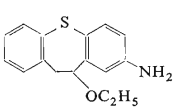


XVI, R = $COCH_3$
XVII, R = NH_2
XVIII, R = CN
XIX, R = Cl
XX, R = H
XXI, R = I
XXII, R = C_6H_5

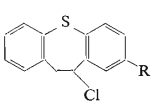
parently by the reduction of a small part of the diazonium salt with sulfur dioxide[25], and probably the diketone *XVI*, the origin of which is not clear. Likewise, during preparation of the propionyl derivative *XIII*, two by-products were detected, apparently merely modifications of the starting compound *X*. After hydrolysis of the crude product with aqueous oxalic acid a small amount of solid oxalate was obtained and recrystallized from ethanol. According to analysis and spectra it is the hydrogen oxalate of 8-amino-10-ethoxy derivative *XXIII* (etherification apparently takes place during crystallization of the compound). Another compound was detected as the most polar component during chromatography of the crude hydroxy ketone *XIII* on silica gel; it crystalizes from benzene and it was characterized as the benzene solvate of the original amino alcohol *X*.

Treatment of alcohols *XI* and *XIII* with hydrogen chloride in chloroform led to chlorides *XXIV* and *XXV* which were further processed by a reaction with excess 1-methylpiperazine in boiling chloroform. The main products obtained were the bases *I* and *II* which were purified in the form of maleates. The substitution reaction was accompanied only in a small extent by the elimination reaction, the products of which were also isolated and identified as 2-acetyldibenzo[*b,f*]thiepin (*XXVI*) and 2-propionyldibenzo[*b,f*]thiepin (*XXVII*).

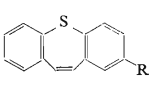
Since even the preliminary pharmacological tests revealed an exceptionally high degree of neuroleptic activity of *I* and *II*, the synthetic attempts were extended to include the formyl derivative *III*. An attempt at applying the Beech method[23] was unsuccessful in this case: after the reaction of the diazotized 8-amino-10-hydroxy--10,11-dihydrodibenzo[*b,f*]thiepin (*X*) with formaldoxime (prepared *in situ*[23]) the product could not be isolated even by chromatography. In this case we had to resort to the 8-cyano derivative *IV*[8] as the starting compound. The preparation of this compound and of the intermediates of its synthesis was conducted partly by novel methods. The starting compound was mostly the 8-aminodibenzo[*b,f*]thiepin--10(11*H*)-one[9,20] (*XVII*). Reaction of the corresponding diazonium chloride with cuprous-potassium cyanide[26] yielded a mixture of ketones which was separated either by crystallization or by chromatography. The desired cyano ketone[8] *XVIII* was obtained in a 23% yield; the other product to be isolated was the corresponding 8-chloro ketone[3] *XIX* formed by a normal Sandmeyer reaction caused by the pre-



XXIII



XXIV, R = $COCH_3$
XXV, R = $COCH_2CH_3$



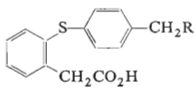
XXVI, R = $COCH_3$
XXVII, R = $COCH_2CH_3$
XXVIII, R = NH_2
XXIX, R = CN

sence of the chloride anions. Application of the diazonium sulfate in the place of chloride prevented the formation of *XIX* but, in its place, the reaction mixture contained the deaminated ketone[24] *XX* formed apparently by reduction of the diazonium salt with cuprous-potassium cyanide[25]. The cyano ketone *XVIII* was reduced to cyano alcohol *XIV* with sodium borohydride as described earlier[8]. Likewise, the further transformation of *XIV* to *IV* was carried out in two steps by a method described earlier[8].

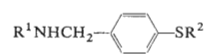
The preparation of the 8-cyano ketone *XVIII* just described is not readily feasible and hence another possibility was tested. The amino ketone[9,20] *XVII* can be diazotized and then reacted with potassium iodide and iodine to a fine yield of 8-iodo ketone[27] *XXI*. A by-product of the reaction was the 8-phenyl ketone *XXII*. Its formation can be accounted for on the basis of the fact that the reaction took place in the presence of benzene; it is somewhat surprising since ref.[28] reports that diazonium salts do not generally react with aromatics and that they must be first converted by treatment with alkali to diazohydroxides. The pure iodo ketone *XXI* reacts with cuprous cyanide in dimethylformamide at 150°C to the cyano ketone *XVIII* in a 62% yield. In a preparative way, it is more suitable to reduce first of all the iodoketone *XXI* with sodium borohydride to the previously described[27] 8-iodo-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin which reacts with cuprous cyanide in dimethylformamide to a 74% yield of the 8-cyano alcohol *XIV*. A by-product isolated in a small yield was the amide *XV* which is formed by hydration of the nitrile. In connection with this work, 2-aminodibenzo[*b*,*f*]thiepin[9] (*XXVIII*) was transformed into the described[8] 2-cyanodibenzo[*b*,*f*]thiepin (*XXIX*) by diazotization and Sandmeyer's reaction.

A novel method of preparing the 8-cyano derivative *IV* is represented by the reaction of the 8-bromo derivative[3] *VI* with cuprous cyanide in hexamethylphosphoramide at 130°C. The desired product is formed in a relatively poor yield and the mixture obtained requires chromatographic separation. Besides the least polar starting compound *VI*, a highly polar component of the mixture was identified as the amide *VII* monohydrate. To convert the nitrile *IV* to the aldehyde *III* reduction with lithium aluminium triethoxyhydride prepared *in situ* by a partial decomposition of lithium aluminium hydride with ethyl acetate[29] was employed. The reaction is highly influenced by the conditions used; when using excess reagent, *IV* is reduced smoothly to the aminomethyl derivative[8] *V*; when using less reagent, some of the compound remains unreduced. The mixture of the bases must be separated chromatographically to obtain the desired crude aldehyde *III* which was then isolated and purified as maleate. The aminomethyl derivative *V* obtained as by-product was worked up by deamination with nitrous acid in acetic acid. A mixture of bases was obtained which, after chromatography on alumina, yielded pure hydroxymethyl derivative *VIII* and acetoxymethyl derivative *IX*; both bases were prepared as maleates.

Another attempt at the preparation of alcohol *VIII* started by a condensation of 4-hydroxymethylthiophenol[30] with 2-(2-iodophenyl)acetic acid[20] in an aqueous solution of potassium hydroxide in the presence of copper which led to 2-(4-hydroxymethylphenylthio)phenylacetic acid (*XXX*). Attempts at protecting the hydroxyl group of the compound by acylation, as well as attempts at direct cyclization with polyphosphoric acid resulted only in polymeric substances. Likewise, the following experiment was unsuccessful. 4-Acetamidomethylbenzenesulfonyl chloride prepared according to ref.[31,32] was reduced with phosphorus and iodine in acetic acid (method[33]) to the novel 4-(acetamidomethyl)thiophenol (*XXXII*) which was condensed with 2-(2-iodophenyl)acetic acid to a low yield of the poorly crystallizing 2-(4-acetamidomethylphenylthio)phenylacetic acid *XXXI*. Further work was then abandoned. The thiophenol *XXXII* was alkylated with benzyl chloride and all the three isomeric chlorobenzyl chlorides and thus converted to the corresponding sulfides *XXXIII*–*XXXVI*. Alkaline hydrolysis of amide *XXXIII* yielded the primary amine *XXXVII*; reduction of amide *XXXIII* with lithium aluminium hydride yielded the secondary amine *XXXVIII*.



XXX, R = OH
XXXI, R = $NHCOCH_3$



XXXII, $R^1 = COCH_3$, $R^2 = H$
XXXIII, $R^1 = COCH_3$, $R^2 = CH_2C_6H_5$
XXXIV, $R^1 = COCH_3$, $R^2 = 2\text{-}CH_2C_6H_4Cl$
XXXV, $R^1 = COCH_3$, $R^2 = 3\text{-}CH_2C_6H_4Cl$
XXXVI, $R^1 = COCH_3$, $R^2 = 4\text{-}CH_2C_6H_4Cl$
XXXVII, $R^1 = H$, $R^2 = CH_2C_6H_5$
XXXVIII, $R^1 = CH_2CH_3$, $R^2 = CH_2C_6H_5$

The new piperazine derivatives *I*–*III* and *VII*–*IX* were tested pharmacologically with a view to the expected central depressant and neuroleptic activity (method[10]) in the form of salts, the values shown in Table I referring to the corresponding bases. Table I includes for reference clorotepin (octoclothepin), *i.e.* 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin[34] (applied as methanesulfonate) and further perphenazine[1,2]. In addition to tests of acute toxicity in mice on intravenous application, they were examined for their central depressant activity in the rotating rod test in mice (effect on motor coordination) after intravenous application, and for their neuroleptic activity in the test of catalepsy in rats after intraperitoneal application. The results are reported in the table both in the form of the usual mean lethal doses (LD_{50}) and in the form of mean effective doses (ED_{50}), always in mg/kg.

The values of Table I indicate that all the three 8-acyl derivatives of perathiepin (*I*–*III*) represent highly effective neuroleptics, the most effective being the acetyl derivative *I*, which is a four times more powerful depressant and a 2–3 times more powerful cataleptic agent than clorotepin. At the same time, it is almost twice more

toxic. A high degree of activity is also displayed by the primary alcohol *VIII* and by its acetate *IX* which are only slightly weaker than clorotepin. The amide *VII* is weaker by an order of magnitude.

Compounds *XXXIII* (*p.o.*, >2500, 300), *XXXVII*-HCl (*i.v.*, 70, 14) and *XXXVIII*-HCl (*p.o.*, 750, 150) were tested by the usual methods of pharmacological screening at the affiliated unit of this institute at Rosice n/L under the direction of Dr J. Němec (showing the mode of administration, orientative acute toxicity LD_{50} for mice and the dose D at which the compound was applied *in vivo*, alway in mg/kg). Compound *XXXIII* showed signs of anticonvulsant activity in mice, both in the pentetrazol and in the electro-shock test. For this reason, the chloro derivatives *XXXIV*—*XXXVI* were synthesized. The reported effect may be seen even there but only in high doses. Thus, *e.g.*, *XXXIV* (it is not toxic up to a *p.o.* dose of 4 g/kg in mice) has a ED_{50} in the corneal electro-shock test in male mice of 130 mg/kg *p.o.* This is considerably higher than with nitrazepam (8·5 mg/kg) and with phenobarbital (18 mg/kg) (Dr A. Dlabač). The hydrochlorides of *XXXVII* and *XXXVIII* show no central depressant activity. The first of these showed a nonspecific spasmolytic effect on rat duodenum against barium chloride contractions.

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 phosphorus pentoxide at room temperature. The UV spectra (in methanol unless stated otherwise) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200 G spectrophotometer or in an Infrascan (Hilger and Watts) spectrophotometer, the NMR spectra (in $CDCl_3$ unless stated otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer, the mass spectra in a MS 902 (AEI) mass spectrometer. The homogeneity of the compounds was checked by chromatography on a thin layer of silica gel. Preparative chromatography was done on alumina of activity II.

8-Amino-10-hydroxy-10,11-dihydrodibenzo[*b*,*f*]thiepin (*X*)

Reduction of 23·3 g 8-aminodibenzo[*b*,*f*]thiepin-10(11*H*)-one[9,20] (*XVII*) using a previously described procedure[9] yielded 15·6 g of product melting at 116—123°C (for the analytically

TABLE I

Pharmacological Properties of the New Piperazine Derivatives (in mg/kg)

Compound	Acute toxicity LD_{50} *i.v.*	Rotating rod ED_{50} *i.v.*	Catalepsy ED_{50} *i.p.*
I	17·2	0·016	0·93
II	26·0	0·044	3·5
III	30·5	0·115	2·7
VII	31·5	1·2	13·0
VIII	47·0	0·097	3·3
IX	43·0	0·152	3·5
Clorotepin	46·3	0·06	2·4
Perphenazine	46·0	0·60	1·3

pure product we reported earlier[9] a m.p. of 123—123·5°C) which rose on crystallization from benzene to 158·5—159·5°C. Analyses an spectra indicate that we are dealing here with a dimorphic modification of amino alcohol *X*. IR spectrum (KBr): 755, 764, 825, 883 (Ar—H), 1 036, 1 053, 1 066 (CHOH in the ring), 1 475, 1 603 (Ar), 3 400 (Ar—NH_2), 3 530 cm^{-1} (OH). NMR spectrum (CD_3COCD_3): δ 6·95—7·40 (m, 5 H, Ar—H in positions 1, 2, 3, 4 and 6), 6·89 (d, J = 2·5 Hz, 1 H, 9-H), 6·38 (q, J = 9·0, 2·5 Hz, 1 H, 7-H), 5·50 (m, 1 H, Ar—CH—O), 4·23 (bs, 3 H, disappears after D_2O, NH_2 and OH), 2·80—3·70 (m, 2 H, $ArCH_2$). For $C_{14}H_{13}NOS$ (243·2) calculated: 5·76% N, 13·16% S; found: 5·63% N, 12·89% S.

8-Acetyl-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XI*)

A solution of 3·4 g 95% $NaNO_2$ in 7 ml water was added dropwise at 3°C to a suspension of 11·3 g amino alcohol *X* in a solution of 45 ml concentrated hydrochloric acid in 135 ml water, the mixture was stirred for 1·5 h. Then an ice-cold solution of 50 g $CH_3CO_2Na.3\,H_2O$ in 50 ml water was added and the mixture formed was poured at once into a mixture of a solution of 20 g acetaldehyde semicarbazone[21] in 100 ml water and 25 g $CH_3CO_2Na.3\,H_2O$ in 30 ml water containing also 1·5 g $CuSO_4.5\,H_2O$ and 0·18 g Na_2SO_3. The solidifying mixture formed was stirred for 3 h, left to stand overnight at room temperature, made acid with 30 ml concentrated HCl and filtered to yield a red-brown precipitate. The substance was refluxed for 3 h with a solution of 40 g oxalic acid (dihydrate) in 200 ml water, the product was cooled and extracted with chloroform. Processing of the extract produced 9·8 g oil which was dissolved in benzene and chromatographed on a column of 440 g alumina. Elution with chloroform then yielded 2·0 g nonhomogeneous fractions and then 2·85 g of a practically homogeneous product, m.p. 120—121°C (benzene–light petroleum). UV spectrum: λ_{max} 241 nm (log ε 4·09), 254 nm (3·91), 306 nm (4·06). IR spectrum: 721, 752, 840, 900 (Ar—H), 1 042 (CHOH in the ring), 1 669 (Ar—CO—R), 3 505 cm^{-1} (OH). For $C_{16}H_{14}O_2S$ (270·3) calculated: 71·08% C, 5·22% H, 11·86% S; found: 71·13% C, 5·39% H, 11·63% S.

Chromatography of the nonhomogeneous fraction on a column of 100 g Al_2O_3 yielded after elution with benzene 0·1 g compound melting at 107—108·5°C (benzene) which is probably 8-acetyldibenzo[*b,f*]thiepin-10(11*H*)-one (*XVI*). UV spectrum: λ_{max} 225 nm (log ε 4·41), inflexion 250 nm (4·28), 295 nm (4·05), infl. 333 nm (3·89). IR spectrum: 750, 765, 842, 870 (Ar—H), 1 242 (CO), 1 550, 1 590 (Ar), 1 678 (Ar—CO in a seven-membered ring), 1 700 cm^{-1} ($ArCOCH_3$). For $C_{16}H_{12}O_2S$ (268·3) calculated: 71·62% C, 4·51% H, 11·95% S; found: 72·20% C, 4·78% H, 11·98% S. Continuation of chromatography and elution with chloroform yielded 0·27 g compound which was recrystallized from cyclohexane to melt at 98—99·5°C and identified as 10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XII*) for which earlier[24] a m.p. of 100°C was reported. NMR spectrum: δ 7·00—7·80 (m, 8 H, Ar—H), 5·26 and 5·40 (2 d, J = 8·0 and 3·0 Hz, 1 H, Ar—CH—O), 3·75 and 3·32 (2 dd, J = 14·0; 3·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·24 (bs, 1 H, disappears after D_2O, OH). For $C_{14}H_{12}OS$ (228·3) calculated: 73·65% C, 5·30% H, 14·04% S; found: 73·56% C, 5·22% H, 13·72% S. Continuation of elution with chloroform yielded a nonhomogeneous fraction (0·94 g) and then 0·59 g of practically pure hydroxy ketone *XI*.

8-Propionyl-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIII*)

As in the previous case, 13·5 g amino alcohol *X* in 50 ml concentrated HCl and 150 ml water was diazotized with 4·1 g 95% $NaNO_2$ in 10 ml water, the solution of the diazonium salt was neutralized with a solution of 55 g $CH_3CO_2Na.3\,H_2O$ in 50 ml water and poured into a mixture containing 25 g propionaldehyde semicarbazone[22], 25 g $CH_3CO_2Na.3\,H_2O$, 2·0 g, $CuSO_4.5\,H_2O$ and 0·24 g Na_2SO_3 in 165 ml water at 10°C. Analogous processing yielded after acidi-

fication with HCl a product which was filtered and refluxed for 3 h with a solution of 40 g oxalic acid in 200 ml water. After cooling, it was shaken with 200 ml chloroform and the mixture was left to stand for 48 h. Then it was filtered to yield 0·22 g precipitate which was purified by crystallization from ethanol; m.p. 126—128°C. It is a hydrogen oxalate of 8-amino-10-ethoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XXIII*). IR spectrum (KBr): 760, 837, 877, 898 (Ar—H), 1 037 (C—O—C), 1 540, 1 580 (Ar), 1 690 (COOH), 1 940 (NH_3^+), 3 420 cm^{-1} ($ArNH_2$). NMR spectrum (CD_3SOCD_3): δ 7·20—8·12 (m, 7 H, Ar—H), 5·80—7·20 (m, 4 H, disappears after D_2O, 2 CO_2H and NH_2), 5·41 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—O), 3·00—3·70 (m, 4 H, $ArCH_2$ and OCH_2), 1·06 (t, J = 6·0 Hz, 3 H, C—CH_3). For $C_{18}H_{19}NO_5S$ (361·4) calculated: 59·82% C, 5·30% H, 3·88% N, 8·87% S; found: 59·65% C, 5·45% H, 3·85% N, 9·26% S.

The chloroform solution was separated from the filtrate, washed with water, dried with $MgSO_4$ and evaporated. The residue (15 g) was dissolved in 50 ml benzene and the solution was chromatographed on a column of 500 g alumina. After separation of the less polar benzene eluates, 6·90 g of fractions containing mainly the desired product was collected. These fractions were rechromatographed on a column of 200 g silica gel using elution with chloroform. A total of 4·98 g of the desired hydroxy ketone *XIII* was obtained, m.p. 87—88°C (cyclohexane). UV spectrum: λ_{max} 241 nm (log ε 4·09), infl. 253 nm (3·93), 304 nm (4·07). IR spectrum: 742, 795, 880 (Ar—H), 1 052 (COH in the ring), 1 230 (C—O), 1 560 and 1 590 (Ar), 1 680 (Ar—CO—R), 3 260 cm^{-1} (OH). NMR spectrum: δ 8·06 (d, J = 2·0 Hz, 1 H, 9-H), 7·68 (q, J = 9·0; 2·0 Hz, 1 H, 7-H), 7·42 (d, J = 9·0 Hz, 1 H, 6-H), 6·90—7·50 (m, 4 H, aromatic protons in positions 1, 2, 3 and 4), 5·40 (m, after D_2O dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—O), 3·65 and 3·25 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$), 2·85 (q, J = 7·5 Hz, 2 H, $COCH_2$), 2·49 (d, J = 9·0 Hz, disappears after D_2O, 1 H, OH), 1·13 (t, J = 7·5 Hz, 3 H, C—CH_3). For $C_{17}H_{16}O_2S$ (284·4) calculated: 71·80% C, 5·67% H, 11·28% S; found: 72·04% C, 5·90% H, 11·36% S.

The most polar chromatographic fractions yielded 0·20 g crystalline substance melting at 192 to 192·5°C (benzene) which is apparently a benzene solvate of the parent amino alcohol *X*. IR spectrum: 748, 890 (Ar—H), 1 060 (CHOH in the ring), 1 600, 1 610 (Ar), 3 060 (C_6H_6), 3 240 cm^{-1} (OH). For $C_{20}H_{19}NOS$ (321·4) calculated: 74·73% C, 5·96% H, 4·36% N, 9·97% S; found: 75·19% C, 6·09% H, 4·38% N, 10·27% S.

8-Acetyl-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XXIV*)

Powdery $CaCl_2$ (2 g) was added to a solution of 2·5 g alcohol *XI* in 100 ml chloroform and the suspension was saturated for 3 h with a stream of anhydrous HCl. After standing overnight it was filtered, the filtrate was evaporated to dryness and the residue recrystallized from cyclohexane; 2·32 g (87%), m.p. 124—125°C. UV spectrum: λ_{max} 242·5 nm infl. (log ε 4·01), 305 nm (3·92). IR spectrum (KBr): 751, 772, 840, 910 (Ar—H), 1 261, 1 271 ($COCH_3$), 1 558, 1 600 (Ar), 1 680 cm^{-1} (Ar—CO). NMR spectrum: δ 8·11 (s, 1 H, 9-H), 7·10—7·85 (m, 6 H, remaining aromatic protons), 5·75 (dd, J = 5·0; 8·0 Hz, 1 H, Ar—CH—Cl), 3·50—4·10 (m, 2 H, $ArCH_2$), 2·50 (s, 3 H, $COCH_3$). For $C_{16}H_{13}ClOS$ (288·8) calculated: 66·54% C, 4·54% H, 12·28% Cl, 11·10% S; found: 66·98% C, 4·57% H, 12·24% Cl, 11·32% S.

8-Propionyl-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XXV*)

In analogy to the previous case, 4·2 g alcohol *XIII* yielded 3·72 g (83%) pure product melting at 143—145°C (benzene–cyclohexane). UV spectrum: λ_{max} 242·5 nm (log ε 4·12), 306 nm (3·99). IR spectrum: 750, 800, 840, 860 (Ar—H), 1 236 (C—O), 1 552 and 1 580 (Ar), 1 680 cm^{-1} (Ar—CO). NMR spectrum: δ 8·05 (d, J = 2·0 Hz; 1 H, 9-H), 7·68 (q, J = 9·0; 2·0 Hz, 1 H, 7-H), 7·42 (d,

J = 9·0 Hz, 1 H, 6-H), 7·10—7·50 (m, 4 H, remaining aromatic protons), 5·72 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·95 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$), 2·91 (q, J = 7·5 Hz, 2 H, $COCH_2$), 1·19 (t, J = 7·5 Hz, 3 H, $C—CH_3$). For $C_{17}H_{15}ClOS$ (302·8) calculated: 67·43% C, 4·99% H, 11·71% Cl, 10·59% S; found: 67·88% C, 4·92% H, 11·69% Cl, 10·88% S.

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

A mixture of 2·5 g chloride *XXIV*, 10 ml 1-methylpiperazine and 10 ml chloroform was refluxed for 8 h. After cooling, it was diluted with 100 ml water and extracted with 100 ml benzene. The extract was washed with water and then extracted with 100 ml 10% hydrochloric acid. Drying and evaporation of the benzene layer yielded 0·32 g 2-acetyldibenzo[*b,f*]thiepin (*XXVI*), m.p. 112—114·5°C (cyclohexane). UV spectrum: λ_{max} 221 nm (log ε 4·41), 247 nm (4·42), 258 nm (4·29). IR spectrum (KBr): 751, 839 and 898 (Ar—H), 787 (*cis* CH=CH), 1 278 ($COCH_3$), 1 556, 1 587 (Ar), 1 681 cm^{-1} (Ar—CO). NMR spectrum: δ 7·83 (m, 2 H, 1- and 3-H), 7·20—7·75 (m, 5 H, remaining protons of the benzene rings), 7·08 (s, 2 H, Ar—CH=CH—Ar), 2·59 (s, 3 H, $COCH_3$). For $C_{16}H_{12}OS$ (252·3) calculated: 76·16% C, 4·79% H, 12·71% S; found: 76·24% C, 5·00% H, 12·34% S.

The acid aqueous layer was made alkaline with NH_4OH and the crude base *I* was extracted with benzene; 2·26 g (74%) oil. Neutralization with maleic acid in ethanol yielded the maleate of base *I* which was crystallised from a mixture of ethanol and ether; m.p. 150—152°C. For $C_{25}H_{28}N_2O_5S$ (468·5) calculated: 64·09% C, 6·02% H, 5·98% N, 6·83% S; found: 63·51% C, 6·38% H, 5·84% N, 6·88% S. Decomposition of pure maleate with NH_4OH and extraction with ether yielded a sample of pure base *I* (oil) used then for analysis of spectra. UV spectrum: λ_{max} 236·5 nm (log ε 4·09), 261 nm infl. (3·92), 306 nm (3·96). IR spectrum (film): 733, 757, 820, 828 and 912 (Ar—H), 1 250 and 1 285 ($COCH_3$), 1 553 and 1 590 (Ar), 1 680 cm^{-1} (ArCO). NMR spectrum: δ 8·37 (d, J = 3·0 Hz, 1 H, 9-H), 7·00—7·80 (m, 6 H, remaining aromatic protons), 3·00—4·10 (m, 3 H, $ArCH_2CHAr$), 2·61 (m, 4 H, $CH_2N^1CH_2$), 2·50 (m, 4 H, $CH_2.N^4CH_2$), 2·50 (s, 3 H, NCH_3), 2·27 (s, 3 H, $COCH_3$).

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

In analogy to the preceding case, 3·64 g chloride *XXV* reacted with 15 ml 1-methylpiperazine in 15 ml chloroform, yielding first of all 0·47 g neutral elimination product, *i.e.* 2-propionyldibenzo[*b,f*]thiepin (*XXVII*), m.p. 78—80°C (cyclohexane). UV spectrum: λ_{max} 222 nm (log ε 4·47), 241 nm (4·50), 279 nm, (4·34). IR spectrum: 755, 800, 835, 888 (Ar—H), 788 (*cis*-CH=CH), 1 055, 1 236 (CO), 1 552, 1 588 (Ar), 1 688 cm^{-1} (ArCO). NMR spectrum: δ 7·80 (q, J = 9·0; 2·0 Hz, 1 H, 1-H), 7·75 (d, J = 2·0 Hz, 1 H, 3-H), 7·48 (d, J = 9·0 Hz, 1 H, 4-H), 7·10—7·50 (m, 4 H, remaining aromatic protons), 7·00 (s, 2 H, Ar—CH=CH—Ar), 2·89 (q, J = 7·5 Hz, 2 H, $COCH_2$), 1·16 (t, J = 7·5 Hz, 3 H, $C—CH_3$). For $C_{17}H_{14}OS$ (266·4) calculated: 76·66% C, 5·30% H, 12·04% S; found: 76·94% C, 5·22% H, 12·09% S. The main product obtained was 3·8 g (86%) of crude base *II* which was converted to crystalline maleate, m.p. 192—193°C (ethanol–ether). IR spectrum: 760, 800, 880 (Ar—H), 1 090 (COOH), 1 570 (COO^-), 1 620 (C=C of maleic acid), 1 683 cm^{-1} (Ar—CO). For $C_{26}H_{30}N_2O_5S$ (482·6) calculated: 64·71% C, 6·27% H, 5·80% N, 6·64% S; found: 64·30% C, 6·53% H, 5·84% N, 6·77% S.

8-Phenyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XXII*)

Using a previously described procedure[27] modified only by adding benzene to the diazonium salt solution before the solution of KI, 16·0 g 8-amino ketone[9,20] *XVII* reacted to 14·1 g crude 8-iodo ketone *XXI* which is only seemingly homogeneous on chromatography on a thin layer of silica gel. In fact it contains some 15% of another compound of about the same R_F. Crystallization from ethanol yielded pure 8-iodo ketone *XXI* melting at 115°C (for an analytically pure compound a m.p. of 115–117°C was reported[27]). Evaporation of the mother liquor and chromatography of the residue on a column of 100 g (Al_2O_3 led to the isolation of the above minor component (1·7 g) in a pure state; it was eluted with benzene as a rather nonpolar compound and identified as ketone *XXII*; m.p. 136–137°C (ethanol). UV spectrum (ethanol): λ_{max} 253 nm (log ε 4·42), 284 nm (4·26), 343 nm (3·56). IR spectrum ($CHCl_3$): 835, 910 (Ar—H), 1042, 1088, 1233, 1463, 1595 (Ar), 1670 cm^{-1} (Ar—CO). NMR spectrum: δ 8·51 (m, 1 H, 9-H), 7·00–7·90 (m, 11 H, remaining aromatic protons), 4·36 (s, 2 H, $ArCH_2$). For $C_{20}H_{14}OS$ (302·4) calculated: 79·44% C, 4·67% H, 10·60% S; found: 79·42% C, 4·82% H, 10·50% S.

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

A. A suspension formed by mixing 12·07 g amino ketone[9,20] *XVII* with 50 ml hydrochloric acid and 150 ml water was diazotized at 0–5°C by adding dropwise a solution of 3·7 g $NaNO_2$ in 10 ml water. The mixture was stirred for 1 h and then poured into a mixture of 12·5 g $CuSO_4.5\,H_2O$ in 50 ml water, 13·0 g KCN in 40 ml water, 20 ml 20% NH_4OH and 200 ml benzene. The stirring was continued for another hour, then the mixture was warmed to 50–65°C and stirred for further 2 h. After cooling, it was filtered, the solid was washed with boiling benzene, the benzene layers were combined, washed with 5% NaOH and with water, dried with $MgSO_4$ and evaporated. A total of 9·2 g oily mixture was obtained which was chromatographed on a column of alumina and eluted with benzene. The first fraction was 2·76 g 8-chlorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIX*), m.p. 123°C (for the pure compound a m.p. of 125°C was reported previously[3]), followed by 2·85 g (23%) desired ketone *XVIII*, m.p. 191°C (for an analytically pure compound a m.p. of 192–194°C was previously reported[8]).

B. A mixture of 10 ml H_2SO_4 and 20 ml water was combined with a solution of 7·24 g amino ketone[9,20] *XVII* in 30 ml dioxane at 70°C. It was then cooled, diazotized at 0–5°C with a solution of 2·5 g $NaNO_2$ in 5 ml water. The mixture was stirred for another 1·5 h and poured into a solution of 3·75 g $CuSO_4.5\,H_2O$, 3·9 g KCN and 30 ml 20% NH_4OH in 20 ml water. After heating for 10 min on a boiling-water bath it was cooled again and extracted with benzene. The extract was washed with a 5% solution of NaOH and water, dried with $MgSO_4$ and evaporated. From the oil obtained (4·9 g) 2·0 g of the starting amino ketone *XVII* (m.p. 181–185°C)[9,20] was isolated by crystallization. The mother liquor was evaporated and the residue was chromatographed on a column of 100 g alumina. The least polar product obtained was eluted with a mixture of benzene and light petroleum to yield dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XX*) in an amount of 0·58 g, m.p. 73–74°C (light petroleum). Previously a m.p. of 72–73°C had been reported for it[24]. NMR spectrum: δ 8·20 (m, 1 H, 9-H), 7·00–7·80 (m, 7 H, remaining aromatic protons), 4·28 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{10}OS$ (226·3) calculated: 74·31% C, 4·45% H, 14·17% S; found: 74·18% C, 4·47% H, 14·16% S. Continuation of the elution yielded 0·6 g cyano ketone *XVIII*, m.p. 190–191°C (benzene). For $C_{15}H_9NOS$ (251·2) calculated: 71·71% C, 3·61% H, 5·57% N, 12·74% S; found: 71·71% C, 3·68% H, 5·44% N, 12·54% S.

C. A mixture of 13·7 g pure iodo ketone *XXI*[27], 13·5 g CuCN and 60 ml dimethylformamide was heated under stirring for 5 h in a 150°C bath. After cooling, it was divided between water

and chloroform, filtered, the chloroform layer was separated, washed with water, dried and evaporated. The residue was chromatographed on a column of 350 g alumina. A mixture of benzene and chloroform eluted 6·07 g (62%) of the desired cyano ketone *XVIII*, m.p. 191—192·5°C, identical with the products prepared under *A* and *B*, and with compound prepared previously[8].

8-Cyano-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIV*)

A mixture of 15·3 g 8-iodo-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin[27], 15 g CuCN and 150 ml dimethylformamide was refluxed under stirring for 4 h. After cooling, it was diluted with water, benzene was added and the mixture filtered. The solid was extracted with warm benzene, the benzene layers were combined, dried with $MgSO_4$ and evaporated. The residue (11·0 g) was dissolved in ethanol, the solution was filtered while hot with charcoal and the filtrate was evaporated. After dissolving the residue (9·35 g) in a small volume of ethanol, 70 mg crystalline substance was obtained, apparently 8-(aminocarbonyl)-10-hydroxy-10,11-dihydrodibenzo-[*b,f*]thiepin (*XV*); m.p. 224—226°C (benzene–ethanol). IR spectrum (KBr): 760, 820 (Ar—H), 1 070 (CHOH in the ring), 1 570, 1 625, 1 683 ($CONH_2$), 3 200, 3 390 cm^{-1} (NH_2, OH). For $C_{15}H_{13}NO_2S$ (271·3) calculated: 66·39% C, 4·83% H, 5·16% N, 11·82% S; found: 65·73% C, 4·83% H, 4·74% N, 11·64% S. The filtrate after the previous compound was chromatographed on a column of 300 g alumina, eluting with a mixture of benzene and chloroform. The first to be eluted was the starting compound (0·20 g), followed by 8·05 g (74%) of the practically pure cyano alcohol *XIV*, the identity of which was demonstrated by a chromatographic comparison with a product obtained as described previously[8].

2-Cyanodibenzo[*b,f*]thiepin (*XXIX*)

A suspension of 3·5 g 2-aminodibenzo[*b,f*]thiepin[9] (*XXVIII*) in 35 ml water was combined with 5 ml H_2SO_4 and, after cooling to 0°C, it was diazotized with a solution of 1·18 g $NaNO_2$ in 10 ml water. The mixture was stirred for 45 min at 0—5°C and combined with a mixture of 1·4 g CuCN, 2·3 g NaCN and 10 ml water. After diluting with 150 ml water, it was heated on a boiling-water bath and the precipitated product was extracted after cooling with benzene. The extract was washed with a dilute solution of NaOH and shaken with dilute hydrochloric acid. This was accompanied by a precipitation of 1·0 g solid which was filtered and purified by crystallization from ethanol, m.p. 195—198°C under decomposition. It is apparently the hydrochloride of amine *XXVIII*. For $C_{14}H_{12}ClNS$ (261·8) calculated: 64·23% C, 4·62% H, 13·55% Cl, 5·35% N, 12·25% S; found: 64·02% C, 4·64% H, 13·45% Cl, 5·30% N, 12·15% S. The benzene layer was separated from the filtrate, washed with water and evaporated. From the residue, ethanol extraction and sublimation *in vacuo* yielded 0·70 g pure nitrile *XXIX*, m.p. 158—161°C, identical with the product prepared earlier by a different procedure (a m.p. of 160—161°C was shown)[8]. For C_{15}-$.H_9NS$ (235·3) calculated: 76·57% C, 3·85% H, 5·95% N; found: 76·60% C, 3·91% H, 5·65% N.

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

A mixture of 8·3 g 8-bromo-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin[3] (*VI*), 33 g CuCN and 80 ml hexamethylphosphoramide was heated under stirring for 28 h to 130°C. After cooling, it was diluted with an aqueous solution of KCN, shaken with benzene and filtered. The benzene layer was separated from the filtrate and shaken with 5% hydrochloric acid. The precipitate was filtered, combined with the acid aqueous phase of the filtrate, the suspension made alkaline with 20% NaOH and the bases were extracted with benzene (8·0 g oil). After dissolving in a small amount of ethanol, 1·43 g base *IV* crystallized from the mixture: m.p. 170 to to 173°C (previously[8] a melting point of 171—173°C was reported for the base). The mother liquor

was evaporated and chromatographed on a column of 400 g Al_2O_3. Using a mixture of benzene and chloroform, 0·99 g base *VI* was eluted first (m.p. 116—118°C; ref.[3] reports for the analytically pure compound a m.p. of 118—119°C), followed by 0·83 g of base *IV* with a m.p. of 172—174°C. Chloroform alone, its mixture with ether and ether alone, eluted 3·0 g nonhomogeneous fractions. Finally, a mixture of chloroform and ethanol was used for the elution, yielding 2·12 g of a very polar compound crystallizing from benzene but firmly retaining the crystal water; m.p. 127°C. It is the monohydrate of amide *VII*, as indicated, among other things, also by the mass spectrum. UV spectrum: λ_{max} 228·5 nm infl. ($\log \varepsilon$ 4·23), 288·5 nm (4·02). IR spectrum (KBr): 753, 810, 835 (Ar—H), 1 546, 1 595 (Ar, $CONH_2$), 1 620 (H_2O), 1 665, 3 120 ($CONH_2$), 3 230 cm^{-1} (H_2O). NMR spectrum: δ 8·06 (s, 1 H, 9-H), 6·80—7·50 (m, 6 H, remaining aromatic protons), 6·40 (bs, disappears after D_2O, 2 H, $CONH_2$), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·53 (m, 4 H, $CH_2N^1CH_2$), 2·40 (m, 4 H, $CH_2N^4CH_2$), 2·19 (s, 3 H, $N—CH_3$). For $C_{20}H_{25}N_3O_2S$ (371·4) calculated: 64·67% C, 6·78% H, 11·31% N, 8·62% S; found: 64·42% C, 6·89% H, 11·40% N, 8·82% S.

Dimethanesulfonate(dihydrate), m.p. 144—146°C (aqueous ethanol). For $C_{22}H_{35}N_3O_9S_3$ (581·7) calculated: 45·42% C, 6·06% H, 7·22% N, 16·54% S; found: 45·69% C, 5·93% H, 7·22% N, 16·05% S.

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

Ethyl acetate (13·2 g) in 20 ml ether was added dropwise at 0—5°C over a period of 90 min in a nitrogen atmosphere to a solution of 3·78 g $LiAlH_4$ in 120 ml ether. The mixture was stirred for further 30 min and, after cooling to —10°C, 3·25 g nitrile[8] *IV* in 40 ml tetrahydrofuran was added at once. The mixture was stirred for 5 h at room temperature, left to stand overnight and decomposed with 80 ml dilute hydrochloric acid (1 : 1) and filtered. The filtrate was combined with 100 ml benzene, the mixture was made alkaline with 20% NaOH, the precipitate was filtered and extracted with 100 ml ethanol. The benzene layer was separated from the filtrate, combined with the ethanol extract and evaporated. Chromatography of the residue on a column of 250 g alumina yielded after elution with chloroform 2·85 g pure base *V*, forming a tri(hydrogen maleate) hydrate melting diffusely at about 100°C (see ref.[8]). The aldehyde *III* was demonstrated in this experiment only qualitatively by thin-layer chromatography as a component of the first chromatographic fraction.

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

The reducing agent was prepared like in the preceding case by decomposition of 0·81 g $LiAlH_4$ in 30 ml ether with the aid of 2·91 g ethyl acetate in 15 ml ether. At —10°C, the reagent was combined with a solution of 3·60 g nitrile[8] *IV* in 45 ml tetrahydrofuran. After 6 h of stirring at room temperature the mixture was processed similarly to the preceding case. A total of 3·6 g base mixture was obtained and this was chromatographed on a column of 240 g Al_2O_3. Elution with a mixture of benzene and chloroform recovered first 1·49 g nitrile *IV*. A small intermediate fraction was followed by 0·90 g homogeneous compound, the aldehyde *III*. The base crystallizes slowly and in the crude state melts at 128—130°C. IR spectrum (KBr): 1 560, 1 598 (Ar), 1 700 and 2 820 cm^{-1} (CHO). NMR spectrum: δ 9·85 (s, 1 H, CHO), 8·10 (d, 1 H, aromatic 9-H), 7·00—7·80 (m, 6 H, remaining aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·60 and 2·40 (2 m, 8 H, CH_2 groups of piperazine), 2·25 (s, 3 H, NCH_3). Maleate, m.p. 192—195°C (acetone—ether). For $C_{24}H_{26}N_2O_5S$ (454·6) calculated: 63·52% C, 5·77% H, 6·16% N, 7·05% S; found: 63·26% C, 6·03% H, 6·13% N, 6·78% S. Chromatography was terminated by elution with chloroform which yielded 0·70 g aminomethyl derivative *V*.

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

A solution of 1·6 g $NaNO_2$ in 3 ml water was added dropwise to a solution of 2·58 g aminomethyl derivative *V* in 50 ml acetic acid at 10°C, the mixture was stirred for 1 h under cooling and then left to stand for 24 h at room temperature. After diluting with water, it was made alkaline with 20% NaOH and the base was extracted with benzene: 2·45 g oil. Thin-layer chromatography showed it to be a mixture of two components. Therefore, it was chromatographed first on a column of 200 g Al_2O_3, using elution with chloroform, and the nonhomogeneous fractions were rechromatographed on further 100 g Al_2O_3 using the more selective mixture of benzene and chloroform and then chloroform and ethanol for the more polar product. The less polar product obtained was 0·9 g 8-acetoxymethyl-10-(4-methylpiperazino)-10,11-dihydrodibenzo-[*b,f*]thiepin (*IX*) which yields a di(hydrogen maleate) melting at 136—136·5°C (ethanol–ether). For $C_{30}H_{34}N_2O_{10}S$ (614·7) calculated: 58·62% C, 5·58% H, 4·56% N, 5·22% S; found: 58·52% C, 5·77% H, 4·66% N, 5·50% S. The base obtained by decomposition of pure maleate by treatment with alkali and extraction with benzene had the following NMR spectrum: δ 6·70—7·55 (m, 7 H, aromatic protons), 4·90 (s, 2 H, $ArCH_2O$), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·55 and 2·43 (2 m, 8 H, CH_2 groups of piperazine), 2·22 (s, 3 H, N—CH_3), 2·01 (s, 3 H, $COCH_3$).

As a highly polar component the alcohol *VIII* was obtained in a 0·56 g yield. This was converted to the crystalline di(hydrogen maleate) solvated with 1/2 H_2O and melting at 132—134°C (ethanol–ether). In mixture with the preceding maleate the salt melts with a deep depression (at 90—100°C). For $C_{28}H_{33}N_2O_{9\cdot5}S$ (581·6) calculated: 57·82% C, 5·72% H, 4·82% N, 5·51% S; found: 57·69% C, 5·74% H, 4·81% N, 5·84% S. The NMR spectrum of the liberated base was the following: δ 6·85—7·55 (m, 7 H, aromatic protons), 4·46 (s, 2 H, $ArCH_2O$), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·38 (bs, disappears after D_2O, 1 H, OH), 2·55 and 2·40 (2 m, 8 H, CH_2 of piperazine), 2·18 (s, 3 H, N—CH_3).

2-(4-Hydroxymethylphenylthio)phenylacetic Acid (*XXX*)

4-Hydroxymethylthiophenol[30] (4·75 g m.p. 50°C) and 8·45 g 2-(2-iodophenyl)acetic acid[20] were successively dissolved in a solution of 6·65 g KOH in 60 ml water. After adding 0·4 g of molecular copper the mixture was refluxed under stirring for 7 h. It was filtered while hot and the filtrate was acidified after cooling with dilute hydrochloric acid. The crude product was purified by crystallization from benzene; 6·25 g (71%), m.p. 117—119°C. UV spectrum: λ_{max} 253 nm ($\log \varepsilon$ 4·13), infl. 273·5 nm (3·84). IR spectrum: 746, 800 (Ar—H), 1005 (CH_2OH), 1588 (Ar), 1695 (COOH), 3345 and 3390 cm^{-1} (OH). For $C_{15}H_{14}O_3S$ (274·3) calculated: 65·69% C, 5·15% H, 11·66% S; found: 65·84% C, 5·17% H, 11·61% S.

4-(Acetamidomethyl)thiophenol (*XXXII*)

A solution of 11·5 g 4-acetamidobenzenesulfonyl chloride[31,32] in 150 ml acetic acid was slowly added dropwise to a hot mixture of 130 ml acetic acid, 30 g red phosphorus and 2·5 g iodine. The mixture was refluxed for 3 h and, after adding 37 ml water, for another hour. After cooling, it was filtered and the filtrate was evaporated at reduced pressure. The residue was heated with 300 ml water for 1 h on a boiling-water bath and the mixture was left to stand overnight at room temperature. The crystalline product was filtered, washed with water and dried *in vacuo* over P_2O_5; 5·3·5 g (64%); after recrystallization from a mixture of ether, a small amount of ethanol and light petroleum, the compound melts at 95—97°C. NMR spectrum: δ 7·13 (s, 4 H, aromatic protons), 6·30 (deformed d, 1 H, NH), 4·27 (d, J = 6·0 Hz, 2 H, $ArCH_2$), 3·42 (s, disappears after D_2O, 1 H, SH), 1·93 (s, 3 H, $COCH_3$). For $C_9H_{11}NOS$ (181·2) calculated: 59·66% C, 6·12% H, 7·73% N, 17·66% S; found: 59·37% C, 6·04% H, 7·68% N, 17·56% S.

2-(4-Acetamidomethylphenylthio)phenylacetic Acid (*XXXI*)

Similarly to the preparation of *XXX*, 5·44 g thiophenol *XXXII* and 7·86 g 2-(2-iodophenyl)acetic acid[20] reacted in the presence of 6·8 g KOH and 1·0 g Cu in 80 ml water. The poorly crystallizing product was obtained in a yield of 2·0 g (21%); m.p. 193—196°C (aqueous ethanol). IR spectrum: 740, 764, 835 (Ar—H), 915, 1263, 2680 (COOH), 1532, 1553, 1626 cm^{-1} (CONHR). For $C_{17}H_{17}NO_3S$ (315·4) calculated: 64·74% C, 5·43% H, 4·44% N, 10·17% S; found: 64·36% C, 5·38% H, 4·73% N, 10·47% S.

N-(4-Benzylthiobenzyl)acetamide (*XXXIII*)

Sodium (3·55 g) was dissolved in 420 ml ethanol, the solution was combined with 28·0 g thiophenol *XXXII* and the mixture was stirred for 15 min at 70°C. After cooling to 20°C, 22·0 g benzyl chloride was added dropwise and the mixture was refluxed for 6 h. The precipitated salt was filtered while hot, the product crystallized from the filtrate on cooling; 27·2 g (65%), m.p. 138°C (ethanol). For $C_{16}H_{17}NOS$ (271·4) calculated: 70·81% C, 6·32% H, 5·16% N, 11·81% S; found: 70·77% C, 6·27% H, 5·02% N, 11·76% S.

N-[4-(2-Chlorobenzylthio)benzyl]acetamide (*XXXIV*)

Similarly to the preceding case, 10·0 g thiophenol *XXXII* reacted with 10·0 g 2-chlorobenzyl chloride to yield 16·0 g (95%) crude product which crystallizes from cyclohexane; m.p. 106 to 108°C. For $C_{16}H_{16}ClNOS$ (305·8) calculated: 62·84% C, 5·27% H, 11·60% Cl, 4·58% N, 10·48% S; found: 63·09% C, 5·40% H, 11·48% Cl, 4·45% N, 10·55% S.

N-[4-(3-Chlorobenzylthio)benzyl]acetamide (*XXXV*)

This was prepared similarly to the preceding cases from thiophenol *XXXII* and 3-chlorobenzyl chloride; m.p. 91—92°C (cyclohexane). NMR spectrum: δ 7·23 (s, 8 H, aromatic protons), 6·12 (bs, 1 H, NH), 4·31 (d, 2 H, $ArCH_2N$), 4·01 (s, 2 H, $ArCH_2S$), 1·96 (s, 3 H, $COCH_3$). For $C_{16}H_{16}ClNOS$ (305·8) calculated: 62·84% C, 5·27% H, 11·60% Cl, 4·58% N, 10·48% S; found: 62·87% C, 5·37% H, 11·74% Cl, 4·57% N, 10·58% S.

N-[4-(4-Chlorobenzylthio)benzyl]acetamide (*XXXVI*)

Similarly to the preceding cases, using 4-chlorobenzyl chloride; m.p. 155—156°C (ethanol). UV spectrum: λ_{max} 257 nm (log ε 3·94). IR spectrum: 840 (Ar—H), 1548, 1630, 1646 and 3285 cm^{-1} (CONHR). For $C_{16}H_{16}ClNOS$ (305·8) calculated: 62·84% C, 5·27% H, 11·60% Cl, 4·58% N, 10·48% S; found: 62·65% C, 5·21% H, 11·35% Cl, 4·57% N, 10·69% S.

4-(Benzylthio)benzylamine (*XXXVII*)

Amide *XXXIII* (8·0 g) was refluxed for 5 h with a solution of 8·0 g KOH in 20 ml ethanol in a 125°C bath. After evaporation of ethanol, the residue was divided between water and benzene. Processing of the benzene layer yielded 6·35 g (90%) crude base. *Hydrochloride*, m.p. 240—245°C (ethanol). For $C_{14}H_{16}ClNS$ (265·8) calculated: 63·26% C, 6·07% H, 13·34% Cl, 5·27% N, 12·06% S; found: 63·87% C, 6·27% H, 13·56% Cl, 5·19% N, 12·28% S.

N-Ethyl-4-(benzylthio)benzylamine (*XXXVIII*)

A suspension of 6·6 g amide *XXXIII* in a mixture of 30 ml tetrahydrofuran and 50 ml ether was added dropwise under stirring to a solution of 2·8 g $LiAlH_4$ in 60 ml ether. The mixture was refluxed for 5 h, cooled and decomposed by slowly adding 2·8 ml water, 2·8 ml 15% NaOH and 8·4 ml water. After filtering the solid, the filtrate was processed to yield 5·8 g (93%) oily base which was converted to the hydrochloride, m.p. 220–221°C (ethanol). For $C_{16}H_{20}ClNS$ (293·8) calculated: 65·40% C, 6·86% H, 12·06% Cl, 4·77% N, 10·91% S; found: 66·07% C, 7·05% H, 12·15% Cl, 4·64% N, 11·30% S.

The authors are indebted to Dr M. Ryska, Institute of Macromolecular Chemistry, Czechoslovak Academy of Sciences, Prague, for measuring the mass spectrum of VII. *Mrs H. Nováková and Mrs E. Princová assisted in the preparatory part of the work, the spectra were measured by Mrs P. Vejdělková. The analyses were carried out by Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová, Miss J. Hrdá, Mrs A. Slavíková, Miss Z. Volková and Mr M. Čech of the analytical department of this institute.*

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Translated by A. Kotyk.