POTENTIAL METABOLITES OF TRICYCLIC NEUROLEPTICS AND THEIR FLUORINATED ANALOGUES; 3-HYDROXY-, 3-METHOXY- AND 3-FLUORO-10-(4-METHYLPIPERAZINO)--10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN*

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4-Methoxy-2-(phenylthio)benzoic acid (*V*) was transformed in four steps to the homologous acid *IXa* which was cyclized to 3-methoxydibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Xa*). The 3-methoxy derivative *III* of perathiepin (*I*) was synthesized *via* the intermediates *XIa* and *XIIa*, and demethylated with boron tribromide to the phenolic compound *II*. The analogous 3-fluoro derivative *IV* was synthesized from (4-fluoro-2-iodophenyl)acetic acid (*XVII*), the preparation of which by several procedures is described. Whereas *III* has only mild tranquilizing activity, *II* is more potent than perathiepin (*I*) in the tests for central depressant and cataleptic effects. The 3-fluoro derivative *IV*, while lacking the properties of a neuroleptic agent, is highly central depressant and this effect shows some prolongation after oral administration.

Out of the potential hydroxylated metabolites of the neuroleptic and tranquilizing agent perathiepin (*I*) (ref.[1,2]), our group has described until now the 2-hydroxy[3], 6-hydroxy[4], 8-hydroxy[5] and 2,3-dihydroxy derivative[6]. In the meantime, information was lacking on the 3-hydroxy derivative *II* which became interesting in connection with the corresponding 3-hydroxy derivative of the neuroleptic agent octoclothepin[1,7]; this compound has been identified as a metabolite[8] and, moreover, it proved a higher degree of neuroleptic activity than the parent compound[9]. The present paper deals with the synthesis of the 3-hydroxy derivative *II* of perathiepin (*I*), proceeding *via* the methoxy compound *III*. Systematic investigations of the blockade of metabolic hydroxylation in the series of neuroleptic 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]-thiepins by fluorination[10,11] led at the same time to the interest in the 3-fluoro derivative *IV*, the synthesis of which is also described in this paper. The pharmacodynamic activity of this compound could be considered an indication whether the phenol *II* is or is not a perathiepin metabolite.

In the synthesis of compounds *II* and *III*, a similar procedure like in the preparation of the analogous octoclothepin derivatives[9] was used. 2-Iodo-4-methoxybenzoic

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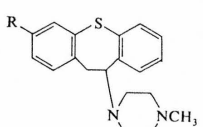
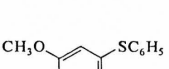
acid[9] was reacted with thiophenol in a boiling potassium hydroxide solution in the presence of copper to give 4-methoxy-2-(phenylthio)benzoic acid (*V*) which was reduced with sodium dihydridobis(2-methoxyethoxy)aluminate to the alcohol *VI*. This



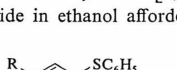
I, R = H
II, R = OH
III, R = OCH_3
IV, R = F

was converted *via* the chloride *VII* to the nitrile *VIII* using a method which was described for the transformation of 4-methoxybenzyl alcohol to 4-methoxyphenylacetonitrile[12]. Alkaline hydrolysis of the nitrile *VIII* afforded [4-methoxy-2-(phenylthio)phenyl]acetic acid (*IXa*).

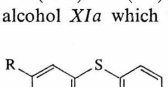


V, R = COOH
VI, R = CH_2OH
VII, R = CH_2Cl
VIII, R = CH_2CN

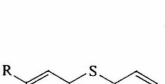
The acid *IXa* was cyclized with polyphosphoric acid in the presence of boiling toluene and gave 3-methoxydibenzo[*b*,*f*]thiepin10(11*H*)-one (*Xa*). Reduction with sodium borohydride in ethanol afforded the alcohol *XIa* which was transformed



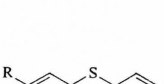
IX



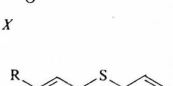
X



XI



XII



XIII

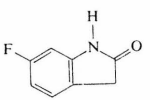
a, R = OCH_3
b, R = F

by treatment with hydrogen chloride in benzene to the chloride *XIIa*. A substitution reaction with 1-methylpiperazine in boiling chloroform resulted in the base *III* as the main product; in a small yield 3-methoxydibenzo[*b*,*f*]thiepin (*XIIIa*) (ref.[13]) was obtained. We are dealing here with the common product of the concomitantly proceeding elimination reaction. Demethylation of compound *III* was carried out similarly like in the analogous cases[3,4,6,9] by means of boron tribromide in chloroform; it was necessary to hydrolyze the primary product with sodium hydroxide in aqueous ethanol. The phenolic base *II* obtained is typical by a high melting point and its character of a zwitterion was proven by the IR spectrum; it could be transformed to crystalline salts (hydrobromide, dimethanesulfonate).

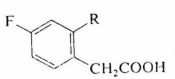
In the synthesis of the fluoro compound *IV*, (4-fluoro-2-iodophenyl)acetic acid (*XVII*) was chosen as the key intermediate. This compound proved also to be a suitable intermediate in the synthesis of the highly active 3-fluoro-8-substituted 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins[14–16]. For this reason, its preparation was investigated using several approaches. The first one started from 3-fluoroaniline, the preparation of which from 3-fluoronitrobenzene[17] (*cf.*[18–21]) was described using a series of reduction methods[20–24]. Reduction with iron in acetic acid, was found well suitable in our experiments. 3-Fluoroaniline was likewise found to be accessible by the Schmidt reaction from 3-fluorobenzoic acid by a procedure described for the preparation of 2-fluoroaniline[25]. The preparation of 3-fluorobenzoic acid by the Schiemann reaction from 3-aminobenzoic acid was described[26] but it proceeds with very low yields. We applied, therefore, the Schiemann reaction to methyl 3-aminobenzoate leading to methyl 3-fluorobenzoate which is volatile and more easily to be isolated; its alkaline hydrolysis afforded the required 3-fluorobenzoic acid. 3-Fluoroaniline was transformed by treatment with chloroacetyl chloride in pyridine to 1-chloroacetamido-3-fluorobenzene which was already mentioned in the literature[27]. Heating this compound with an excess of aluminium chloride to 200–210°C gave 6-fluoroxindole (*XIV*) (for a general method[28]). Compound *XIV* was hydrolyzed with an aqueous barium hydroxide solution (for analogy, *cf.*[29,30]) and the resulting solution of the barium salt of the amino acid *XVI* was transformed by treatment with carbon dioxide and sodium carbonate to an aqueous solution of the sodium salt of this acid. In an attempt to isolate the free acid *XVI* by acidification of the aqueous solution of the sodium salt with acetic acid, a backward cyclization to the oxindole *XIV* took partly place resulting in an inhomogeneous product. For this reason, the crude sodium salt of acid *XVI* was used for further work; diazotization and treatment of the diazonium salt solution with potassium iodide (for analogy in the non-fluorinated series, *cf.*[30]) afforded the required (4-fluoro-2-iodophenyl)acetic acid (*XVII*).

A further method of synthesis of the acid *XVII* started from 4-fluorotoluene which is easily nitrated to 4-fluoro-2-nitrotoluene[31]. The following reaction with diethyl oxalate in a solution of potassium ethoxide resulted in the potassium salt of ethyl

(4-fluoro-2-nitrophenyl)pyruvate which was oxidized with hydrogen peroxide in an alkaline solution to give (4-fluoro-2-nitrophenyl)acetic acid (*XV*) (mentioned in a patent[32]). Hydrogenation of this acid on palladium afforded again the amino acid *XVI* which has to be processed in a crude state.

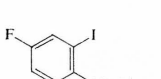


XIV

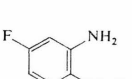


XV, R = NO_2
XVI, R = NH_2
XVII, R = I

4-Fluoro-2-nitrotoluene[31] may be reduced with hydrazine resulting in the known 2-amino-4-fluorotoluene[14], affording by diazotization and further reaction of the diazonium salt with potassium iodide 4-fluoro-2-iodotoluene (*XVIII*) (mentioned in patents[33]). Bromination with N-bromosuccinimide in tetrachloromethane in the presence of dibenzoyl peroxide and under illumination gave the bromo compound *XIX*, affording by treatment with sodium cyanide in dimethylformamide the nitrile *XX*. Its alkaline hydrolysis represents an alternative method for preparing the fluoroiodo acid *XVII*. In another connection, 3-fluoroacetanilide was nitrated according to the literature[34] to 5-fluoro-2-nitraniline. To this end, a solution of 3-fluoroacetanilide in a mixture of acetic anhydride and sulfuric acid was first prepared. In one case, this solution was allowed to stand to the other day; a crystalline compound separated and was identified as 2-amino-4-fluorobenzenesulfonic acid (*XXI*).



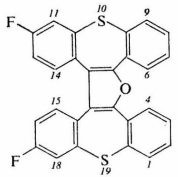
XVIII, R = H
XIX, R = Br
XX, R = CN



XXI

Reaction of the acid *XVII* with thiophenol in a boiling aqueous potassium hydroxide solution in the presence of copper gave the acid *IXb* which was cyclized with polyphosphoric acid at 120°C to 3-fluorodibenzo[*b*,*f*]thiepin-10(11*H*)-one (*Xb*). In an attempt to cyclize at 160°C, a high-melting substance was obtained, for which by analysis and mass spectrum the empirical formula $C_{28}H_{24}F_2OS_2$ was estimated. On the basis of analogy[30,35], we ascribe to this compound the structure of the

heptacyclic furan derivative *XXII* which is in agreement with the UV and IR spectra. By reduction of the ketone *Xb* with sodium borohydride, the alcohol *XIb* was obtained affording by treatment with hydrogen chloride the chloro compound *XIIb*. A substitution reaction with 1-methylpiperazine, carried our similarly like in the preparation of the base *III*, gave the base *IV*. As a by-product, 3-fluorodibenzo[*b*,*f*]-thiepin (*XIIIb*) was isolated and characterized.



XXII

Compounds *II*, *III* and *IV* were pharmacologically evaluated in the form of methanesulfonates. The doses given were calculated for bases. The compounds were administered orally to mice and rats; their acute toxicity in mice was estimated, further the incoordinating activity in the rotating rod test in mice (mean effective doses ED_{50} bringing about ataxia) and finally their cataleptic activity in rats (mean effective doses ED_{50}). The results are summarized in Table I including for comparison perathiepin (*I*) (ref.[1,2]) and its known monohydroxy and monofluoro derivatives which were tested on oral administration.

Values in the table show that the hydroxy derivative *II* has the same central depressant activity like perathiepin, but cataleptically, it is significantly more active. There thus appears the same relation as betweeen octoclothepin and its 3-hydroxy derivative[9]. The methoxy derivative *III* is weaker than perathiepin in the test of rotating rod and it is practically inactive in the catalepsy test. The compound was also tested for its antiapomorphine activity in rats. Whereas a dose of 25 mg/kg was completely inactive, a dose of 50 mg/kg did not influence the chewing, but it significantly reduced the apomorphine agitation in 60% animals in the group. It indicates the absence of the neuroleptic activity but proves a tranquilizing effect. The fluoro derivative *IV* is highly active as a central depressant but practically devoid of the cataleptic activity. In higher doses, ataxia lasts in 30% of mice for more than 24 hours. In the test of locomotor activity, followed by the photo-cell method, the compound is also highly active; the mean effective dose D_{50} is 0·48 mg/kg. This effect disappears within 24 hours. For an orientation evaluation of the antiapomorphine effect in rats,

an oral dose of 40 mg/kg was used. This dose does not influence the apomorphine chewing but reduces the apomorphine agitation to 78% of the control value (100%); this effect disappears within 24 hours. The compound has to be considered a rather potent tranquilizer which is devoid of the neuroleptic activity. In comparison with the neuroleptically highly and prolonged active 3-fluoro-8-substituted analogues[14-16], it appears that for attaining the high and prolonged neuroleptic activity, the presence of the fluorine atom in position 3 is not sufficient; the simultaneous presence of the ,,neuroleptic substituent" in position 8 is absolutely necessary.

When comparing the known monohydroxy derivatives of perathiepin, it is apparent that the 3-hydroxy derivative *II* differs from them by having neuroleptic activity; the 2-hydroxy and 6-hydroxy derivative are only weak tranquilizers. A direct comparison with the 8-hydroxy derivative of perathiepin[5] was not possible because this compound was evaluated only on parenteral administration.On intraperitoneal administration, it proved a considerable cataleptic activity indicating similarity with the 3-hydroxy derivative. Comparison of the monofluoro derivatives of perathiepin showed that the 3-fluoro derivative is the most active tranquilizer, the 2-fluoro and 8-fluoro compound are somewhat weaker in this respect but they have a clear cataleptic activity. The 6-fluoro derivative is the least active one showing cataleptic activity in toxic doses only. On the basis of the high tranquilizing activity of the

TABLE I

Pharmacological Effects of the 3-Substituted Derivatives of Perathiepin and Some Related Compounds (oral doses in mg/kg)

Compound[a]	Ref.	Name or code number	Acute toxicity LD_{50}	Ataxia ED_{50}	Catalepsy[b] ED_{50}
I	1, 2	Perathiepin	63	2·4	45
II	—	VÚFB-12.286	[c]	2·6	10
III	—	VÚFB-12.252	175	9·6	>100 (10)
IV	—	VÚFB-12.326	61	0·55	> 50 (10)
2-HO-I	3	VÚFB-12.285	550	15·5	>100 (0)
6-HO-I	4	VÚFB-10.508	175	5·1	> 50 (30)
2-F-I	36	VÚFB-10.002	78	3·5	38
6-F-I	37	VÚFB-12.489	54	3·1	>100 (40)
8-F-I	38	VÚFB- 6·271	102	3·3	20

[a] The compounds were tested in the form of salts (maleates, methanesulfonates); the doses given were calculated for bases. [b] The values in the parentheses indicate the percentage of the animals which were cataleptic after the dose given. [c] Was not estimated.

3-fluoro derivative *IV*, one can predict that the corresponding 3-hydroxy derivative *II* is a perathiepin metabolite. Blockade of the possibility of the metabolic 3-hydroxylation led to a substantial enhancement of the tranquilizing activity of *I*, and perathiepin (*I*), anyway, has to be considered rather as a tranquilizer than a neuroleptic agent.

Compounds *III* and *IV* in the form of salts were also tested for the antimicrobial activity *in vitro* (carried out by Dr J. Turinová and Dr A. Čapek, bacteriological department of this Institute). Microorganisms, number of compounds and the minimum inhibitory concentrations in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus β-haemolyticus*, *III* 50, *IV* 50; *Streptococcus faecalis*, *III* 100, *IV* 100; *Staphylococcus pyogenes aureus*, *IV* 50; *Pseudomonas aeruginosa*, *III* 100; *Mycobacterium tuberculosis* H37Rv, *III* 12·5, *IV* 12·5; *Saccaromyces pasterianus*, *III* 100; *Trichophyton mentagrophytes*, *III* 50, *IV* 50; *Candida albicans*, *III* 100.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were registered with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) were produced with a Tesla BS 487C (80 MHz) spectrometer, and ^{19}F-NMR spectra (in $CHCl_3$, $\delta_{CFCl_3} = 0$) with the same instrument. The mass spectrum was recorded on a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

4-Methoxy-2-(phenylthio)benzoic Acid (*V*)

Thiophenol (38 g) was added to a solution of 84 g KOH in 820 ml water, the mixture was stirred for 30 min at 55°C, then treated with 2·0 g „molecular" copper and 95 g 2-iodo-4-methoxybenzoic acid[9]; the mixture was refluxed for 7 h. It was then filtered while hot with 15 g charcoal and the filtrate was acidified with hydrochloric acid. The precipitated product was filtered, washed with, water and recrystallized from 1 600 ml ethanol; 53 g (60%), m.p. 221—222°C. Analytical sample m.p. 222—223°C (ethanol). For $C_{14}H_{12}O_3S$ (260·3) calculated: 64·59% C, 4·65% H, 12·32% S; found: 64·44% C, 4·78% H, 12·20% S.

4-Methoxy-2-(phenylthio)benzyl Alcohol (*VI*)

A suspension of 47 g *V* in 500 ml benzene was stirred and treated over 30 min with 146 ml 50% sodium dihydridobis(2-methoxyethoxy)aluminate solution in benzene. The solution obtained was stirred for 3 h at room temperature, decomposed under cooling with 360 ml 10% NaOH solution, added dropwise over 30 min. The aqueous layer was separated, extracted with benzene, benzene solutions were combined, washed with water, dried with $MgSO_4$ and evaporated under reduced pressure. The oily residue (40·5 g, 91%) is the crude product which is chromatographically homogeneous and was used for further work without purification. The analytical sample was purified by chromafography on a column of alumina (activity II); the product was eluted with benzene containing 2% ethanol and was analyzed as the oily residue obtained after the evaporation of the eluate *in vacuo*. For $C_{14}H_{14}O_2S$ (246·3) calculated: 68·26% C, 5·73% H; found: 67·80% C, 5·69% H.

[4-Methoxy-2-(phenylthio)phenyl]acetonitrile (*VIII*)

A mixture of 72 g *VI* and 80 ml hydrochloric acid was shaken for 15 min at room temperature. The emulsion formed was extracted with benzene, the extract was dried with $CaCl_2$ and evaporated. The residue (crude *VII*) was dissolved in 140 ml acetone, the solution treated with 21·5 g NaCN and 2·8 g NaI, and the mixture was stirred and refluxed for 20 h. After cooling, the solid was filtered off and washed with acetone. The filtrate was evaporated, the residue dissolved in benzene, the solution washed with water at 40°C, dried with $MgSO_4$ and evaporated; 73·5 g (98%) crude nitrile *VIII* which was used in this form for further work. A sample for analysis was distilled; b.p. 135—140°C/80 Pa. IR spectrum (film): 690, 741 (C_6H_5), 1 239, 1 248, 1 289 (ArOR), 1 480, 1 492, 1 573, 1 581, 1 600 (Ar), 2 252 (R—CN), 2 842 cm^{-1} (OCH_3). For $C_{15}H_{13}NOS$ (255·3) calculated: 70·56% C, 5·13% H, 5·49% N, 12·56% S; found: 70·05% C, 5·25% H, 5·23% N, 12·50% S.

3-Fluorobenzoic Acid

3-Nitrobenzoic acid (664 g) was refluxed (6 h) with 350 ml methanol and 20 ml H_2SO_4. Processing gave 650 g (90%) of methyl 3-nitrobenzoate, m.p. 78—79°C. The literature[39] reports m.p. 78°C for a product obtained by a different method. Methyl 3-nitrobenzoate (640 g) was reduced with 800 g Fe and 130 ml acetic acid in 500 ml water (2 h at 95°C). Processing gave 467 g (87%) of methyl 3-aminobenzoate, b.p. 168—170°C/2·7 kPa, m.p. 48—52°C. The literature[40] reported a m.p. of 49—52°C for a product prepared by a different way.

Methyl 3-aminobenzoate (59 g) was added to a stirred mixture of 100 ml water and 80 ml hydrochloric acid. The mixture was cooled to 0°C and the suspension of the hydrochloride was diazotized with a solution of 28·2 g $NaNO_2$ in 40 ml water. The diazonium salt solution was stirred and treated with 94 ml HBF_4 solution (prepared from 104 ml 40% H_2F_2 and 36·8 g H_3BO_3), the mixture was stirred for 30 min and the precipitated 3-methoxycarbonylbenzenediazonium fluoroborate was filtered, washed with methanol and ether, and dried *in vacuo*; 86 g (88%). It was decomposed by direct heating and the formed crude methyl 3-fluorobenzoate distilled at 180—200°C; 44·1 g (83%). The literature[41] reported for the pure ester prepared in another way, the b.p. of 192—194°C. A solution of 44·1 g crude ester in 40 ml ethanol was hydrolyzed by refluxing (1·5 h) with a solution of 22 g KOH in 50 ml water. The mixture was filtered while hot, the filtrate was cooled and acidified with hydrochloric acid; 27·9 g (70%) crude 3-fluorobenzoic acid, m.p. 121—123°C, useful for further work. The literature[26] reported for the pure acid a m.p. of 124°C.

3-Fluoroaniline

A. A mixture of 165 g 3-fluoronitrobenzene[17], 105 ml acetic acid, 425 ml water and 105 g powdered Fe was stirred and refluxed for 5 h (bath temperature of 125°C). During this time, additional 105 g Fe were added in five equal parts. After standing overnight, the mixture was made alkaline with 100 ml 30% NaOH solution and the product distilled with steam (4 l distillate). From the distillate, the product was extracted with ether, the extract was washed with 5% NaOH and water, dried with K_2CO_3 and distilled; 85·5 g (66%), b.p. 82°C/2·4 kPa. The literature[21] reported for a product obtained by catalytic hydrogenation a b.p. of 64—66°C/0·5 kPa.

B. A mixture of 210 ml H_2SO_4 and 105 g 3-fluorobenzoic acid was treated under stirring at 44—48°C over 3 h with 54·4 g NaN_3. The mixture was stirred for 12 h at 48°C, then poured on 1·5 kg ice, made alkaline with a solution of 300 g NaOH in 800 ml water and after cooling extracted with ether. The extract was dried with K_2CO_3 and distilled; 62·4 g (75%), b.p. 75°C/2 kPa.

1-Chloroacetamido-3-fluorobenzene

A solution of 111 g 3-fluoroaniline and 79 g pyridine in 600 ml benzene was stirred and treated at 5—10°C over 30 min with a solution of 113 g chloroacetyl chloride in 300 ml benzene, added dropwise. The mixture was stirred for 3 h at room temperature and allowed to stand for 24 h. The benzene layer was separated by decantation from the oily product and evaporated. The residue was combined with the oily product, dissolved in chloroform, the solution was washed with 2% hydrochloric acid and with water, it was dried with $CaCl_2$ and evaporated. The residue crystallized; 168 g (90%), m.p. 120—121°C. The literature[27] which did not disclose any experimental data about the preparation, reported for the product a m.p. of 122°C.

6-Fluoroxindole (*XIV*)

A mixture of 45·5 g 3-fluoro(chloroacet)anilide and 115 g powdered $AlCl_3$ was heated for 3·5 h to 200—210°C and the hot melt was decomposed with 150 g ice and 100 ml hydrochloric acid. After cooling, the crude product was filtered, dissolved in 300 ml ethanol and the solution filtered with charcoal. After evaporation *in vacuo*, the residue was crystallized from 950 ml water; 34·5 g (94%), m.p. 136—138°C. Recrystallization from water gave the analytical sample, m.p. 139 to 141°C. IR spectrum: 839, 890 (2 adjacent and solitary Ar—H), 1503, 1613 (Ar), 1658, 1725 (CONH), 3150 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 9·70 (bs, 1 H, NH), *c.* 7·10 (m, 1 H, 7-H), *c.* 6·60 (m, 2 H, 4,5-H_2), 4·48 (mcs, 2 H, $ArCH_2CO$). ^{19}F-NMR: —113·6 (m). For C_8H_6FNO (151·1) calculated: 63·57% C, 4·00% H, 12·57% F, 9·27% N; found: 63·50% C, 4·13% H, 12·06% F, 9·24% N.

(4-Fluoro-2-nitrophenyl)acetic Acid (*XV*)

Potassium (23·4 g) was dissolved in a mixture of 100 ml ethanol and 320 ml ether in a nitrogen atmosphere, the solution was cooled to 10°C and treated with a solution of 62 g 4-fluoro-2-nitrotoluene[31] and 87·6 g diethyl oxalate in 100 ml toluene. The mixture was stirred for 5 h, allowed to stand for 48 h at room temperature and the precipitated potassium ethyl (4-fluoro-2-nitrophenyl)pyruvate was filtered with suction. It was dissolved in 500 ml water, the solution was washed with ether, filtered with charcoal, treated with 100 ml 20% NaOH and in 5 min intervals with 6 equal parts of 60 ml 30% H_2O_2 (the temperature kept by external cooling below 40°C). The mixture was stirred for 5 h, allowed to stand for 48 h and acidified with hydrochloric acid. The precipitated crude product (containing some oxalic acid) was crystallized from water; 27·0 g (34%), m.p. 158—160°C. UV spectrum: λ_{max} 255 nm (log ε 3·70), infl. 292 nm (3·31). IR spectrum: 818, 838, 890 (2 adjacent and solitary Ar—H), 910, 1259 (COOH), 1365, 1545 ($ArNO_2$), 1715, 2570, 2650, 2680, 2760 (COOH), 3129 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 7·90 (mcd, J_{H-F} = 9·0 Hz, 1 H, 3-H), *c.* 7·58 (m, 2 H, 5,6-H_2), 3·90 (s, 2H, $ArCH_2CO$). For $C_8H_6FNO_4$ (199·1) calculated: 48·25% C, 3·04% H, 9·54% F, 7·03% N; found: 48·44% C, 3·06% H, 9·31% F, 7·40% N.

(2-Amino-4-fluorophenyl)acetic Acid (*XVI*)

A. A mixture of 47·7 g *XIV*, 90 g $Ba(OH)_2.8\ H_2O$ and 400 ml water was refluxed for 24 h. The mixture was diluted with 800 ml water and saturated at 50°C with CO_2 until neutral reaction was reached (phenolphthalein). After the addition of a small excess of a 15% Na_2CO_3 solution, the mixture was filtered and the filtrate evaporated *in vacuo*. The residue was mixed with a small amount of acetone, filtered and dried *in vacuo*; 60·3 g crude Na salt of *XVI* which was used for further work.

B. XV (43·0 g) was dissolved in a solution of 10 g NaOH in 300 ml water, 5·0 g 10% Pd on charcoal were added and the mixture hydrogenated at room temperature and atmospheric pressure. After the theoretical consumption of hydrogen (5·5 h), the catalyst was filtered off and the filtrate directly used for transformation to the acid *XX*.

2-Amino-4-fluorotoluene

A solution of 222 g 4-fluoro-2-nitrotoluene[31] in 800 ml ethanol was treated with 142 ml 80% hydrazine hydrate, 15 g charcoal and a solution of 5·0 g $FeCl_3$ in 50 ml ethanol. The mixture was stirred and refluxed for 10 h, filtered and ethanol was evaporated *in vacuo*. The residue was extracted with benzene, the extract was dried with Na_2SO_4 and distilled; 158 g (89%), b.p. 92°C/1·6 kPa. For the same compound, prepared in another way, we reported[14] a b.p. of 95°C/2 kPa.

4-Fluoro-2-iodotoluene (*XVIII*)

2-Amino-4-fluorotoluene (68 g) was added at 50°C to a stirred mixture of 700 ml water and 100 ml hydrochloric acid, the mixture was cooled to 0—5°C and diazotized at this temperature with a solution of 46 g $NaNO_2$ in 100 ml water. The ice-cold diazonium salt solution was added over 1 h to a stirred solution of 157 g KI in a mixture of 250 ml water and 25 ml H_2SO_4. The mixture was stirred and heated for 2 h to 100°C. After cooling, the mixture was separated by decantation from iodine and the product was extracted with benzene. The extract was washed with a solution of $Na_2S_2O_3$, 5% NaOH and water, dried with $MgSO_4$, filtered with charcoal and distilled; 105 g (83%), b.p. 92—95°C/2·3 kPa. For analysis, the product was redistilled, b.p. 88—90°C/2kPa. For C_7H_6FI (236·0) calculated: 35·62% C, 2·56% H, 8·05% F, 53·77% I; found: 35·92% C, 2·76% H, 7·79% F, 54·03% I. Patents[33] report the b.p. of 67—68°C/60 Pa.

4-Fluoro-2-iodobenzyl Bromide (*XIX*)

A solution of 23·6 g *XVIII* in 50 ml CCl_4 was treated with 0·2 g dibenzoyl peroxide and 19·6 g N-bromosuccinimide and the mixture was refluxed for 6 h under illumination with a 220 W bulb. After cooling, succinimide was filtered off, washed with CCl_4 and the filtrate was distilled; 24·8 g (78%), b.p. 130—140°C/2·7 kPa. The crude product (strongly lachrymatory) was crystallized from light petroleum, m.p. 71—73°C. For C_7H_5BrFI (314·9) calculated: 26·69% C, 1·60% H, 25·37% Br, 6·03% F, 40·30% I; found: 26·67% C, 1·65% H, 25·55% Br, 6·25% F, 40·08% I.

(4-Fluoro-2-iodophenyl)acetonitrile (*XX*)

A solution of 57 g *XIX* in 150 ml dimethylformamide was treated with 28 g NaCN and the mixture was heated under stirring for 8 h to 105—110°C. After cooling, NaBr was filtered off, washed with dimethylformamide and the filtrate evaporated *in vacuo*. The residue was mixed with 1 l water and the product extracted with benzene. The extract was washed with water, dried with $MgSO_4$, filtered with charcoal and distilled; 39·6 g (80%), b.p. 160°C/2·7 kPa, m.p. 45—47°C. Analytical sample was obtained by crystallization from a mixture of benzene and light petroleum, m.p. 52—53°C. IR spectrum: 779, 829, 861, 870 (2 adjacent and solitary Ar—H), 1 223 (Ar—F), 1 481, 1 591, 3 072 (Ar), 2 240, 2 258 cm^{-1} (R—CN). For C_8H_5FIN (261·0) calculated: 36·81% C, 1·93% H, 7·28% F, 48·62% I, 5·36% N; found: 37·18% C, 2·18% H, 7·51% F, 48·73% I, 5·51% N.

(4-Fluoro-2-iodophenyl)acetic Acid (*XVII*)

An attempt to apply the method of Taylor and coworkers[42] was not successful: Treatment of (4-fluorophenyl)acetic acid[43] with thallic trifluoroacetate in trifluoroacetic acid, followed by KI in water led to a mixture from which none individual product could be isolated.

A. Crude Na salt of *XVI* (43·6 g) and 16·6 g $NaNO_2$ were dissolved in 350 ml water and the solution was added dropwise over 2 h to a stirred mixture of 100 ml hydrochloric acid and 100 ml water at 0—5°C. The diazonium salt solution was then treated with a solution of 57·4 g KI in 100 ml water, the mixture was stirred for 2 h at room temperature and allowed to stand overnight. It was then heated to 100°C and iodine was removed by steam distillation. From the cooled residue, the aqueous layer was separated by decantation from the product which was dissolved in 300 ml benzene. The solution was washed with 150 ml 10% $NaHSO_3$ solution, filtered and evaporated under reduced pressure. The residue was crystallized from aqueous ethanol; 22·4 g (35%), m.p. 105—106°C. Recrystallization from aqueous ethanol gave the analytical sample, m.p. 110—113°C. IR spectrum: 798, 831, 862 (2 adjacent and solitary Ar—H), 899, 1172, 1230, 1379 (COOH), 1482, 1590 (Ar), 1670, 1700, 3150 cm^{-1} (COOH); in $CHCl_3$ only one band in the carbonyl region at 1703 cm^{-1} corresponding to COOH. ^{1}H-NMR spectrum: δ 10·40 (bs, 1 H, COOH), 7·75 (mcd, J = 8·0; 2·0 Hz, 1 H, 3-H), 6·85—7·40 (m, 2 H, 5,6-H_2), 3·80 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR: δ —113·9 (dt). For $C_8H_6FIO_2$ (280·0) calculated: 34·31% C, 2·16% H, 6·78% F, 45·32% I; found: 34·06% C, 2·24% H, 6·60% F, 44·96% I.

B. A solution of 38·5 g *XX* in 200 ml ethanol was treated with a solution of 41·5 g KOH in 170 ml water and the mixture was refluxed for 12 h. Ethanol was evaporated under reduced pressure, the residue diluted with water and the solution washed with benzene. After filtration with charcoal, the filtrate was acidified with dilute hydrochloric acid. The precipitated product was filtered, washed with water and dried *in vacuo*; 34 g (82%) pure acid, m.p. 112—114°C.

2-Amino-4-fluorobenzenesulfonic Acid (*XXI*)

A solution of 30·6 g 3-fluoroacetanilide[34] in 40 ml acetic anhydride and 20 ml H_2SO_4 was allowed to stand overnight. The precipitated solid was filtered and a sample recrystallized repeatedly from water; m.p. 318—323°C with decomposition. UV spectrum: λ_{max} 250 nm (log ε 4·22), 282 nm (3·41). IR spectrum: 830, 880 (2 adjacent and solitary Ar—H), 1030, 1190, 1210, 1250 ($ArSO_3H$), 1490, 1559, 1562, 1600 (Ar), 1614 ($ArNH_2$), 2618, 2680 (NH_3^+), 3082 (Ar), 3108, 3180 cm^{-1} (NH_2). ^{1}H-NMR spectrum: δ 8·80 (bs, 3 H, SO_3H and NH_2), 7·70 (m, 1 H, 3-H), 7·00 (m, 2 H, 5,6-H_2). For $C_6H_6FNO_3S$ (191·2) calculated: 37·69% C, 3·16% H, 9·94% F, 7·33% N, 16·77% S; found: 37·98% C, 3·11% H, 10·16% F, 7·23% N, 16·89% S.

[4-Methoxy-2-(phenylthio)phenyl]acetic Acid (*IXa*)

A solution of 73·5 g *VIII* in 504 ml ethanol was treated with a solution of 97 g KOH in 110 ml H_2O and the mixture was refluxed for 8 h. Ethanol was evaporated under reduced pressure, the residue was diluted with water, the solution filtered with charcoal and the filtrate acidified with hydrochloric acid. The crude acid obtained (58·5 g, m.p. 70°C) was purified *via* the aqueous solution of the Na salt and pure acid obtained by its acidification; 54 g (69%), m.p. 84—89°C. Analytical sample was obtained by crystallization from aqueous ethanol, m.p. 94—96°C. IR spectrum: 696, 749, 758, 802, 890 (5 and 2 adjacent and solitary Ar—H), 929, 1054 (COOH), 1250 (ArOR), 1489, 1500, 1563, 1602 (Ar), 1710, 2640 cm^{-1} (COOH). For $C_{15}H_{14}O_3S$ (274·3) calculated: 65·67% C, 5·14% H, 11·69% S; found: 66·13% C, 5·26% H, 11·73% S.

[4-Fluoro-2-(phenylthio)phenyl]acetic Acid (*IXb*)

Thiophenol (6·7 g) was added to a stirred solution of 11·2 g KOH in 50 ml H_2O, the mixture was treated with 0·4 g Cu and 17 g *XVII* and refluxed under stirring for 7 h. After cooling, the mixture was filtered with charcoal and the filtrate was acidified with dilute hydrochloric acid. After standing overnight, the precipitated product was filtered and crystallized from aqueous ethanol; 10·0 g (63%), m.p. 105—110°C. Analytical sample, m.p. 114—115°C (aqueous ethanol). IR spectrum: 693, 750, 805, 885 (5 and 2 adjacent and solitary Ar—H), 925, 1 245 (COOH), 1 480, 1 580 (Ar), 1 710, 2 660, 2 750 (COOH), 3 070 cm^{-1} (Ar). For $C_{14}H_{11}FO_2S$ (262·3) calculated: 64·10% C, 4·23% H, 7·24% F, 12·23% S; found: 64·00% C, 4·23% H, 7·10% F, 12·58% S.

3-Methoxydibenzo[*b,f*]thiepin-10(11*H*)-one (*Xa*)

A mixture of 57 g *IXa*, 170 g polyphosphoric acid and 220 ml toluene was stirred and refluxed for 6 h. After cooling to 50°C, it was decomposed with ice and water and extracted with toluene. The extract was washed with 5% NaOH and water, dried with K_2CO_3 and evaporated. The residue (50·5 g, 95%) crystallized slowly on standing, m.p. 91—94°C. Analytical sample was obtained by recrystallization from a mixture of benzene and light petroleum, m.p. 99—100°C. UV spectrum: λ_{max} 235 nm (log ε 4·34). 255 nm (4·09), 290 nm (3·52), 327 nm (3·60). IR spectrum (KBr): 776, 781, 813, 883 (4 and 2 adjacent and solitary Ar—H), 1 118, 1 246, 1 296 (ArOR), 1 498, 1 504, 1 605 (Ar), 1 673 (Ar—CO), 2 849 ($ArOCH_3$), 3 000, 3 055, 3 085 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 8·15 (m, 1 H, 9-H), 7·20—7·70 (m, 3 H, 6,7,8-H_3), 7·28 (d, J = 8·0 Hz, 1 H, 1-H), 7·14 (mcs, J = 2·5 Hz, 1 H, 4-H), 6·85 (mcd, J = 8·0; 2·5 Hz, 1 H, 2-H), 4·22 (s, 2 H, $ArCH_2CO$), 3·71 (s, 3 H, OCH_3). For $C_{15}H_{12}O_2S$ (256·3) calculated: 70·28% C, 4·72% H, 12·51% S; found: 70·50% C, 4·73% H, 12·53% S.

3-Fluorodibenzo[*b,f*]thiepin-10(11*H*)-one (*Xb*)

A mixture of 8·0 g *IXb* and 130 g polyphosphoric acid was stirred and heated for 2 h to 120°C. After decomposition with ice and water, the product was isolated by extraction with benzene and the extract was processed like in the preceding case; 7·3 g (99%), m.p. 120—122°C. Analytical sample, m.p. 127—128°C (benzene). UV spectrum: λ_{max} 238 nm (log ε 4·27), infl. 265 nm (3·96), 325 nm (3·73). IR spectrum: 753, 811, 841, 877 (4 and 2 adjacent and solitary Ar—H), 1 480, 1 586 (Ar), 1 680 cm^{-1} (Ar—CO). ^{1}H-NMR spectrum: δ 8·20 (m, 1 H, 9-H), 6·90—7·70 (m, 6 H, remaining ArH), 4·30 (s, 2 H, $ArCH_2CO$). ^{19}F-NMR: δ −114·9 (dt). For $C_{14}H_9FOS$ (244·3) calculated: 68·83% C, 3·71% H, 7·77% F, 13·13% S; found: 68·72% C, 3·74% H, 7·57% F, 13·15% S.

12,17-Difluorobisdibenzo[2,3;6,7]thiepino[4,5-*b*;4′,5′-*d*]furan (*XXII*)*

A mixture of 9·5 g *IXb* and 155 g polyphosphoric acid was stirred and heated for 2·5 h to 160°C. The mixture was decomposed with 500 g ice and water and extracted with chloroform. The extract was washed with 5% NaOH and water, dried with K_2CO_3, filtered with charcoal and the filtrate evaporated. The residue was mixed with some ether and filtered; 4·5 g (53%), m.p. 330—340°C. Analytical sample, m.p. 352—354°C (benzene). The mass spectrum with the molecular ion *m/e*

* A new name for the system and its numbering is introduced in accord with a recent authoritative publication[44] and at variance with our previous papers[30,35].

468·057 determined the formula $C_{28}H_{14}F_2OS_2$. UV spectrum (saturated solution): λ_{max} 258 nm, infl. 310 and 325 nm. IR spectrum: 740, 764, 770, 825, 861, 891 (4 and 2 adjacent and solitary Ar—H), 1209, 1255 (=C—O—C=), 1489, 1552, 1571, 1590 cm^{-1} (Ar). For $C_{28}H_{14}F_2OS_2$ (468·5) calculated: 71·78% C, 3·01% H, 8·11% F, 13·69% S; found: 71·66% C, 3·25% H, 8·44% F, 13·80% S.

3-Methoxy-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIa*)

A solution of 10·0 g *Xa* in 180 ml ethanol was stirred and treated at 70°C over 5 min with a solution of 0·55 g $NaBH_4$ in 5 ml water containing 0·1 ml 20% NaOH. The mixture was reflexed for 3 h, ethanol was distilled off, the residue decomposed with 100 ml water and extracted with benzene. The extract was washed with 3% NaOH and water, dried with $MgSO_4$, filtered with charcoal and evaporated under reduced pressure. The residue (10·1 g, 100%) crystallized on standing and was recrystallized from a mixture of benzene and light petroleum; m.p. 64—66°C. IR spectrum: 755, 818, 848, 879 (4 and 2 adjacent and solitary Ar—H), 1030 (CHOH in a ring), 1242 ($ArOCH_3$), 1492, 1598 (Ar), 3350 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·80—7·50 (m, 6 H, 1,4,6,7,8,9-H_6), 6·65 (mcd, J = 8·0; 3·0 Hz, 1 H, 2-H), 5·20 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·60 and 3·28 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 3·72 (s, 3 H, OCH_3), 2·15 (bs, 1 H, OH). For $C_{15}H_{14}O_2S$ (258·3) calculated: 69·74% C, 5·46% H, 12·41% S; found: 69·86% C, 5·54% H, 12·30% S.

3-Fluoro-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XIb*)

Xb (8·7 g) in 140 ml) ethanol was reduced like in the preceding case with 0·5 g $NaBH_4$ in 5 ml water and gave 7·0 g (80%) product, m.p. 92—93°C (benzene–light petroleum). IR spectrum: 762, 820, 861, 893 (4 and 2 adjacent and solitary Ar—H), 1043, 1051 (CHOH in a ring), 1492, 1590, 1601 (Ar), 3210 cm^{-1} (OH). For $C_{14}H_{11}FOS$ (246·3) calculated: 68·27% C, 4·50% H, 7·71% F, 13·02% S; found: 68·17% C, 4·58% H, 7·59% F, 12·91% S.

10-Chloro-3-methoxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XIIa*)

XIa (8·5 g) was dissolved in 75 ml benzene at 50°C, the solution was cooled to 20°C and saturated for 4 h with anhydrous HCl in the presence of 7·0 g $CaCl_2$ powder. After filtration with charcoal, the filtrate was evaporated under reduced pressure; 8·5 g (93%), m.p. 95—98°C. Analytical sample, m.p. 101—103°C (benzene–light petroleum). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 6 H, 1,4,6,7,8,9-H_6), 6·85 (mcd, J = 8·0; 3·0 Hz, 1 H, 2-H), 5·70 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·90 and 3·62 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 3·72 (s, 3 H, OCH_3). For $C_{15}H_{13}ClOS$ (276·8) calculated: 65·09% C, 4·73% H, 12·81% Cl, 11·59% S; found: 65·05% C, 4·59% H, 13·04% Cl, 11·32% S.

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

A solution of 8·0 g *XIb* in 60 ml benzene was processed like in the preceding case; 7·5 g (94%), m.p. 102—103°C (benzene–light petroleum). ^{1}H-NMR: δ 6·70—7·60 (m, 7 H, Ar—H), 5·70 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·95 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$). For $C_{14}H_{10}ClFS$ (264·7) calculated: 63·51% C, 3·82% H, 13·39% Cl, 7·17% F, 12·11% S; found: 63·36% C, 3·80% H, 13·62% Cl, 7·02% F, 12·40% S.

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

A mixture of 7·5 g *XIIa*, 12 ml chloroform and 8·1 g 1-methylpiperazine was refluxed for 6 h. After diluting with 200 ml benzene, the solution was washed with 50 ml 2·5M-NaOH and with water. The base was then transferred by shaking with an excess of 1·25M-H_2SO_4 into the aqueous phase, the solution was separated, made alkaline with NH_4OH and the base extracted with benzene. The extract was washed with ether, dried with $MgSO_4$ and evaporated; 7·0 g (77%), m.p. 119—122°C. Analytical sample, m.p. 124—125°C (benzene–light petroleum). ^{1}H-NMR spectrum: δ 6·90—7·60 (m, 6 H, 1,4,6,7,8,9-H_6), 6·68 (mcd, J = 8·0; 3·0 Hz, 1 H, 2-H), 3·00—4·10 (m, 3 H, $ArCH_2CHAr$), 3·70 (s, 3 H, OCH_3), 2·60 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·18 (s, 3 H, NCH_3). For $C_{20}H_{24}N_2OS$ (340·5) calculated: 70·55% C, 7·10% H, 8·23% N, 9·42% S; found: 71·03% C, 7·31% H, 8·28% N, 9·34% S.

Neutralization with an equivalent of methanesulfonic acid in ethanol gave a sesquimethanesulfonate crystallizing from 95% ethanol as a hemihydrate, m.p. 174—176°C. For $C_{20}H_{24}N_2OS + 1{\cdot}5\ CH_4O_3S + 0{\cdot}5\ H_2O$ (493·6) calculated: 52·31% C, 6·33% H, 5·67% N, 16·24% S, 29·21% CH_3SO_3H; found: 52·43% C, 6·40% H, 5·40% N, 16·34% S, 29·71% CH_3SO_3H.

Evaporation of the original organic layer, containing neutral products, gave 1·2 g crude 3-methoxydibenzo[*b,f*]thiepin (*XIIIa*), m.p. 74—76°C (light petroleum). It melts without depression with a sample obtained previously[13] for which a m.p. of 78—80°C was reported.

3-Fluoro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*IV*)

A mixture of 7·0 g *XIIb*, 11 ml chloroform and 8·0 g 1-methylpiperazine was processed like in the preceding case; 7·3 g (84%) base, m.p. 110—112°C. Analytical sample, m.p. 114—115°C (ethanol). ^{1}H-NMR spectrum: δ 6·70—7·70 (m, 7 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·65 (t, 4 H, $CH_2N^1CH_2$ of piperazine), 2·45 (t, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3). For $C_{19}H_{21}FN_2S$ (328·4) calculated: 69·48% C, 6·44% H, 5·78% F, 8·53% N, 9·76% S; found: 69·58% C, 6·41% H, 5·75% F, 8·40% N, 9·96% S.

Dimethanesulfonate, m.p. 180—181°C (ethanol). For $C_{21}H_{29}FN_2O_6S_3$ (520·7) calculated: 48·44% C, 5·61% H, 3·65% F, 5·38% N, 18·48% S; found: 48·02% C, 5·50% H, 3·71% F, 5·49% N, 18·30% S.

As the neutral product, 1·0 g 3-fluorodibenzo[*b,f*]thiepin (*XIIIb*) was obtained; m.p. 71—72°C (light petroleum). UV spectrum: λ_{max} 260·5 nm (log ε 4·39), 292·5 nm (3·66). ^{1}H-NMR spectrum: δ 6·70—7·50 (m, Ar—H and CH=CH). For $C_{14}H_9FS$ (228·3) calculated: 73·66% C, 3·97% H, 8·32% F, 14·05% S; found: 73·36% C, 3·98% H, 8·58% F, 13·96% S.

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

A solution of 6·8 g *III* in 20 ml chloroform was stirred and treated over 10 min at 20°C with a solution of 15 g BBr_3 in 10 ml chloroform, added dropwise. The mixture was stirred for 5 h at room temperature, allowed to stand overnight, chloroform was evaporated and the residue hydrolyzed by refluxing (1 h) with 40 ml ethanol and 5 ml 20% NaOH. Ethanol was evaporated, the residue was dissolved in dilute hydrochloric acid and the solution made alkaline with $NaHCO_3$; 3·0 g crude base *II* which was crystallized from a mixture of benzene, ethanol and light petroleum, m.p. 211—214°C. IR spectrum (KBr): 748, 778, 809, 851 (4 and 2 adjacent and solitary Ar—H), 1134, 1150, 1250, 1261 (ArOH), 1498, 1582, 1600 (Ar), 2575, 2665 (NH^+), 3425 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 9·40 (bs, 1 H, OH), 6·90—7·60 (m, 5 H, 1,6,7,8,9-H_5), 6·80 (mcs, J = 2·0 Hz, 1 H, 4-H), 6·58 (mcd, J = 8·0; 2·0 Hz, 1 H, 2-H), 2·80—4·00 (m, 3 H, $ArCH_2CHAr$), 2·40 (m, $CH_2N^1CH_2$ of piperazine), 2·18 (t, 4 H, $CH_2N^4CH_2$ of piperazine),

2·00 (s, 3 H, NCH_3). For $C_{19}H_{22}N_2OS$ (211·4) calculated: 69·92% C, 6·79% H, 8·58% N, 9·82% S; found: 69·94% C, 6·95% H, 8·08% N, 9·75% S.

Dimethanesulfonate, m.p. 197—199°C (aqueous ethanol–ether). For $C_{21}H_{30}N_2O_7S_3$ (518·7) calculated: 48·63% C, 5·83% H, 5·40% N, 18·55% S; found: 48·52% C, 5·99% H, 5·42% N, 18·34% S.

Hydrobromide, m.p. 232—233°C with decomposition (ethanol–benzene). For $C_{19}H_{23}BrN_2OS$ (407·4) calculated: 56·02% C, 5·69% H, 19·62% Br, 6·88% N, 7·87% S; found: 56·04% C, 5·80% H, 19·67% Br, 6·96% N, 7·78% S.

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