HIGHLY POLAR POTENTIAL METABOLITES OF THE NEUROLEPTIC AGENT OXYPROTHEPIN: SYNTHESIS OF 2-HYDROXY-8-METHYLSULFONYL AND 3-HYDROXY-8-METHYLSULFONYL DERIVATIVES OF 10-[4-(3-HYDROXYPROPYL)PIPERAZINO]--10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN

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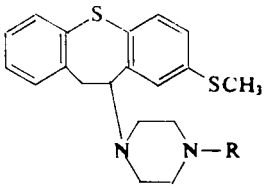
Received June 26th, 1984

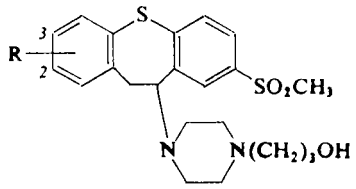
The acid *XI*, obtained by reaction of (2-iodo-5-methoxyphenyl)acetic acid with 4-(methylsulfonyl)-thiophenol (*VIII*) in dimethylformamide in the presence of potassium carbonate and copper, was transformed *via* intermediates *XIIa*–*XIVa* to compound *XVa*. Demethylation with boron tribromide afforded compound *III*, the potential metabolite of oxyprothepin (*II*). Its oxidation with hydrogen peroxide in acetic acid gave the sulfoxide *XVII*, which is a further potential metabolite. A reaction of 2-iodo-4-methoxybenzoic acid with *VIII* and potassium carbonate in dimethylformamide in the presence of copper afforded the acid *XIX* whose ester *XXI* was reduced with diborane to the alcohol *XXII*; hydrogenolysis to compound *XXIII* was also observed. The alcohol *XXII* was processed *via* compounds *XXIV* and *XXV* to the acid *XXVI* which was cyclized in a low yield to the ketone *XIIb*. A further processing *via* the intermediates *XIIIb* and *XIVb* led to compound *XVb*. Demethylation gave compound *IV*, another potential metabolite.

Combination of gas chromatography and mass spectrometry, used in the metabolic study[1] of the neuroleptic agent methiothepin (*I*) (ref.[2]) in rats, dogs and men, could prove totally 38 metabolites out of which 15 are sulfones. With regard to the fact that a similar situation was to be expected with the neuroleptic oxyprothepin (*II*) (ref.[3,4]) and also with oxyprothepin decanoate[5], we have carried out the synthesis of 8 sulfones[6] which could be oxyprothepin metabolites. Until now no 8-sulfones derived from oxyprothepin (*II*) were known, which would simultaneously be hydroxylated in the benzene ring. In the case of methiothepin metabolism[1] at least 8 such compounds were characterized in a preliminary way, out of which one "hydroxy 8-sulfone" was the main metabolite in dog faeces, and a further one, "hydroxy 5-oxide 8-sulfone", was found in the dog urine. In order to fill up the mentioned gap and to prepare conditions for a successful metabolic investigation of oxyprothepin (*II*) with the use of the GC-MS technique, we have now carried out the syntheses of the 2-hydroxy 8-sulfone *III* and the 3-hydroxy 8-sulfone *IV* derived from oxyprothepin (*II*).

For preparing a common thiol intermediate, we started from the reduction of 4-(methylsulfonyl)nitrobenzene (*V*) (ref.[7-9]) to 4-(methylsulfonyl)aniline (*VI*) (ref.[7,8]), which was carried out with hydrazine hydrate in boiling ethanol in the presence of iron(III) chloride and active carbon (*cf.*[10]). In a small batch, this method gave a very good yield but in a larger batch, 4-(methylsulfinyl)aniline (*IX*) (ref.[11,12]) was isolated as a by-product. We are not aware of any other case of the reduction of a sulfone to a sulfoxide with hydrazine. A very useful way of preparing 4-(methylsulfonyl)aniline (*VI*) proved to be the reaction of 4-(methylsulfonyl)bromobenzene (*VII*) (ref.[13,14]) with aqueous ammonia in the autoclave at 200°C (a similar reaction of 4-(methylsulfonyl)chlorobenzene was described[15]). The preparation of 4-(methylsulfonyl)thiophenol (*VIII*) was described by reaction of compound *VII* with sodium disulfide and by the following reduction with glucose[14] and a patent[16] mentioned the preparation of compound *VIII* from the amine *VI* by the xanthate method[17,18].

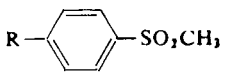


I, R = CH_3
II, R = $(CH_2)_3OH$

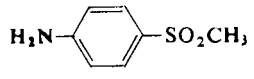


III, R = 2-OH
IV, R = 3-OH

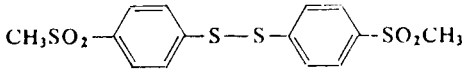
In Experimental, the synthesis of compound *VIII* by the last mentioned method is described; the disulfide *X* was isolated as a by-product and afforded by reduction with glucose[14] a further quantity of the desired thiol *VIII*. It is interesting to note that the disulfide *X* was isolated prior to the alkaline hydrolysis of the arylxanthate intermediate.



V, R = NO_2 *VII*, R = Br
VI, R = NH_2 *VIII*, R = SH

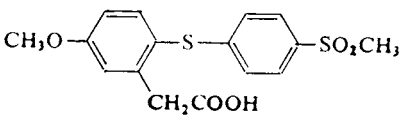


IX



X

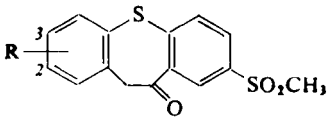
For continuing the synthesis of compound *III*, the preparation of [5-methoxy--2-(4-methylsulfonylphenylthio)phenyl]acetic acid (*XI*) had to be elaborated. The compound was first obtained by reaction of (2-iodo-5-methoxyphenyl)acetic acid[19] with *VIII* in a boiling aqueous potassium hydroxide in the presence of copper but the yield was 50% only. The acid aqueous filtrate evidently contained the unreacted thiol *VIII* because its evaporation and extraction with chloroform gave a mixture from which crystallization afforded in the first line the disulfide *X* (evidently resulting from the thiol *VIII* by processing under the access of air). Crystallization of the mother liquor resulted in a small amount of 5-methoxybenzo[*b*]furan-2(3*H*)-one, *i.e.* lactone of (2-hydroxy-5-methoxyphenyl)acetic acid. Until now, this compound was obtained only by reaction of (2,5-dimethoxyphenyl)acetyl chloride with aluminium chloride[20]; in our case its formation has to be explained by the intramolecular nucleophilic substitution of the atom of iodine in the starting (2-iodo-5-methoxyphenyl)acetic acid by phenylacetate anion. In a much better yield the acid *XI* was obtained by reaction of (2-iodo-5-methoxyphenyl)acetic acid[19] with the thiol *VIII* in dimethylformamide in the presence of potassium carbonate and copper at 140°C in nitrogen atmosphere.



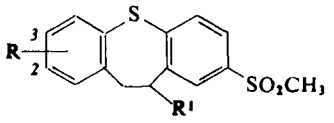
XI

While the cyclization of [2-(4-methylsulfonylphenylthio)phenyl]acetic acid to 8-(methylsulfonyl)dibenzo[*b*,*f*]thiepin-10(11*H*)one[21] with polyphosphoric acid at 140°C proceeded with a yield of 86%, an analogous attempt at cyclization of the acid *XI* gave only 4% of the ketone *XIIa*. Working in boiling toluene raised the yield only to 13%. Attempts at cyclizing the acid *XI* with a mixture of phosphorus pentoxide and methanesulfonic acid[22,23] or with polyphosphoric ester[24,25] were unsuccessful; the formation of the ketone *XIIa* could be proved only qualitatively by thin-layer chromatography. The cyclization with polyphosphoric acid in boiling mixture of benzene and chloroform led to a progress and increase of the yield first to 17%. A further increase of the yield (to 37%) was achieved by increased quantity of polyphosphoric acid and prolonging the reaction time to 36 h; in this form the reaction was considered useful for preparative purpose. Reduction of the ketone *XIIa* with sodium borohydride in boiling aqueous ethanol gave the alcohol *XIIIa* in a yield of over 90%. The product crystallized in two modification: *A*, m.p. 123–124°C, and *B*, m.p. 161–162°C. ^{1}H NMR spectra of both modifications, recorded in solutions in [6 ^{2}H]dimethyl sulfoxide, were identical; neither the IR spectra in Nujol, however, did show substantial differences. Transformation of the alcohol *XIIIa*

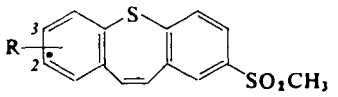
to the chloro derivative *XIVa* by treatment with hydrogen chloride in chloroform proceeded in theoretical yield. Substitution reaction of the chloro compound *XIVa* with 1-(3-hydroxypropyl)piperazine[26] in boiling chloroform afforded the base *XVa* in a yield of 68%; structure of the crystalline product was confirmed by spectra. The neutral product of this reaction was a mixture which could not be completely separated by crystallization. The prevailing component of a substance, obtained by repeated recrystallization, was identified by analysis and spectra as the expected 2-methoxy-8-(methylsulfonyl)dibenzo[*b*,*f*]thiepin (*XVIa*), but as well the mass spectrum (*m*/*z* 336 and 652) as the ^{1}H NMR spectrum indicate the presence of smaller amounts of the alcohol *XIIIa* and the corresponding ether (all these compounds are products of reactions of the primary intermediate of the substitution reaction, *i.e.* the corresponding carbocation, *cf.*[27]).



XII



XIII, R^1 = OH
XIV, R^1 = Cl
XV, R^1 = N N(CH$_2$)$_3$OH



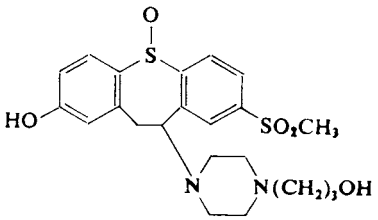
XVI

In formula *XII*—*XVI*: *a*, R = 2-OCH$_3$; *b*, R = 3-OCH$_3$

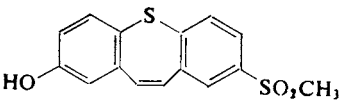
Demethylation of compound *XVa* was carried out with boron tribromide in dichloromethane at room temperature (method[28-34]); the primary product was subjected to alkaline hydrolysis and the 2-hydroxy derivative of oxyprothepin 8-sulfone (*III*) was obtained in a satisfactory yield. Oxidation of this compound in the aqueous solution of methanesulfonate with hydrogen peroxide at room temperature resulted in the sulfoxide *XVII* crystallizing as a monohydrate. Its structure was confirmed by the ^{1}H NMR spectrum and the presence of the S-oxide group was proven by polarographic reduction. A similar oxidation, carried out in acetic acid, gave as the only crystalline product a nitrogen-free and high-melting substance (m.p. 215–216°C); elimination of the piperazine part of the molecule took place. The analyses corresponded completely to the S-oxide derived from compound *XVIII*

but an attempt to prove the sulfoxide by polarography gave a negative result. In agreement with that, the mass spectrum registered the molecular ion of composition $C_{15}H_{12}N_2O_2$ (*m/z* 304). On the basis of this evidence we ascribe to the product the structure of monohydrate of the sulfide *XVIII*.

The following circumstances are considered controversial: the extremely high melting point, the necessity to suppose solvation with water after crystallization from acetone, the fact that on recording the mass spectrum by chemical ionization with heating to 300°C and higher there appeared in the spectrum peaks with higher masses (*m/z* 544, 590, 636), and finally the obscurity of the reason why simultaneously with the elimination the easy S-oxidation did not take place. It is also necessary to point out that the compound was isolated in a very low yield.



XVII



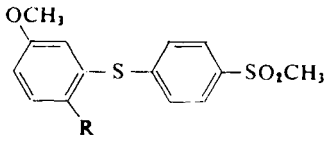
XVIII

In the synthesis of compound *IV* the starting step was the preparation of 4-methoxy-2-(4-methylsulfonylthio)benzoic acid (*XIX*) which was carried out by reaction of 2-iodo-4-methoxybenzoic acid[35] with the thiophenol *VIII* in dimethylformamide in the presence of potassium carbonate and copper at 140°C. The immediate precursor in the synthesis of 2-iodo-4-methoxybenzoic acid[35], *i.e.* 2-amino-4-methoxybenzoic acid, was prepared by reduction of 4-methoxy-2-nitrobenzoic acid with hydrazine hydrate in boiling ethanol in the presence of a small amount of ferric chloride and active carbon.

With regard to the fact that attempts at reducing the acid *XIX* with lithium aluminium hydride in tetrahydrofuran or with sodium dihydridobis(2-methoxyethoxy)-aluminate in benzene led only to mixtures of neutral products, the acid *XIX* was subjected to treatment with boiling thionyl chloride in the presence of pyridine and in this way transformed to the acid chloride *XX*. The ethanolysis of this compound gave the ethyl ester *XXI* which crystallized from ethanol in two modifications: A, m.p. 96–97°C, B, m.p. 112–113°C. UV and ^{1}H NMR spectra of both modifications in solutions were identical; IR spectra in Nujol exhibited some differences. An attempt at a direct esterifying of the acid *XIX* with boiling ethanol in the presence of a small amount of sulfuric acid was unsuccessful probably because of the very low solubility of the starting acid which was quantitatively recovered. We have no explanation for the unsuccessful results of attempts at reducing the ester *XXI* by the

mentioned hydride: the starting ester *XXI* disappeared in both cases from the reaction mixtures but attempts at purifying the products by crystallization or chromatography did not lead to desired results. Only the reduction of the ester *XXI* with diborane, generated *in situ* by reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran, afforded the desired alcohol *XXII* in a satisfactory manner. Both modifications of the ester *XXI* gave the same product. One larger batch of this reduction took an anomalous course: a mixture was obtained from which about one third of the starting ester *XXI* was recovered by crystallization; chromatography of the mother liquor on aluminium oxide gave a considerable amount of a very little polar substance $C_{15}H_{16}O_3S_2$ (mass spectrum and analysis). By means of the ^{1}H NMR spectrum this substance was identified as the methyl derivative *XXIII* (signal of the toluene methyl as a singlet at 2·20 ppm). We are dealing here with a product of hydrogenolysis which was observed earlier on reduction of an analogous acid with lithium aluminium hydride in ether[21].

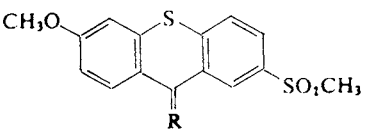
The alcohol *XXII* was transformed by shaking with hydrochloric acid at 60 to 70°C to the crude chloro compound *XXIV* which was treated with sodium cyanide in boiling acetone in the presence of a small amount of sodium iodide (for the method for converting 4-methoxybenzyl alcohols to (4-methoxyphenyl)acetonitriles, *cf.*[36,37]) to give the nitrile *XXV* crystallizing as a benzene solvate. Hydrolysis of this nitrile with a boiling solution of potassium hydroxide in aqueous ethanol gave [4-methoxy-2-(4-methylsulfonylphenylthio)phenyl]acetic acid (*XXVI*), crystallizing as a benzene solvate.



XIX, R = COOH
XX, R = COCl
XXI, R = $COOC_2H_5$
XXII, R = CH_2OH
XXIII, R = CH_3
XXIV, R = CH_2Cl
XXV, R = CH_2CN
XXVI, R = CH_2COOH

The cyclization of the acid *XXVI* to 3-methoxy-8-(methylsulfonyl)dibenzo[*b*,*f*]-thiepin-10(11*H*)-one (*XIIb*) was featured with the same difficulties like the preparation of the isomeric ketone *XIIa*. *XIIb* was obtained, indeed, already in the first experiment, which was carried out like the optimum cyclization in series *a*. but the yield was very low. The use of polyphosphoric acid without solvent at 140°C or at room temperature proved completely unsuitable. The yield of 9% was noted in the cyclization with polyphosphoric acid in the presence of boiling toluene. Modifica-

tion of the reaction conditions led to a procedure affording a reliable yield of 20% of the ketone *XIIb*.



XXVII, R = O
XXVIII, R = H_2

Reduction of the ketone *XIIb* was carried out again with sodium borohydride in boiling aqueous ethanol and gave the alcohol *XIIIb*, crystallizing as a benzene solvate. Similarly like in series *a*, the transformation to the chloro derivative *XIVb* was carried out, and the product was subjected to the substitution reaction with 1-(3-hydroxypropyl)piperazine[26] in boiling chloroform. The desired base *XVb* was obtained in a relatively low yield and its identity was confirmed by spectra. An important product of the reaction was the neutral mixture of several substances especially in the case of a larger batch, starting from the crude chloride *XIVb*, in the synthesis of which neither the intermediates *XIIb* and *XIIIb* were purified. Its benzene solution gave by crystallization a small amount of a high-melting substance having the elemental composition $C_{15}H_{12}O_4S_2$ (mass spectrum and analysis). Its UV spectrum indicated a high degree of double bond conjugation and the IR spectrum the presence of a keto group conjugated with two aromatic nuclei (band at 1 632 cm^{-1}). All the facts available led to formulating the product as 6-methoxy-2-(methylsulfonyl)thioxanthone (*XXVII*). Its formation has to be explained similarly like in analogous cases[38]: the primary carbocation, resulting from the chloro derivative *XIVb*, is evidently stabilized by elimination of a proton under simultaneous rearrangement to the corresponding 9-methylenethioxanthene derivative which is very easily oxidized by air oxygen to the thioxanthone *XXVII*. Chromatography of the mother liquor after compound *XXVII* gave a substance $C_{16}H_{14}O_3S_2$ (analysis), being evidently the normal elimination product, *i.e.* 7-methoxy-2-(methylsulfonyl)dibenzo[*b*,*f*]-thiepin (*XVIb*); spectra are not at variance with this conclusion. Continuing the chromatography afforded a very small amount of a further homogeneous substance $C_{15}H_{14}O_3S_2$ to which only on the basis of analysis and mass spectrum the structure of 6-methoxy-2-(methylsulfonyl)thioxanthene (*XXVIII*) is assigned. This substance was probably formed already in the stage of cyclization of the acid *XXVI* by decarbonylation of a small part of the acylium cation and by cyclization of the cationic species formed (*cf.*[39]). Demethylation of the base *XVb* was carried out similarly like in series *a* and there was obtained the phenolic amine *IV*.

EXPERIMENTAL

The melting points of analytical preparations were determined in an automatic Mettler FP-5 melting point recorder; the samples were dried at about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (almost exclusively in Nujol) with a Perkin Elmer 298 spectrophotometer, ^1H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer, and mass spectra with MCH 1320 and Varian MAT 44S spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure.

4-(Methylsufonyl)aniline (*VI*)

A) A stirred suspension of 2·7 g *V* (ref.[9]) in 12ml ethanol was treated with 0·30 g charcoal, a solution of 0·10 g $FeCl_3$. 6 H_2O in 1 ml ethanol and 1·8 ml 100% $N_2H_4.H_2O$. The mixture was slowly heated to the boiling point and refluxed for 4 h. After cooling to 40°C charcoal was filtered off and the filtrate was evaporated *in vacuo*. The solid residue was crystallized from 15 ml water; 2·0 g (87%) *VI*, m.p. 134—135°C. Crystallization from water raised the m.p. to 135 to 136°C. IR spectrum: 774, 837 (2 adjacent Ar—H), 1 130, 1 140, 1 273, 1 284 ($ArSO_2R$), 1 504, 1 594, 3 008, 3 030 (Ar), 1 629 ($ArNH_2$), 3 380, 3 498 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3.SOC^2H_3$): δ 7·52 (d, J = 8·5 Hz, 2 H, 3,5-H_2), 6·65 (d, J = 8·5 Hz, 2 H, 2,6-H_2), 6·10 (bs, 2 H, NH_2), 3·03 (s, 3 H, SO_2CH_3). Lit[7,8], m.p. 133°C and 134°C.

B) A mixture of 31·2 g *V* (ref.[9]), 150 ml ethanol, 3·0 g charcoal, 1·0 g $FeCl_3.6\ H_2O$ and 20 ml $N_2H_4.H_2O$ was stirred and refluxed for 4 h. Similar processing like under *A*) gave 28·2 g residue which was crystallized from 250 ml water; 6·4 g (24%) crude *VI* which melted after recrystallization from ethanol at 134—135°C. The mother liquor was evaporated in vacuo and the residue allowed to stand for 2 weeks. The separated crystalline product was repeatedly recrystallized from ethyl acetate; 3·6 g (15%) 4-(methylsulfinyl)aniline (*IX*), m.p. 94—95°C (last crystallization from a mixture of benzene and ethanol). IR spectrum: 829 (2 adjacent Ar—H), 1 025 (ArSOR), 1 500, 1 590, 3 020, 3 035 (Ar), 1 640, 3 220, 3 330, 3 395 cm^{-1} (NH_2). ^1H NMR spectrum: δ 7·35 (d, J = 8·5 Hz, 2 H, 3,5-H_2), 6·65 (d, J = 8·5 Hz, 2 H, 2,6-H_2), 4·39 (bs, 2 H, NH_2), 2·62 (s, 3 H, $SOCH_3$). Polarographic reduction in 0·025M-H_2SO_4 (towards a saturated calomel electrode), $E_{1/2}$ −1·10 V (S—O). Lit.[11], m.p. 95—96°C.

C) A mixture of 280 g *VII* (ref.[14]) and 2 l aqueous NH_3 was stirred and heated for 20 h in an autoclave to 200—210°C. After 48 h standing the precipitate was filtered, suspended in 800 ml water, the suspension was treated with 120 ml hydrochloric acid and the mixture stirred for 30 min at 50—70°C. The undissolved part was filtered off (recovery of 10·0 g starting *VII*, m.p. 98—101°C), the filtrate was made alkaline with 75 ml 50% NaOH and after standing for 12 h at 0°C the produced *VI* was filtered, washed with 150 ml water and dried; 146·8 g (75% per conversion), m.p. 132—135°C.

4-(Methylsulfonyl)thiophenol (*VIII*)

A) A mixture of 150 g *VI*, 270 ml water and 175 ml hydrochloric acid was stirred and heated to 60°C, then cooled to 0°C and diazotized over 1 h by a solution of 70 g $NaNO_2$ in 180 ml water, added dropwise at 0—2°C. It was stirred for another 30 min at the same temperature and added over 2 h to a stirred solution of 140 g Na_2CO_3 and 205 g potassium ethyl xanthate in 1 100 ml

water at 22–23°C. The mixture was heated to 40°C and stirred for 30 min at this temperature. The separated oily layer was extracted with ether and the insoluble solid was filtered; 69 g (21%) bis(4-methylsulfonylphenyl)disulfide (*X*), m.p. 190–193°C. Analytical sample, m.p. 191–193°C (ethanol–chloroform). Mass spectrum, *m/z* (%): 374 (M^+ corresponding to $C_{14}H_{14}O_4S_4$, 29%), 125 (100), 109 (23), 108 (33), 63 (83). Lit.[14], m.p. 190–192°C.

The extract was washed with water and evaporated, the residue was dissolved in 560 ml ethanol, the solution refluxing under nitrogen was treated with 150 g KOH over 30 min and the mixture was stirred and refluxed for 10 h. Ethanol was evaporated, the residue dissolved in 700 ml water, the solution was washed with ether, treated with 14 g Zn powder, and acidified under stirring and cooling with 215 ml hydrochloric acid. The product was extracted with ether, the extract was dried and evaporated. The residue was dissolved in 50 ml chloroform and the solution was induced to crystallize by the addition of 100 ml pentane; 45 g (27%) *VIII*, m.p. 63–65°C. Lit.[14,16], m.p. 66–68°C, and 66–69°C, respectively.

B) A mixture of 69 g *X*, 95 g glucose and 260 ml ethanol was stirred and heated under nitrogen to 60°C, treated over 10 min with a solution of 42 g NaOH in 110 ml water, stirred for 20 min at 60–70°C and poured into 1·7 l water. The solution obtained was filtered and the filtrate was added into a stirred mixture of 1·5 kg ice and 175 ml hydrochloric acid. Isolation procedure like under *A*) gave 37·5 g (54%) *VIII*, m.p. 63–65°C (chloroform–pentane) (*cf.*[14]).

2-Amino-4-methoxybenzoic Acid

A suspension of 255 g 4-methoxy-2-nitrobenzoic acid[40] in 1 250 ml ethanol was stirred and slowly treated with 165 ml 80% $N_2H_4.H_2O$, 20 g charcoal and a solution of 6·5 g $FeCl_3$ in 60 ml ethanol were added and the mixture was heated to the boiling point (in the first 15 min vigorous nitrogen formation). It was then refluxed for 10 h, ethanol was distilled off under reduced pressure, the residue was dissolved in a mixture of 1 l 5M-NaOH and 2·5 l water, the solution was filtered with 20 g charcoal and the filtrate was acidified with 410 ml acetic acid under cooling. After 2 h cooling and stirring the precipitated product was filtered, washed with water and dried; 147·5 g (68%), m.p. 175–179°C. A sample, recrystallized from ethanol, melted at 190°C. UV spectrum: λ_{max} 260 nm (log ε 4·04), 322 nm (3·74). IR spectrum: 820, 834, 916 (2 adjacent and solitary Ar–H), 916, 1 215, 1 240, **1 660**, 2 535, 2 605, infl. 3 100 (ArCOOH), 1 025, 1 240 ($ArOCH_3$), 1 504, 1 560, 1 600 (Ar), 1 630 ($ArNH_2$), 3 350, 3 450 cm^{-1} (NH_2). ^1H NMR spectrum ($C^2H_3.SOC^2H_3$): δ 7·69 (d, J = 8·5 Hz, 1 H, 6-H), 6·30 (d, J = 2·5 Hz, 1 H, 3-H), 6·15 (dd, J = 8·5; 2·5 Hz, 1 H, 5-H), 3·75 (s, 3 H, OCH_3). Lit[40–42], m.p. 166–172°C, 180–181°C, and 182 to 189°C, respectively.

4-Methoxy-2-(4-methylsulfonylphenylthio)benzoic Acid (*XIX*)

A solution of 28·0 g *VIII* and 41·7 g 2-iodo-4-methoxybenzoic acid[35] in 200 ml dimethylformamide was treated with 70 g K_2CO_3 and 3·0 g Cu and the mixture was stirred for 5 h at 140°C under nitrogen. After cooling the solid was filtered off and the filtrate was evaporated *in vacuo*. The residue was combined with the solid and the mixture was dissolved in 600 ml water, the solution was filtered and the filtrate was cooled and acidified with hydrochloric acid. The crude product was filtered, washed with water and dissolved in a heated mixture of 300 ml ethanol, 150 ml water and 20 ml NH_4OH. The warm solution was filtered with charcoal and the filtrate was acidified with 35 ml acetic acid. The product was filtered after standing overnight in a refrigerator, it was washed with aqueous ethanol and dried; 43·6 g (86%), m.p. 248–250°C. Analytical sample, m.p. 250–251°C (the procedure with dissolving in aqueous ethanol–NH_4OH and acidification with acetic acid was repeated). UV spectrum: λ_{max} 240 nm (log ε 4·46), 295 nm (3·93), 310 nm

(3·88), inflex at 263 nm (4·16). IR spectrum: 770, 834, 882 (2 adjacent and solitary Ar—H), 914, 1 240, **1 662**, 2 535, 2 650, 2 685, 3 100 (ArCOOH), 1 020, 1 240 ($ArOCH_3$), 1 155, 1 330 ($ArSO_2R$) 1 490, 1 550, 1 590, 3 000, 3 020 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·98 (d, J = = 8·5 Hz, 2 H, 3,5-H_2 in methylsulfonylphenylthio), 7·95 (d, J = 8·5 Hz, 1 H, 6-H), 7·69 (d, J = 8·5 Hz, 2 H, 2,6-H_2 in methylsulfonylphenylthio), 6·84 (dd, J = 8·5; 2·5 Hz, 1 H, 5-H), 6·32 (d, J = 2·5 Hz, 1 H, 3-H), 3·68 (s, 3 H, OCH_3), 3·25 (s, 3 H, SO_2CH_3). For $C_{15}H_{14}O_5S_2$ (338·4) calculated: 53·24% C, 4·17% H, 18·95% S; found: 53·12% C, 4·20% H, 18·52% S.

4-Methoxy-2-(4-methylsulfonylphenylthio)benzoyl Chloride (*XX*)

A mixture of 40 g *XIX*, 400 ml $SOCl_2$ and 5 ml pyridine was stirred and refluxed for 6 h. The excess of $SOCl_2$ was evaporated *in vacuo* and the residue was crystallized from benzene; 34·5 g (82%), m.p. 130—134°C. For $C_{15}H_{13}ClO_4S_2$ (356·8) calculated: 50·48% C, 3·67% H, 9·94% Cl, 17·97% S; found: 50·41% C, 3·71% H, 10·05% Cl, 17·80% S.

Ethyl 4-Methoxy-2-(4-methylsulfonylphenylthio)benzoate (*XXI*)

XX (33 g) was dissolved in 300 ml ethanol, the solution was refluxed for 5 h and allowed to crystallize by standing overnight in a refrigerator; 29·0 g (85%), m.p. 95—96°C. Recrystallization from ethanol gave modification A of *XXI*, prisms melting at 96—97°C. UV spectrum: λ_{max} 227 nm (log ε 4·34), 242 nm (4·41), inflexes at 267 nm (4·17) and 310 nm (3·84). IR spectrum: 768, 835, 855. 875, 890 (2 adjacent and solitary Ar—H), 1 155, 1 320 (SO_2), 1 242, 1 265 ($ArOCH_3$, ArCOOR), 1 478, 1 482, 1 550, 1 590 (Ar), **1 690** cm^{-1} (ArCOOR). ^1H NMR spectrum: δ 7·98 (d, J = 8·5 Hz, 1 H, 6-H), 7·92 (d, J = 8·5 Hz, 2 H, 3,5-H_2 in methylsulfonylphenylthio), 7·60 (d, J = 8·5 Hz, 2 H, 2,6-H_2 in methylsulfonylphenylthio), 6·72 (dd, J = 8·5; 2·5 Hz, 1 H, 5-H), 6·46 (d, J = 2·5 Hz, 1 H, 3-H), 4·35 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 3·70 (s, 3 H, OCH_3), 3·08 (s, 3 H, SO_2CH_3), 1·38 (t, J = 7·0 Hz, 3 H, CH_3 in ethyl). For $C_{17}H_{18}O_5S_2$ (366·4) calculated: 55·72% C, 4·95% H, 17·50% S; found: 55·72% C, 5·02% H, 17·25% S.

In another experiment, carried out similarly like the preceding one, crystallization of the crude product gave modification *B* of *XXI*, m.p. 112—113°C (ethanol). UV spectrum: λ_{max} 227 nm (log ε 4·32), 242 nm (4·39), infl. at 267 nm (4·15) and 310 nm (3·82). IR spectrum: 770, 779, 858, 872 (2 adjacent and solitary Ar—H), 1 145, 1 310 (SO_2), 1 265, **1 695** (ArCOOR), 1 485, 1 560, 1 580, 1 600, 3 010, 3 080 cm^{-1} (Ar). ^1H NMR spectrum was identical with that of modification A. For $C_{17}H_{18}O_5S_2$ (366·4) calculated: 55·72% C, 4·95% H, 17·50% S; found: 55·43% C, 4·99% H, 17·31% S. It was then observed that heating the modification A above the melting point leads to a new crystallization and new melting at 112—113°C, *i.e.* the melting point of modification *B*.

4-Methoxy-2-(4-methylsulfonylphenylthio)benzyl Alcohol (*XXII*)

A) A solution of 3·0 g *XXI* (modification *A*) in 20 ml tetrahydrofuran was stirred and treated with 1·2 g $NaBH_4$ and over 30 min with a solution of 4 ml $BF_3.O(C_2H_5)_2$ in 10 ml tetrahydrofuran. The mixture was stirred for 5 h at room temperature and refluxed for 2 h, the solvent was evaporated *in vacuo*, the residue was decomposed with 15 ml 1·5M-HCl and the product was extracted with 50 ml chloroform. The extract was washed with 5% NaOH, dried and evaporated. The inhomogeneous residue was chromatographed on 70 g silica gel. Chloroform eluted first 0·3 g least polar components and then 2·32 g (88%) homogeneous *XXII* which crystallized from a mixture of benzene and hexane, m.p. 76°C. IR spectrum: 775, 820, 877 (2 adjacent and solitary Ar—H), 1 053 (CH_2OH), 1 145, 1 300 ($ArSO_2R$), 1 230 ($ArOCH_3$), 1 480, 1 560, 1 582, 1 597 (Ar), 3 350 cm^{-1} (OH). ^1H NMR spectrum: δ 7·73 (d, J = 8·5 Hz, 2 H, 3,5-H_2

in methylsulfonylphenylthio), 7·52 (bd, J = 8·5 Hz, 1 H, 6-H), 7·19 (d, J = 8·5 Hz, 2 H, 2,6-H_2 in methylsulfonylphenylthio), 7·03 (m, 2 H, 3,5-H_2), 4·68 (d, J = 5·0 Hz, 2 H, $ArCH_2O$), 3·81 (s, 3 H, OCH_3), 3·02 (s, 3 H, SO_2CH_3), 2·59 (bt, J = 5·0 Hz, 1 H, OH). For $C_{15}H_{16}O_4S_2$ (324·4) calculated: 55·53% C, 4·97% H, 19·77% S; found: 55·52% C, 5·04% H, 19·70% S.

B) A similar reduction of 20·0 g *XXI* (modification *B*) with 9·5 g $NaBH_4$ and 32 ml $BF_3.O(C_2H_5)_2$ in 160 ml tetrahydrofuran gave 17·5 g almost homogeneous oil which crystallized from a mixture of benzene and hexane; 13·7 g (77%) *XXII*, m.p. 73–75°C.

4-(5-Methoxy-2-methylphenylthio)phenyl Methyl Sulfone (*XXIII*)

A solution of 156 g *XXI* in 1 250 ml tetrahydrofuran was treated with 73·5 g $NaBH_4$ and with stirring over 1 h with 250 ml $BF_3.O(C_2H_5)_2$, added dropwise. The mixture was stirred for 5 h at room temperature, refluxed for 5 h and evaporated. The cooled residue was decomposed under stirring with 750 ml water and 350 ml 3M-HCl, and extracted with chloroform. The extract was washed with 5% NaOH and water, dried and evaporated. The residue was dissolved in 230 ml benzene and the dark solution was treated with 115 ml hexane. After 3 days standing 42 g starting ester *XXI* (m.p. 93–97°C, comparison by TLC) crystallized, were filtered and the filtrate was evaporated. The residue was chromatographed on 1·1 kg neutral Al_2O_3 (activity II). Benzene eluted as the least polar product 71 g (74% per conversion) *XXIII*, m.p. 90–91°C (ethanol). Mass spectrum, m/z (composition): 308 (M^+ corresponding to $C_{15}H_{16}O_3S_2$), 277 ($C_{14}H_{13}.O_2S_2$), 275 ($C_{15}H_{15}O_3S$), 229 ($C_{14}H_{13}OS$), 214 ($C_{13}H_{10}OS$), 120 (C_8H_8O). UV spectrum. λ_{max} 279 nm (log ε 4·22), infl. 221 nm (4·21). IR spectrum: 770, 824, 830, 880 (2 adjacent and solitary Ar—H), 1 093, 1 236 ($ArOCH_3$), 1 148, 1 293, 1 310 (SO_2), 1 490, 1 560, 1 578, 1 600, 3 000, 3 010 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·70 (d, J = 8·5 Hz, 2 H, 3,5-H_2 in methylsulfonylphenylthio), 7·20 (d, J = 8·5 Hz, 1 H, 3-H of methoxymethylphenyl), 7·10 (d, J = 8·5 Hz, 2 H, 2,6-H_2 in methylsulfonylphenyl), 7·00 (d, J = 3·0 Hz, 1 H, 6-H in methoxymethylphenyl), 6·88 (dd, J = 8·5; 3·0 Hz, 1 H, 4-H in methoxymethylphenyl), 3·71 (s, 3 H, OCH_3), 2·95 (s, 3 H, SO_2CH_3), 2·20 (s, 3 H, $ArCH_3$). For $C_{15}H_{16}O_3S_2$ (308·4) calculated: 58·41% C, 5·23% H, 20·79% S; found: 58·24% C, 5·18% H, 20·60% S.

[4-Methoxy-2-(4-methylsulfonylphenylthio)phenyl]acetonitrile (*XXV*)

A mixture of 33·3 g *XXII* and 70 ml hydrochloric acid was stirred and heated for 30 min to 60 to 70°C. After cooling the crude oily *XXIV* was extracted with benzene, the extract was dried with $CaCl_2$ and evaporated. The residue was dissolved in 70 ml acetone, the solution was treated with 15·4 g NaCN and 1·4 g NaI and the mixture was stirred and refluxed for 20 h. After standing overnight the separated solid was filtered off and the filtrate was evaporated *in vacuo*. The residue was crystallized from benzene; 30·5 g (83%) *XXV*, 3 : 1 solvate with benzene, m.p. 107–108°C. Mass spectrum, m/z (composition and/or %): 333 (M^+ corresponding to $C_{16}H_{15}NO_3S_2$, 93%), 291 ($C_{14}H_{11}O_3S_2$, 21), 227 ($C_{14}H_{11}OS$, 100), 226 ($C_{14}H_{10}OS$, 66), 151 (24); the presence of benzene was confirmed. IR spectrum: 774, 823, 875 (2 adjacent and solitary Ar—H), 1 143, 1 290, 1 300 ($ArSO_2R$), 1 233 ($ArOCH_3$), 1 480, 1 492, 1 580, 1 602, 3 010, 3 080, 3 090 (Ar), 2 240 cm^{-1} (R—CN). ^1H NMR spectrum: δ 7·80 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of methylsulfonylphenylthio), 7·55 (d, J = 8·5 Hz, 1 H, 6-H), 7·31 (s, 2 H, CH=CH of benzene), 7·18 (d, J = = 8·5 Hz, 2 H, 2,6-H_2 of methylsulfonylphenylthio), *c.* 7·10 (m, 2 H, 3,5-H_2), 3·82 (s, 3 H, OCH_3), 3·78 (s, 2 H, $ArCH_2CN$), 3·01 (s, 3 H, SO_2CH_3). For $C_{16}H_{15}NO_3S_2 + 1/3\ C_6H_6$ (359·4) calculated: 60·16% C, 4·77% H, 3·90% N, 17·80% S; found: 60·31% C, 4·81% H, 3·96% N, 17·32% S.

[5-Methoxy-2-(4-methylsulfonylphenylthio)phenyl]acetic Acid (*XI*)

A) *VIII* (18·8 g) was added to a solution of 22·4 g KOH in 250 ml water and the mixture was stirred for 20 min at 70°C. It was then treated with 29·2 g (2-iodo-5-methoxyphenyl)acetic acid[19] and 3·0 g Cu and the mixture was stirred and refluxed for 9 h. It was filtered while hot, the filtrate was cooled and acidified with 1 : 1 dilute hydrochloric acid. After standing overnight, the crystalline *XI* was filtered, washed with water and dried; 17·6 g (50%), m.p. 149—151°C. Analytical sample, m.p. 159·5—160°C (aqueous ethanol). IR spectrum: 775, 819, 822, 860 (2 adjacent and solitary Ar—H), 950, 1 235, **1 694**, 2 550, 2 628, 2 728, infl. 3 080 and 3 200 (COOH), 1 150, 1 315 (SO_2), 1 483, 1 580, 1 592 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·70 (d, J = 9·0 Hz, 2 H, 3,5-H_2 of methylsulfonylphenyl), 7·48 (d, J = 8·5 Hz, 1 H, 3-H), 7·10 (d, J = 9·0 Hz, 2 H, 2,6-H_2 of methylsulfonylphenyl), 7·08 (d, J = 3·0 Hz, 1 H, 6-H), 6·94 (dd, J = = 8·5; 3·0 Hz, 1 H, 4-H), 3·80 (s, 3 H, OCH_3), 3·68 (s, 2 H, $ArCH_2CO$), 3·12 (s, 3 H, SO_2CH_3). For $C_{16}H_{16}O_5S_2$ (352·4) calculated: 54·53% C, 4·58% H, 18·19% S; found: 54·69% C, 4·71% H, 17·90% S.

The aqueous filtrate was evaporated *in vacuo* and the residue was extracted with 300 ml boiling chloroform, the extract was filtered and evaporated. The residue (5·0 g) was dissolved in 20 ml boiling benzene and the solution was allowed to crystallize; 0·50 g solid melting at 192—193°C which was identified as the disulfide *X*. The mother liquor slowly continued to crystallize; 0·40 g 5-methoxybenzo[*b*]furan-2(3*H*)-one, m.p. 99—100°C (benzene). Mass spectrum, *m/z* (%): 164·0461 (M^+ corresponding to $C_9H_8O_3$, calculated 164·0473, 100%), 136 (95), 121 (5), 108 (45), 78 (22), 65 (24). IR spectrum: 812, 859, 870 (2 adjacent and solitary Ar—H), 1 025, 1 149, 1 219, 1 250 ($ArOCH_3$), 1 482, 1 604, 3 008, 3 098 (Ar), 1 795 cm^{-1} ($ArOCOCH_2$ in a five-membered lactone ring). ^1H NMR spectrum: δ 6·60—7·00 (m, 3 H, ArH), 3·72 (s, 3 H, OCH_3), 3·62 (s, 2 H $ArCH_2CO$). For $C_9H_8O_3$ (164·2) calculated: 65·85% C, 4·91% H; found: 65·84% C, 5·04% H. Lit.[20], m.p. 90—91°C.

B) A solution of 18·0 g *VIII* in 80 ml dimethylformamide was treated with 45 g K_2CO_3, the mixture was stirred for 5 min under nitrogen and treated with a solution of 26·0 g (2-iodo--5-methoxyphenyl)acetic acid[19] in 45 ml dimethylformamide and finally with 2·0 g Cu. The mixture was stirred and heated for 4 h to 140°C, cooled, filtered, and the filtrate was evaporated *in vacuo*. The residue was dissolved in 350 ml hot water, the undissolved solid was filtered off and the filtrate was acidified with 17 ml hydrochloric acid. After standing overnight the crude product was filtered and crystallized from 120 ml aqueous ethanol; 23·9 g (76%), m.p. 155—156°C.

[4-Methoxy-2-(4-methylsulfonylphenylthio)phenyl]acetic Acid (*XXVI*)

A solution of 35·8 g crude *XXV* in 200 ml ethanol was treated with a solution of 32 g KOH in 50 ml water and the mixture was stirred and refluxed for 9 h. Ethanol was evaporated *in vacuo*, the aqueous residue was diluted with 600 ml water, the solution was filtered at 40—50°C with charcoal and the filtrate was acidified with 50 ml hydrochloric acid under cooling. The product was filtered after 24 h standing, washed with water and dried; 29·9 g (79%), m.p. 132—138°C. Crystallization from benzene gave a 2 : 1 solvate with benzene. Mass spectrum, *m/z* (%): 352 (M^+ corresponding to $C_{16}H_{16}O_5S_2$, 23%), 334 (16, $C_{16}H_{14}O_4S_2$), 308 (26), 305 (16), 291 (12), 229 (21), 228 (57), 227 (100, $C_{14}H_9OS$), 226 (50), 197 (18, $C_{13}H_9S$), 184 (17), 152 (19). IR spectrum: 777, 820, 869, 885 (2 adjacent and solitary Ar—H), 1 185, 1 236 ($ArOCH_3$, COOH), 1 150, 1 300 (SO_2), 1 490, 1 560, 1 580, 1 600 (Ar), 965, **1 705**, infl. 3 100 cm^{-1} (R—COOH). ^1H NMR spectrum: δ 9·90 (bs, 1 H, COOH), 7·80 (d, J = 8·5 Hz, 2 H, 3,5-H_2 of methylsulfonylphenyl), 7·30 (s, 3 H, 1/2 C_6H_6), 7·15 (d, J = 8·5 Hz, 2 H, 2,6-H_2 of methylsulfonylphenyl),

6·90—7·40 (m, 3 H, 3,5,6-H_3), 3·79 (s, 3 H, OCH_3), 3·75 (s, 2 H, $ArCH_2CO$), 2·99 (s, 3 H, SO_2CH_3). For $C_{16}H_{16}O_5S_2 + 1/2\ C_6H_6$ (391·5) calculated: 58·29% C, 4·89% H, 16·38% S; found: 58·08% C, 5·01% H, 16·27% S.

2-Methoxy-8-(methylsulfonyl)dibenzo[*b*,*f*]thiepin-10(11*H*)one (*XIIa*)

A solution of 23·8 g *XI* in 300 ml chloroform was slowly added to a stirred mixture of 420 g polyphosphoric acid and 300 ml benzene at 60°C and the mixture obtained was refluxed under stirring for 36 h. The organic layer was separated by decantation, the polyphosphoric acid layer was decomposed by 1·5 kg ice and water and the mixture was extracted with 1 l chloroform. The extract was combined with the separated organic layer, washed with 5% NaOH and water, dried. filtered and evaporated. The residue was mixed with 80 ml acetone which was heated to boil and then allowed to stand overnight. The product was filtered, washed with acetone and dried, 8·25 g (37%), m.p. 200—204°C. Analytical sample, m.p. 204—205°C (acetone). UV spectrum: λ_{max} 227·5 nm (log ε 4·47), 250 nm (4·32), 287 nm (3·92), 340 nm (3·73). IR spectrum: 795, 803, 827, 841, 873 (2 adjacent and solitary Ar—H), 1 148, 1 249 ($ArSO_2R$), 1 480, 1 571, 1 596, 3 000, 3 030, 3 090 (Ar), 1 675 cm^{-1} (ArCO). For $C_{16}H_{14}O_4S_2$ (334·4) calculated: 57·46% C, 4·22% H, 19·18% S; found: 57·94% C, 4·31% H, 18·95% S.

3-Methoxy-8-(methylsulfonyl)dibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIIb*)

Polyphosphoric acid was prepared from 250 g P_2O_5 and 250 g 85% H_3PO_4, 500 ml toluene and 25·0 g *XXVI* were added and the mixture was stirred and refluxed for 2 h (bath temp. 130 to 140°C). After cooling the mixture was decomposed with 1·3 kg ice and water and extracted with 1 l boiling chloroform with stirring for 1 h under reflux. The organic layer was cooled, washed with 5% NaOH and water, dried and evaporated. The residue was crystallized from 40 ml toluene; 4·8 g (20%), m.p. 187—192°C. Analytical sample, m.p. 196—199°C (benzene). UV spectrum: λ_{max} 233 nm (log ε 4·36), 243 nm (4·35), 284 nm (3·99), 332 nm (3·67). IR spectrum: 810, 822, 872 (2 adjacent and solitary Ar—H), 1 055, 1 235 ($ArOCH_3$), 1 134, 1 142, 1 296 ($ArSO_2R$), 1 484, 1 576, 1 598, 3 000, 3 020, 3 058, 3 070 (Ar), **1 670** cm^{-1} (ArCO). ^1H NMR spectrum (60°C): δ 8·59 (d, J = 2·5 Hz, 1 H, 9-H), 7·85 (dd, J = 8·0; 2·5 Hz, 1 H, 7-H), 7·62 (d, J = 8·0 Hz, 1 H, 6-H), 7·36 (d, J = 8·0 Hz, 1 H, 1-H), 7·06 (d, J = 3·0 Hz, 1 H, 4-H), 6·84 (dd, J = 8·0; 3·0 Hz, 1 H, 2-H), 4·20 (s, 2 H, $ArCH_2CO$), 3·71 (s, 3 H, OCH_3), 2·98 (s, 3 H, SO_2CH_3). For $C_{16}H_{14}O_4S_2$ (334·4) calculated: 57·46% C, 4·22% H, 19·18% S; found: 57·24% C, 4·37% H, 18·90% S.

2-Methoxy-8-(methylsulfonyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XIIIa*)

A) solution of 0·2 g $NaBH_4$ in 1 ml water was diluted with 30 ml ethanol and 0·70 g *XIIa* were added. The mixture was stirred and refluxed for 3 h, evaporated *in vacuo*, the residue decomposed with 20 ml water and 5 ml 10% NaOH, and extracted with benzene. The extract was washed with water, dried and evaporated; 0·65 g (93%) residue melting at 118—123°C. Analytical sample was obtained by crystallization from benzene, modification A with m.p. 123—124°C. When heated above the melting point, the substance resolidifies at 140—145°C and remelts sharply at 160—161·5°C. IR spectrum: 820, 830, 896 (2 adjacent and solitary Ar—H), 1 050 ($ArOCH_3$, CHOH in the ring), 1 150, 1 166, 1 310 ($ArSO_2R$), 1 480, 1 553, 1 580, 1 595, 3 000, 3 010 (Ar), 3 460 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·02 (bs, 1 H, 9-H), 7·65 (bs, 2 H, 6,7-H_2), 7·38 (d, J = 8·0 Hz, 1 H, 4-H), 6·90 (d, J = 2·5 Hz, 1 H, 1-H), 6·70 (dd, J = 8·0; 2·5 Hz, 1 H, 3-H), 5·95 (d, J = 6·0 Hz, 1 H, OH), 5·18 (bm, 1 H, Ar—CH—O), 3·73(s, 3 H, OCH_3), 3·40 (m, 2 H, $ArCH_2$), 3·18 (s, 3 H, SO_2CH_3). For $C_{16}H_{16}O_4S_2$ (336·4) calculated: 57·12% C, 4·79% H, 19·06% S; found: 57·30% C, 4·87% H, 18·40% S.

B) A stirred mixture of 8·25 g *XIIa* and 300 ml ethanol was heated to 50°C and treated with a solution of 3·2 g $NaBH_4$ in 15 ml water, containing 1 drop of 10% NaOH, added dropwise. It was refluxed for 3·5 h, evaporated *in vacuo* and the residue distributed between 300 ml benzene and 300 ml dilute NaOH (60 ml 10% NaOH and 240 ml water) at 40°C. The benzene layer was washed with water, dried and evaporated. The residue represented 7·7 g (93%) modification B of *XIIIa*, m.p. 160—161°C. Analytical sample, m.p. 161—162°C (benzene–ethanol). The IR and NMR spectra of modification B are identical with those of modification A. For $C_{16}H_{16}O_4S_2$ (336·4) calculated: 57·12% C, 4·79% H, 19·06% S; found: 57·36% C, 4·95% H, 18·73% S.

Modification B is the stable modification: 300 mg modification A was dissolved in a mixture of 5 ml benzene and 1 ml ethanol and the solution was nucleated with a small amount of modification B; crystallization afforded 250 mg modification *B*, m.p. 161·5°C.

3-Methoxy-8-(methylsulfonyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XIIIb*)

XIIb (6·5 g) was added to 200 ml ethanol and treated with a solution of 0·8 g $NaBH_4$ in 3 ml water containing 1 drop of 10% NaOH. The mixture was stirred and refluxed for 3·5 h and evaporated *in vacuo*. The residue was distributed between 150 ml benzene and 150 ml 10% NaOH, the solid (0·8 g) was filtered off and the benzene layer was evaporated; 5·70 g (87%) homogeneous glassy *XIIIb*. It crystallized after dissolution in 30 ml benzene as a 1 : 1 solvate with benzene, m.p. 80—85°C. Mass spectrum, *m/z* (composition): 336 (M^+ corresponding to $C_{16}H_{16}O_4S_2$), 321 ($C_{15}H_{13}O_4S_2$), 167 ($C_8H_7O_2S$), 145 ($C_9H_5O_2$). IR spectrum: 759, 823, 830, 895 (2 adjacent and solitary Ar—H), 1 050, 1 245 ($ArOCH_3$, CHOH in the ring), 1 150, 1 300 (SO_2), 1 495, 1 550, 1 578, 1 600, 3 000, 3 010, 3 030, 3 060 (Ar), 3 440 cm^{-1} (OH). ^1H NMR spectrum: δ 8·05 (bs, 1 H, 9-H), 7·62 (bd, J = 8·5 Hz, 1 H, 7-H), 7·50 (bd, J = 8·5 Hz, 1 H, 6-H), 7·30 (s, 6 H, C_6H_6), 7·10 (d, J = 8·5 Hz, 1 H, 1-H), 6·98 (d, J = 2·5 Hz, 1 H, 4-H), 6·71 (dd, J = 8·5; 2·5 Hz, 1 H, 2-H), 5·25 (bm, 1 H, Ar—CH—O), 3·70 (s, 3 H, OCH_3), *c.* 3·40 (m, 2 H, $ArCH_2$), 2·95 (s, 3 H, SO_2CH_3), 2·62 (d, J = 8·0 Hz, 1 H, OH). For $C_{16}H_{16}O_4S_2 + C_6H_6$ (414·5) calculated: 63·74% C, 5·35% H, 15·47% S; found: 63·31% C, 5·36% H, 15·20% S.

10-Chloro-2-methoxy-8-(methylsulfonyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIVa*)

$CaCl_2$ (1·5 g) was added to a solution of 1·25 g *XIIIa* in 40 ml chloroform and the stirred suspension was saturated with HCl for 3 h. After standing overnight the mixture was diluted with 20 ml chloroform, filtered and the filtrate was evaporated in vacuo. The residue was crystallized from a mixture of 13 ml benzene and 8 ml light petroleum; 1·10 g (85%), m.p. 157—158°C. IR spectrum: 770, 828, 876 (2 adjacent and solitary Ar—H), 1 140, 1 290 (SO_2), 1 245, 1 260 ($ArOCH_3$), 1 474, 1 570, 1 600, 3 010, 3 035 cm^{-1} (Ar). ^1H NMR spectrum: δ 8·01 (bs, 1 H, 9-H), 7·65 and 7·50 (ABq, J = 8·5 Hz, 2 H, 6,7-H_2), 7·40 (d, J = 8·5 Hz, 1 H, 4-H), 6·88 (d, J = = 2·5 Hz, 1 H, 1-H), 6·70 (dd, J = 8·5; 2·5 Hz, 1 H, 3-H), 5·71 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·98 and 3·68 (2 dd, J = 13·0; 4·0 and 13·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 3·80 (s, 3 H, OCH_3), 3·00 (s, 3 H, SO_2CH_3). For $C_{16}H_{15}ClO_3S_2$ (354·9) calculated: 54·15% C, 4·26% H, 9·99% Cl, 18·07% S; found: 54·39% C, 4·32% H, 9·99% Cl, 17·75% S.

11-Chloro-7-methoxy-2-(methylsulfonyl)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XIVb*)

A similar reaction of 5·6 g *XIIIb* with HCl in 60 ml chloroform in the presence of 5·0 g $CaCl_2$ gave 5·9 g (100%) crude product, m.p. 156—158°C. Crystallization from benzene is accompanied by a partial decomposition. UV spectrum: λ_{max} 225 nm (log ε 4·44), 290 nm (4·00). IR spectrum: 820, 880, 890 (2 adjacent and solitary Ar—H), 1 109, 1 240 ($ArOCH_3$), 1 142, 1 287, 1 295 (SO_2),

1 487, 1 565, 1 579, 1 600, 3 015, 3 055, 3 064 cm^{-1} (Ar). For $C_{16}H_{15}ClO_3S_2$ (354·9) calculated: 54·15% C, 4·26% H, 9·99% Cl, 18·07% S; found: 54·44% C, 4·28% H, 10·30% Cl, 17·86% S.

10-[4-(3-Hydroxypropyl)piperazino]-2-methoxy-8-(methylsulfonyl)-10,11-dihydrodibenzo-[*b*,*f*]thiepin (*XVa*)

A solution of 6·30 g *XIVa* and 7·8 g 1-(3-hydroxypropyl)piperazine[26] in 20 ml chloroform was stirred and refluxed for 9 h, evaporated *in vacuo* and the residue was distributed between 250 ml benzene and 250 ml water. The benzene layer was washed with water and shaken with an excess of 3M-HCl. The precipitated hydrochloride was filtered, suspended in 200 ml water, the base *XVa* was released by NH_4OH and extracted with benzene. Processing of the extract gave 5·6 g (68%) *XVa*, m.p. 158–159°C (benzene). IR spectrum: 810, 838, 860, 896 (2 adjacent and solitary Ar—H), 1 048, 1 240 ($ArOCH_3$), 1 058 (CH_2OH), 1 140, 1 303 (SO_2), 1 480, 1 578, 1 590 (Ar), 3 220, infl. 3 370 cm^{-1} (OH). ^1H NMR spectrum: δ 8·34 (bs, 1 H, 9-H), 7·60 and 7·48 (ABq, 2 H, 6,7-H_2), 7·40 (d, J = 8·5 Hz, 1 H, 4-H), 6·82 (d, J = 2·5 Hz, 1 H, 1-H), 6·64 (dd, J = 8·5; 2·5 Hz, 1 H, 3-H), 5·15 (bs, 1 H, OH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·80 (s, 3 H, OCH_3), 3·80 (*t*, J = 6·5 Hz, 2 H, CH_2O), 3·00 (s, 3 H, SO_2CH_3), 2·60 (bm, 10 H, 5 NCH_2), 1·70 (bm, 2 H, CH_2 in the middle of the propane chain). For $C_{23}H_{30}N_2O_4S_2$ (462·6) calculated: 59·70% C, 6·54% H, 6·06% N, 13·86% S; found: 60·02% C, 6·66% H, 6·09% N, 13·65% S.

The benzene layer from the filtrate after the isolation of the hydrochloride of *XVa* was washed with water, dried, evaporated and the residue was crystallized from benzene; 0·57 g (10%) inhomogeneous 2-methoxy-8-(methylsulfonyl)dibenzo[*b*,*f*]thiepin (*XVIa*), m.p. 150–152°C. Mass spectrum, *m/z*: 318 (M^+ corresponding to $C_{16}H_{14}O_3S_2$), 303, 329; the peak with *m/z* 336 indicates the presence of *XIIIa*. The chemical ionization technique confirmed *XVIa* (*m/z* 318) but exhibited also peaks with *m/z* 636, 652 and 668. UV spectrum: λ_{max} 235 nm (log ε 4·55), 277·5 nm (4·23), infl. 312 nm (3·66). IR spectrum: 770 (CH=CH), 830, 855, 900 (2 adjacent and solitary Ar—H), 1 025, 1 245 ($ArOCH_3$), 1 145, 1 300 ($ArSO_2R$), 1 479, 1 589, 3 010 (Ar), 1 655 (Ar—C=C—Ar), 3 390 cm^{-1} (a weak band corresponding to OH of *XIIa* present in a small amount). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·80–8·00 (m, 8 H, ArH and CH=CH), 3·72 (s, 3 H, OCH_3), 3·20 (s, 3 H, SO_2CH_3), weak signals corresponding to Ar—CH=O and $ArCH_2$. For $C_{16}H_{14}O_3S_2$ (318·4) calculated: 60·35% C, 4·43% H, 20·14% S; found: 59·79% C, 4·49% H, 19·70% S.

11-[4-(3-Hydroxypropyl)piperazino]-7-methoxy-2-(methylsulfonyl)-10,11-dihydrodibenzo-[*b*,*f*]thiepin (*XVb*)

A) A mixture of 0·60 g *XIVb*, 0·80 g 1-(3-hydroxypropyl)piperazine[26] and 4 ml chloroform was processed similarly like in the preceding case; 0·30 g (38%) homogeneous *XVb*, m.p. 144 to 145°C (benzene). UV spectrum: λ_{max} 230 nm (logε 4·35), 287 nm (4·03). IR spectrum: 805, 821, 863 (2 adjacent and solitary Ar—H), 1 032, 1 240 ($ArOCH_3$), 1 050 (CH_2OH), 1 143, 1 310 (SO_2), 1 490, 1 565, 1 583, 1 600, 3 000, 3 010, 3 050 (Ar), 2 750, 2 770, 2 820 (N—CH_2), 3 200 cm^{-1} (OH). ^1H NMR spectrum: δ 8·30 (bs, 1 H, 1-H), 7·60 (bd, J = 8·5 Hz, 1 H, 3-H), 7·48 (d, J = 8·5 Hz, 1 H, 4-H), 7·14 (d, J = 8·5 Hz, 1 H, 9-H), 7·00 (d, J = 2·5 Hz, 1 H, 6-H), 6·78 (dd, J = 8·5; 2·5 Hz, 1 H, 8-H), 5·10 (bs, 1 H, OH), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·75 (*t*, J = 6·0 Hz, 2 H, CH_2O), 3·75 (s, 3 H, OCH_3), 2·98 (s, 3 H, SO_2CH_3), 2·60 (bs, 10 H, 5 NCH_2), 1·65 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{23}H_{30}N_2O_4S_2$ (462·6) calculated: 59·71% C, 6·54% H, 6·06% N, 13·86% S; found: 59·98% C, 6·60% H, 5·98% N, 13·74% S.

B) A larger batch of this preparation was carried out from 5·9 g crude *XIVb* in the synthesis of which crude intermediates *XIIb* and *XIIIb* were used. The basic product (obtained *via* the hydro-

chloride) was chromatographed on 30 g silica gel. Elution with chloroform containing 8% ethanol gave 2·40 g (31%) homogeneous oily product which crystallized from 8 ml benzene; 1·85 g *XVb*, m.p. 143–145°C.

The neutral product (2·45 g), obtained by evaporation of the benzene layer after the removal of the basic substances, was dissolved in 10 ml benzene and the solution was allowed to crystallize for 48 h; 0·27 g 6-methoxy-2-(methylsulfonyl)thioxanthone (*XXVII*), m.p. 238–239°C (toluene). Mass spectrum, *m/z*: 320 (M^+ corresponding to $C_{15}H_{12}O_4S_2$), 257 ($C_{14}H_9O_3S$). UV spectrum: λ_{max} 253 nm (log ε 4·48), 288 nm (4·49), 366 nm (3·70). IR spectrum: 775, 800, 835, 855, 889 (2 adjacent and solitary Ar—H), 1 065, 1 254 ($ArOCH_3$), 1 150, 1 308 (SO_2), 1 485, 1 583, 1 596, 3 010, 3 075 (Ar), 1 632 cm^{-1} (ArCOAr). For $C_{15}H_{12}O_4S_2$ (320·4) calculated: 56·23% C, 3·78% H, 20·02% S; found: 56·62% C, 3·93% H, 19·94% S.

The mother liquor after the preceding product was evaporated and the residue (2·10 g) was chromatographed on 80 g neutral Al_2O_3 (activity II). Elution with benzene removed first 0·11 g impurities and gave then 0·60 g oil which was rechromatographed on 17 g silica gel. After 50 mg oil benzene eluted first 0·23 g crystalline fractions which were combined and recrystallized from a mixture of benzene and light petroleum; 0·10 g 7-methoxy-2-(methylsulfonyl)dibenzo[*b,f*]-thiepin (*XVIb*), m.p. 149–154°C. UV spectrum: λ_{max} 239 nm (log ε 4·55), inflexes at 247 nm (4·52), 278 nm (4·14) and 320 nm (3·80). IR spectrum: 758, 765 (C=C), 820, 890 (2 adjacent and solitary Ar—H), 1 050, 1 230, 1 248 ($ArOCH_3$), 1 149, 1 304 (SO_2), 1 488, 1 585, 1 600, 3 060 (Ar), 1 638 cm^{-1} (C=C in conjugation). ^1H NMR spectrum: δ 6·70–7·90 (m, 8 H, ArH and CH=CH), 3·78 (s, 3 H, OCH_3), 3·00 (s, 3 H, SO_2CH_3). For $C_{16}H_{14}O_3S_2$ (318·4) calculated: 60·35% C, 4·43% H, 20·14% S; found: 60·36% C, 4·52% H, 19·91% S.

Continued elution with benzene gave 50 mg homogeneous substance which was crystallized from benzene; 6-methoxy-2-(methylsulfonyl)thioxanthene (*XXVIII*), m.p. 178–180°C. Mass spectrum, *m/z* (composition): 306 (M^+ corresponding to $C_{15}H_{14}O_3S_2$), 275 ($C_{14}H_{11}O_2S_2$), 227 ($C_{14}H_{11}OS$), 196 ($C_{13}H_8S$). For $C_{15}H_{14}O_3S_2$ (306·3) calculated: 58·82% C, 4·61% H; found: 59·23% C, 4·77% H.

10-[4-(3-Hydroxypropyl)piperazino]-8-(methylsulfonyl)-10,11-dihydrodibenzo[*b,f*]thiepin-2-ol (*III*)

A stirred and cooled solution of 2·0 g *XVa* in 20 ml dichloromethane was treated over 15 min with a solution of 3·8 g BBr_3 in 10 ml dichloromethane, added dropwise. The mixture was stirred for 7 h at room temperature, allowed to stand overnight and evaporated *in vacuo*. The residue was treated under cooling with 35 ml ethanol and under stirring with 25 ml 5% NaOH and the pH was adjusted with 10% NaOH to 9–10. The clear solution was allowed to stand for 24 h at room temperature and then evaporated *in vacuo*. The residue was neutralized with dilute acetic acid and distributed between 50 ml chloroform and 50 ml 5% Na_2CO_3. The organic layer was washed with water, dried and evaporated. The amorphous residue was crystallized from 8 ml acetone; 1·20 g (62%), m.p. 164–165°C. IR spectrum: 815, 870, 900 (2 adjacent and solitary Ar—H), 1 065 (CH_2OH), 1 146, 1 300 ($ArSO_2R$), 1 240 (ArOH), 1 480, 1 580, 1 610 (Ar), 3 150 cm^{-1} (O—H...N). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·20 (bs, 1 H, 9-H), 7·65 and 7·49 (ABq, J = 8·5 Hz, 2 H, 6,7-H_2), 7·29 (d, J = 8·5 Hz, 1 H, 4-H), 6·85 (d, J = 2·5 Hz, 1 H, 1-H), 6·54 (dd, J = 8·5; 2·5 Hz, 1 H, 3-H), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·45 (t, J = 6·5 Hz, 2 H, CH_2O), 3·10 (s, 3 H, SO_2CH_3), 2·55 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·35 (bm, 6 H, $3N^4CH_2$). 1·60 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{22}H_{28}$-$.N_2O_4S_2$ (448·6) calculated: 58·90% C, 6·29% H, 6·25% N, 14·29% S; found: 58·56% C, 6·46% H, 6·22% N, 14·04% S.

10-[4-(3-Hydroxypropyl)piperazino]-8-(methylsulfonyl)-10,11-dihydrodibenzo[*b,f*]thiepin-3-ol (*IV*)

A similar reaction of 1·65 g *XVb* with 3·2 g BBr_3 in 25 ml dichloromethane and a similar processing gave an amorphous product which was induced to crystallize by rubbing with water. The product was filtered, washed with water and dried; 0·70 g (44%), m.p. 145—148°C. An attempt at recrystallization failed. Mass spectrum, *m/z* (% and composition): 448 (M^+ corresponding to $C_{22}H_{28}N_2O_4S_2$, 0·3%), 306 (22, $C_{15}H_{14}O_3S_2$), 304 (17, $C_{15}H_{12}O_3S_2$), 291 (100, $C_{14}H_{11}O_3S_2$), 225 (22, $C_{13}H_7NOS$, ?), 212 (49, $C_{12}H_6NOS$?), 102 (27), 99 (54, $C_5H_{11}N_2$), 70 (39, C_4H_8N), 58 (73), 56 (68). UV spectrum: λ_{max}: 231 nm (log ε 4·32), 288 nm (4·02). IR spectrum (KBr): 815, 855 (2 adjacent and solitary Ar—H), 1 045 (CH_2OH), 1 148, 1 306 (SO_2), infl. 1 250 (ArOH), 1 495, 1 580, 1 600 (Ar), 2 690, 2 775, 2 815 (NH^+), 3·260 cm^{-1} (OH). For $C_{22}H_{28}N_2O_4S_2$ (448·6) calculated: 58·90% C, 6·29% H, 6·25% N, 14·29% S; found: 58·26% C, 6·22% H, 6·09% N, 14·10% S.

10-[4-(3-Hydroxypropyl)piperazino]-8-(methylsulfonyl)-10,11-dihydrodibenzo[*b,f*]thiepin-2-ol 5-Oxide (*XVII*)

III (1·23 g) was dissolved in a solution of 0·48 g methanesulfonic acid in 10 ml water, the solution was treated with 0·7 ml 30% H_2O_2 and allowed to stand at room temperature for 55 h. It was made alkaline with NH_4OH and the precipitate was filtered and dried; 0·45 g (35%) crude *XVII* hydrate. Crystallization from 350 ml acetone gave 0·25 g homogeneous *XVII* monohydrate, m.p. 176—177°C. Polarographic reduction in 0·5M-HCl (towards the saturated calomel electrode), $E_{1/2}$ −0·51 V (S—O). IR spectrum: 840, 880 (2 adjacent and solitary Ar—H), 1 030, 1 070 (CH_2OH and S—O), 1 135, 1 145, 1 290, 1 305 (SO_2 and ArOH), 1 568, 1 598, 1 610, 3 080 (Ar), infl. 2 680 (NH^+), infl. 3 190 (O—H...N), 3 400 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 8·25 (bs, 1 H, 9-H), 7·88 and 7·78 (ABq, 2 H, 6,7-H_2), 7·40 (d, 1 H, 4-H), 6·70 (m, 2 H, 1,3-H_2), 4·20 (m, 1 H, Ar—CH—N), 2·35—4·00 (m, $ArCH_2$ and 5 NCH_2), 3·45 (bt, 2 H, CH_2O), 3·12 (s, 3 H, SO_2CH_3), 1·60 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{22}H_{28}N_2O_5S_2 + H_2O$ (482·6) calculated: 54·74% C, 6·26% H, 5·81% N, 13·29% S; found: 55·04% C, 5·94% H, 5·86% N, 13·37% S.

8-(Methylsulfonyl)dibenzo[*b,f*]thiepin-2-ol (*XVIII*)

A solution of 1·0 g *III* in 10 ml acetic acid was treated with 0·43 g methanesulfonic acid and 0·50 g 30% H_2O_2 and the mixture was allowed to stand for 24 h at room temperature. It was diluted with 45 ml water and treated with 7 ml NH_4OH. The precipitated solid was partly extracted with chloroform, partly isolated by filtration. The extract was evaporated, the residue was combined with the filtered solid (both fractions are according to TLC indetical) and the obtained 0·70 g mixture were dissolved in 3 ml chloroform and chromatographed on 30 g silica gel. After a small quantity of the least polar components, eluted with chloroform, there were obtained 0·33 g fraction, eluted with chloroform containing 4% ethanol. This fraction was crystallized from acetone; 0·12 g (17%) *XVIII* monohydrate, m.p. 215—216°C with decomposition. Mass spectrum, *m/z* (%): 304 (M^+ corresponding to $C_{15}H_{12}O_3S_2$), 272 (23, $C_{15}H_{12}O_3S$), 193 (23, $C_{14}H_9O$), 175 (12), 80 (11), 64 (100.) UV spectrum: λ_{max} 237·5 nm (log ε 4·65), 295 nm (3·87). IR spectrum: 805, 830, 865 (2 adjacent and solitary Ar—H), 1 140, 1 295 ($ArSO_2R$), 1 230 (ArOH), 1 553, 1 578, 1 591, 3 025, 3 060 (Ar), 3 430 cm^{-1} (OH). For $C_{15}H_{12}O_3S_2 + H_2O$ (322·4) calculated: 55·88% C, 4·38% H, 19·89% S; found: 56·21% C, 3·91% H, 19·73% S.

The authors thank Drs M. Ryska and I. Koruna (Physico-chemical department of this institute) for a part of the mass spectrometric work, Mrs A. Hrádková and Miss Z. Ployerová for recording

the UV *and* IR *spectra, and finally Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech and Mrs J. Kropáčová (Analytical department) for carrying out the analyses.*

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Translated by the author (M. P.).