TRICYCLIC COMPOUNDS CONTAINING TWO CHALCOGEN ATOMS IN THE CENTRAL SEVEN-MEMBERED RINGS AS POTENTIAL DRUGS: SYNTHESIS OF 3-CHLORO-6-(1-METHYL-4-PIPERIDYL)--6*H*-DIBENZ[*b*,*e*]-1,4-OXATHIEPIN AND 6-OXODIBENZ[*b*,*e*]-1,4-OXATHIEPIN-2-ACETIC ACID

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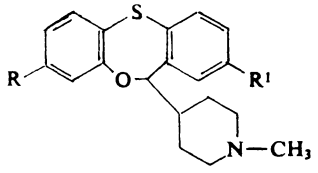
Received February 28th, 1984

2-(4-Chloro-2-fluorophenylthio)benzaldehyde (*IIa*) was subjected to treatment with 1-methyl--4-piperidylmagnesium chloride and the resulting secondary alcohol *IIIa* was cyclized with sodium hydride to the title compound *Ia*. In this synthesis, two by-products were isolated and identified as compounds *IV* and *VIa*. Repeating the synthesis of compound *Ib* by a similar way led to isolation of *Vb* and *VII*. Reaction of thiosalicylic acid with (3-iodo-4-methoxyphenyl)acetic acid in boiling aqueous potassium hydroxide in the presence of copper gave the methoxy diacid *IX* which was demethylated with hydrogen bromide in acetic acid to the hydroxy diacid *X*. Heating with acetic anhydride afforded the title lactone acid *VIII*. Compound *Ia* is an almost noncataleptic neuroleptic with a rather low antidopaminergic activity in the test of influencing the dopamine turnover and metabolism in the rat brain striatum. The acid *VIII* showed some anti-inflammatory activity in the test of carrageenan-induced edema of rat's paw.

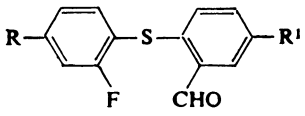
In a previous communication[1] we have described the synthesis of 8-chloro-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*Ib*) which disclosed properties of a potent neuroleptic agent with strong cataleptic and discoordinating and a very low peripheral antiadrenergic activity[2]. It is well known that in compounds of similar structure a shifting of the neuroleptic substituent (in this case the atom of chlorine) into the quasi-symmetrical position, which is more distant from the basic nitrogen atom, leads to deriving noncataleptic substances, with which some antidopaminergic activity is sometimes maintained. This may form a basis for their antipsychotic



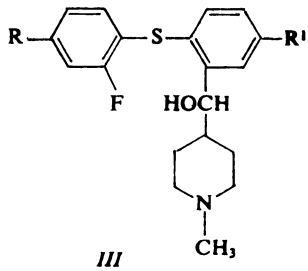
I

In formulae *I*–*III*, *V* and *VI*:
a, R = Cl, R¹ = H *b*, R = H, R¹ = Cl

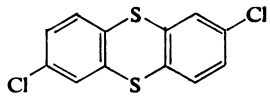
effects; clozapine[3] is the best example of this type. In our studies, we also used several times the same approach in the effort to find useful noncataleptic neuroleptic agents[4-9]. The present communication describes a further attempt in this direction and deals in the first line with the synthesis of 3-chloro-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*Ia*).



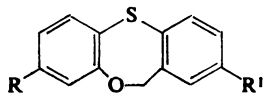
II



III



IV



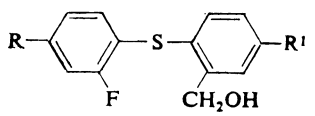
V

The procedure used for the synthesis of compound *Ia* was analogous to that described for the synthesis of compound *Ib* (ref.[1]). 4-Chloro-2-fluorothiophenol[10] was reacted with 2-chlorobenzaldehyde in hexamethylphosphoric triamide in the presence of sodium hydroxide at 100°C and gave the aldehyde *IIa* in a good yield. Chromatography of the mother liquors on aluminium oxide resulted in a small amount of a compound $C_{12}H_6Cl_2S_2$ (mass spectrum and analysis) which was identified as 2,7-dichlorothianthrene (*IV*), being evidently a product of a double substitution reaction of two molecules of the starting 4-chloro-2-fluorothiophenol. The preparation of compound *IV* (designated as 2,6-dichlorothianthrene by using a different numbering of the system) was described in the literature[11] by different methods. The following treatment of the aldehyde *IIa* with the Grignard reagent[12], prepared from 4-chloro-1-methylpiperidine[13], gave the oily secondary alcohol *IIIa* which was used without purification and characterization in the treatment with sodium hydride in dimethylformamide at 50°C. A part of the base *Ia* crystallized directly from the crude product. Chromatography of the mother liquor on aluminium oxide gave first in smaller amounts two little polar substances. The first one was again 2,7-dichlorothianthrene (*IV*) having its origin in the crude aldehyde *IIa* used. It was followed by a substance $C_{13}H_9ClOS$ (mass spectrum) which was contaminated with some 2,7-dichlorothianthrene (*IV*) (mass spectrum and analysis). On the basis of our previous work[14] we assign to this compound the structure of 3-chloro-6*H*-di-

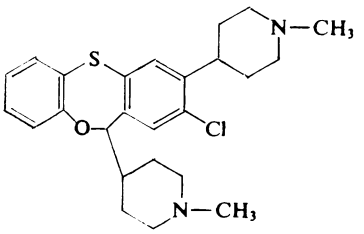
benz[*b*,*e*]-1,4-oxathiepin (*Va*) which was evidently formed by cyclization of the primary alcohol *VIa*, representing a nonisolated product of the reduction of the aldehyde *IIa* by the Grignard reagent. The continued chromatography gave then the main part of the base *Ia* which was characterized by spectra and transformed to the hydrogen maleate.

The interest in the isomer *Ib* led to the necessity of repeating its preparation which proceeded similarly like earlier described[1]. Some new phenomena, however, were observed which are worth mentioning. The crude secondary alcohol *IIIb*, which was obtained by treatment of the aldehyde *IIa* (ref.[1]) with 1-methyl-4-piperidylmagnesium chloride[12] in tetrahydrofuran, was separated by extraction of the basic product (mainly *IIb*) into an aqueous solution of (+)-tartaric acid. The neutral product did not contain the starting aldehyde *IIb* but was a mixture of two more polar components (TLC). One of them was isolated in pure form by crystallization and was identified as the primary alcohol *VIb* (*cf.*[10]). The isolation of this product in this series represents a confirmation of the hypothesis, disclosed in the previous paragraph, which explained the formation of the by-product *Va*. The cyclization of the partly purified fluoro alcohol *IIIb* with sodium hydride in dimethylformamide at 100°C gave a mixture of basic products with strongly prevailing *Ib* which was isolated by a simple chromatography on aluminium oxide in a much better yield than in the previous experiment[1]. A new homogeneous more polar by-product was isolated from the chromatography and gave a crystalline bis(hydrogen maleate). The substance was shown by the mass spectrum to have the surprising elemental composition $C_{25}H_{31}ClN_2OS$ (in agreement with analysis of the maleate). Its molecule contains two 1-methyl-4-piperidyl residues, one of them being attached to an aliphatic carbon and the other to an aromatic carbon (indicated by the most abundant fragments with *m*/*z* 96 and 70, *cf.*[1,14]). The IR spectrum indicates the presence of an Ar—O—R fragment and the bands in the region between 700 and 900 cm^{-1} show 4 adjacent and solitary aromatic C—H bonds. The ^1H NMR spectrum resulted in formulating the product as *VII* which is compatible with all results given by the mass and IR spectra. The main arguments are the two singlets at 7·40 and 7·20 ppm corresponding to two ArH in positions 7 and 10 of the skeleton, further two singlets at 2·26 and 2·24 ppm corresponding to the two NCH_3 groups and finally the signal at 5·68 ppm (doublet) belonging to the proton of the Ar—CH—O fragment. In order to explain the formation of this unprecedented structure we assume that the first step must be a 1,6-addition of the Grignard reagent to the dipole formed by enolization of the aldehyde *IIb* (*cf.*[15–19]); during this step the 1-methyl-4-piperidyl residue enters the position 4 of the starting aldehyde *IIb*. The second step is then a 1,4-addition of a second molecule of the Grignard reagent to the conjugated double bond system of the still nonaromatized species; in this step the 1-methyl-4-piperidyl is being attached to the α-carbon. The final hydrolysis must be accompanied by the loss of two hydrogen atoms (air oxygen dehydrogenation) and rearomatization of the ring

in order to afford the secondary alcohol which would be able to give compound *VII* in the cyclization step.



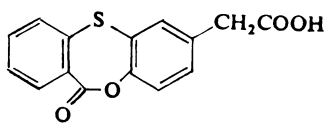
VI



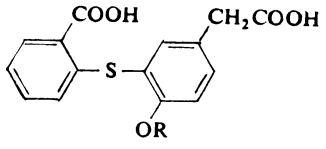
VII

In the second part of this paper we are describing the synthesis of 6-oxodibenz-[*b*,*e*]-1,4-oxathiepin-2-acetic acid (*VIII*) which was prepared as a potential anti-inflammatory agent (this type of activity was claimed for a number of oxodibenzo-xepin- and oxodibenzothiepinacetic acids[20-27]). A reaction of (3-iodo-4-methoxy-phenyl)acetic acid[28] with thiosalicylic acid[29] in a boiling aqueous solution of potassium hydroxide in the presence of copper afforded the diacid *IX* in a good yield. The following demethylation with hydrogen bromide in acetic acid at 90–100°C gave the hydroxy diacid *X* which was treated with boiling acetic anhydride.

In a small batch the desired lactone acid *VIII* was obtained by a direct crystallization of the crude product. In a larger batch a more polar product predominated and separation by chromatography on silica gel was necessary. The main product obtained was the acetoxy diacid *XI* which crystallized from a mixture of benzene and acetone as a benzene solvate. Both acids (*VIII* and *XI*) were characterized by spectra which corroborated their structures.



VIII



IX, R = CH_3
X, R = H
XI, R = $COCH_3$

Compound *Ia* (bis(hydrogen maleate)) was pharmacologically tested as a potential noncataleptic neuroleptic agent at oral administration; the doses in mg/kg were calculated for the base. Acute toxicity in mice, LD_{50} = 170. Discoordinating activity in the rotarod test in mice, ED_{50} = 2·15 (maximum in 2·5 h after the administration). Cataleptic activity in rats: a dose of 50 mg/kg brought about catalepsy in 10% ani-

mals. Antiapomorphine activity in rats: doses of 10–40 mg/kg inhibit significantly the apomorphine agitation but do not influence the stereotypies (the effect of a dose of 40 mg/kg on the agitation disappears within 3 h). A dose of 80 mg/kg increased significantly the homovanillic acid level in the rat brain striatum by 116% in the interval of 3 h, and decreased significantly the dopamine level by 22%. For comparison with the effects of docloxythepin (2-chloro-10-[4-(2-hydroxyethyl)-piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin[6]) *cf.* ref.[30–32], and for comparison with our last noncataleptic series, *cf.*[33]. The compound *Ia* exhibited some antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentration in μg/ml given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus* 50, *Streptococcus faecalis* 100, *Staphylococcus pyogenes aureus* 25, *Escherichia coli* 50, *Proteus vulgaris* 100, *Mycobactrium tuberculosis* H37Rv 100, *Trichophyton mentagrophytes* 50.

The pharmacological data on the most interesting cataleptic compound of this series[1,14], *i.e. Ib* (cloxathiepin, VÚFB-14 107) were completed (*cf.*[1,2]): Discoordinating activity in the rotarod test in rats, ED_{50} = 0·92 mg/kg (oral administration in all of the tests mentioned). The substance inhibits effectively the locomotor activity in the photo-cell method (Dews), D_{50} = 1·8 mg/kg (after 24 h the effect is over even with a higher dose of 4 mg/kg). The duration of thiopental sleeping time is significantly potentiated starting with a dose of 1 mg/kg (administered 1 h before thiopental). The compound antagonizes effectively the apomorphine stereotypies in rats, D_{50} = 3·7 mg/kg (the effect disappears within 24 h). The statement about the low peripheral antiadrenergic activity[2] was substantiated by the following two findings: Antagonization of the adrenaline toxicity in mice, PD_{50} = 2·4 mg/kg (for comparison the PD_{50} values for other neuroleptics are the following ones: clorothepin, 0·44 mg/kg; oxyprothepin[34], 0·22 mg/kg; chlorpromazine, 3·9 mg/kg; perphenazine, 7·6 mg/kg). Antagonization of the noradrenaline toxicity in rats, PD_{50} = 16·9 mg/kg. The compound increases significantly the homovanillinic acid level in the rat striatum in a dose of 0·05 mg/kg (by 139%); it decreases significantly the dopamine level (by 19%) in a dose of 0·015 mg/kg (both in the interval of 3 h after the administration). These effects are at least comparable with those of clorothepin[32,35,36].

The acids *VIII* and *XI* were tested for antiinflammatory activity and showed some effects in the test of carrageenan-induced edema of rat's paw[37] in doses of 25 and 50 mg/kg orally (percent inhibition of the edema given): *VIII*, by 25%; *XI*, by 18% (for ibuprofen as a standard inhibition by 60% after a dose of 25 mg/kg).

EXPERIMENTAL

The melting points of analytical preparations were determined in an automatic Mettler FP-5 melting point recorder. The samples were dried *in vacuo* of 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, the IR spectra (mostly in Nujol) with a Unicam SP 200G and a Perkin Elmer 298 spectrophotometers, the ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with Varian MAT 44S and MCH 1320 spectrometers. The homogeneity of the compounds was checked by thin layer chromatography on silica gel (Silufol).

2-(4-Chloro-2-fluorophenylthio)benzaldehyde (*IIa*)

A solution of 43·25 g 4-chloro-2-fluorothiophenol[10] in 65 ml hexamethylphosphoric triamide was treated with a solution of 10·65 g NaOH in 18 ml water, the temperature rose spontaneously to 75°C, 35·7 g 2-chlorobenzaldehyde were immediately added and the mixture was stirred and heated for 5·5 h to 100°C. After cooling it was distributed between 500 ml water and 600 ml benzene (in three portions), the organic layer was washed with 200 ml 5% NaOH and water, dried with $MgSO_4$ and evaporated. The residue crystallized after mixing with 100 ml light petroleum and the crude product was recrystallized from a mixture of 50 ml benzene and 100 ml light petroleum; 30·8 g (45%) *IIa*, m.p. 87·5–91°C. Analytical sample, m.p. 89–91·5°C (benzene–light petroleum). UV spectrum: λ_{max} 226 nm (log ε 4·36), 233 nm (4·33), 328 nm, inflexes at 252 nm (4·08), 261 nm (4·03), 283 nm (3·77). IR spectrum: 765, 825, 850, 861 (4 and 2 adjacent and solitary Ar—H), 1 460, 1 470, 1 560, 1 583 (Ar), **1 677**, 2 740 cm^{-1} (ArCHO). ^{1}H NMR spectrum: δ 10·35 (s, 1 H, CHO), 7·90 (m, 1 H, 6-H), 6·90–7·60 (m, 6 H, remaining ArH). For C_{13}.H_8ClFOS (266·7) calculated: 58·54% C, 3·02% H, 13·30% Cl, 7·12% F, 12·02% S; found: 58·52% C, 3·02% H, 13·40% Cl, 7·06% F, 11·93% S.

The mother liquors were evaporated and chromatographed on 1 kg neutral Al_2O_3 (activity II). Only the least polar fractions, eluted with light petroleum and a mixture 1 : 1 of light petroleum and benzene led to a homogeneous and crystalline compound, identified as 2,7-dichlorothianthrene (*IV*), m.p. 181·5–183°C (cyclohexane). Mass spectrum, *m/z*: 284 (M^+ corresponding to $C_{12}H_6Cl_2S_2$ in agreement with the analysis). IR spectrum (KBr): 805, 868 (2 adjacent and solitary Ar—H), 1 540, 1 558 cm^{-1} (Ar). Lit.[11], m.p. 181·5°C (186°C with correction).

3-Chloro-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*Ia*)

The Grignard reagent[12] was prepared from 23·2 g 4-chloro-1-methylpiperidine[13] and 4·7 g Mg in 150 ml tetrahydrofuran and was treated under stirring over 15 min with a solution of 30·8 g *IIa* in 85 ml tetrahydrofuran. The mixture was refluxed for 4 h, decomposed with 150 ml 20% NH_4Cl and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated. The residue (42·3 g crude *IIIa*) was dissolved in 200 ml dimethylformamide, the solution was added to a suspension of 4·0 g 80% NaH (suspension in oil) in 200 ml dimethylformamide, the mixture was stirred under nitrogen for 1 h at room temperature, then for 14 h at 50°C and was poured into water. It was extracted with ether, the extract was dried with K_2CO_3 and evaporated. The residue was crystallized twice from a mixture of cyclohexane and light petroleum giving the first 4·1 g homogeneous *Ia*, m.p. 107–109·5°C. IR spectrum: 769, 810, 898 (4 and 2 adjacent and solitary Ar—H), 995 (Ar—O—R), 1 552, 1 580 (Ar), 2 741, 2 785 cm^{-1} (N—CH_3). ^{1}H NMR spectrum: δ 7·55 (m, 1 H, 7-H), 6·70–7·00 (m, 6 H, remaining ArH), 5·90 (d, J = 9·5 Hz, 1 H, Ar—CH—O), 2·30 (s, 3 H, NCH_3). For $C_{19}H_{20}ClNOS$ (345·9) calculated: 65·98% C, 5·83% H, 10·25% Cl, 4·05% N, 9·27% S; found: 65·24% C, 5·71% H, 10·42% Cl, 3·66% N, 9·34% S.

Hydrogen maleate, m.p. 184–185°C (acetone–ethanol–ether). For $C_{23}H_{24}ClNO_5S$ (462·0) calculated: 59·80% C, 5·24% H, 7·68% Cl, 3·03% N, 6·94% S; found: 59·51% C, 5·36% H, 7·87% Cl, 2·83% N, 6·72% S.

The mother liquors after the first crop of *Ia* were evaporated and the residue was chromatographed on a column of 1 kg neutral Al_2O_3 (activity II). Elution with benzene gave first 1·71 g homogeneous compound which crystallized from cyclohexane and melted at 180°C. It was identified as 2,7-dichlorothianthrene (*IV*)(ref.[11]) and found identical with the product, described in the preceding experiment. The next product, eluted also with benzene, were 3·27 g 3-chloro-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*Va*). Even by repeated crystallization from various solvents (cyclohexane, ethanol, methanol) it did not succeed to remove *IV*, present as a contamination. The analytical product melted at 90—94°C (methanol). Mass spectrum, *m/z*: 248 (M^+ corresponding to $C_{13}H_9ClOS$); contamination with *IV* (*m/z* 284, *i.e.* $C_{12}H_6Cl_2S_2$) proven.

Continued elution with benzene gave 21·4 g homogeneous *Ia*, the total yield being thus 25·5 g (64%).

5-Chloro-2-(2-fluorophenylthio)-α-(1-methyl-4-piperidyl)benzyl Alcohol (*IIIb*)

The Grignard reagent[12] was prepared from 26·7 g 4-chloro-1-methylpiperidine[13] and 7·0 g Mg in 165 ml tetrahydrofuran and was treated under stirring over 15 min with a solution of 36·6 g *IIb* (ref.[1]) in 50 ml tetrahydrofuran and the mixture was refluxed for 1·5 h. It was decomposed with 20% NH_4Cl and water and extracted with ether. The organic layer was shaken with 10% tartaric acid and with water. The aqueous layer was made alkaline with NH_4OH, the released base was extracted with benzene, the extract was dried with K_2CO_3 and evaporated giving 37·0 g (74%) crude *IIIb* which was used for the next step.

The organic layer containing neutral by-products was evaporated and the residue was characterized by TLC as a mixture of two components, both of them being more polar than the starting *IIb*. Crystallization from ethanol yielded one of these by-products in pure form; 3·35 g (9%) 5-chloro-2-(2-fluorophenylthio)benzyl alcohol (*VIb*), m.p. 101—103°. Mass spectrum, *m/z* (%): 268 (M^+ corresponding to $C_{13}H_{10}ClFOS$ in agreement with the analysis, 100%), 231 ($C_{13}H_8ClS$), 249 ($C_{13}H_7ClFS$, 58). 172 (C_7H_5ClOS, 38), 139 (C_7H_4ClO, 66), 128 (C_6H_5FS, 25), 77 (27). ^{1}H NMR spectrum: δ 7·50 (bs, 1 H, 6-H), 6·90—7·30 (m, 6 H, remaining ArH), 4·75 (bs, 2 H, $ArCH_2O$), 2·31 (bs, 1 H, OH). Lit[10], m.p. 104—106°C.

8-Chloro-6-(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*Ib*)

Crude *IIIb* (37·0 g) was cyclized by heating with 3·4 g 80% NaH in 300 ml dimethylformamide for 5 h to 100°C (*cf.*[1]). After cooling the mixture was poured into water, extracted with ether, the extract was dried with K_2CO_3 and evaporated. The residue (31·2 g) was chromatographed on a column of 450 g Al_2O_3. After a small least polar fraction benzene eluted 24·8 g (71%) homogeneous *Ib* which afforded 25·75 g hydrogen maleate, m.p. 186—189°C (ethanol). Lit.[1], m.p. 188·5—190°C.

Continued elution with benzene gave 2·0 g homogeneous and more polar oily base which was identified as 8-chloro-6,9-bis(1-methyl-4-piperidyl)-6*H*-dibenz[*b*,*e*]-1,4-oxathiepin (*VII*) and was transformed to the maleate proved to be a bis(hydrogen maleate), m.p. 125—128°C (acetone–ether). Mass spectrum, *m/z* (%): 442·1837 (M^+ corresponding to $C_{25}H_{31}ClN_2OS$, calculated 442·1846, 5%), 407, 372 (6), 344 (7), 317, 281, 221, 99, 96 (100), 70 (98). For $C_{33}H_{39}$·.ClN_2O_9S (675·2) calculated: 58·70% C, 5·82% H, 5·25% Cl, 4·15% N, 4·75% S; found: 57·82% C, 6·15% H, 5·50% Cl, 3·81% N, 4·78% S.

The released base was used for recording spectra. IR spectrum: 750, 770, 870, 896 (4 adjacent and solitary Ar—H), 1 069, 1 079 (Ar—O—R), 1 567, 1 589, 3 060 (Ar), 2 680, 2 735, 2 780 cm^{-1} (N—CH_3 and N—CH_2). ^{1}H NMR spectrum: δ 7·40 and 7·20 (2 s, 1 + 1 H, 7,10-H_2), 6·70 to 7·20 (m, 4 H, remaining ArH), 5·68 (d, J = 9·0 Hz, 1 H, Ar—CH—O), 2·26 and 2·24 (2 s, 3 + 3 H, 2 NCH_3), 1·40—3·00 (m, remaining 8 CH_2 and 2 CH).

[3-(2-Carboxyphenylthio)-4-methoxyphenyl]acetic acid (*IX*)

To a solution of 5·0 g KOH in 50 ml water there were added at 50°C 3·08 g thiosalicylic acid[29] and after 10 min stirring 5·8 g (3-iodo-4-methoxyphenyl)acetic acid[28] and 0·4 g Cu. The mixture was refluxed for 7 h, filtered while hot and the filtrate was acidified with hydrochloric acid. The precipitated crude product was filtered after cooling and boiling with 350 ml 80% aqueous ethanol. A small quantity of a high-melting solid (0·15 g, m.p. 241—242°C) was filtered off, the filtrate was evaporated *in vacuo* to a volume of 50 ml and allowed to crystallize; 5·03 g (79%), m.p. 209—213°C (aqueous ethanol). UV spectrum: λ_{max} 224 nm (log ε 4·42), 252 nm (3·99), 295 nm (3·79), 311 nm (3·75), infl. 320 nm (3·74). IR spectrum: 746, 802, 818, 899 (4 and 2 adjacent and solitary Ar—H), 938, 1 253, 1 269, 1 317, infl. **1 652**, **1 690**, 2 560, 2 625, 2 655, 2 710, infl. 3 100 (COOH), 1 491, 1 555, 1 589, 1 600 cm^{-1} (Ar). ^1H NMR spectrum (C^2H_3.SOC^2H_3): δ *c.* 12·70 (flat band, COOH), 7·91 (m, 1 H, 3-H in the carboxyphenylthio residue), 6·90—7·50 (m, 5 H, 2,5,6-H_3 and 4,5-H_2 of carboxyphenylthio), 6·61 (m, 1 H, 6-H in carboxyphenylthio), 3·69 (s, 3 H, OCH_3), 3·52 (s, 2 H, $ArCH_2CO$). For $C_{16}H_{14}O_5S$ (318·3) calculated: 60·37% C, 4·43% H, 10·07% S; found: 60·39% C, 4·62% H, 9·86% S.

[3-(2-Carboxyphenylthio)-4-hydroxyphenyl]acetic Acid (*X*)

A mixture of 85 ml acetic acid, 20 ml acetic anhydride, 48 ml 48% HBr and 16·5 g *IX* was stirred for 3 h at 90—100°C and saturated by anhydrous HBr. After standing overnight the mixture was diluted with 150 ml water and the precipitated product was filtered after standing for 6 h. It was washed with 20 ml water and dried *in vacuo*. Processing of the mother liquor gave a second crop, the total yield being 14·7 g (74%), m.p. 186—193°C. Analytical sample, m.p. 192—195°C (water). UV spectrum: λ_{max} 297 nm (log ε 3·75), inflexes at 254 nm (3·89) and 320 nm (3·67). IR spectrum: 747, 811, 895 (4 and 2 adjacent and solitary Ar—H), 910, 1 264, 1 276, 1 318, **1 678**, **1 709**, 2560, 2 650, 2 720, infl. 3 100 (COOH), 3 465 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·90 (dd, J = 8·0; 2·0 Hz, 1 H, 3-H in the carboxyphenylthio residue), *c.* 7·20 (m, 4 H, 2,6-H_2 and 4,5-H_2 in carboxyphenylthio), 6·90 (d, J = 8·0 Hz, 1 H, 5-H), 6·65 (bd, J = 8·0 Hz, 1 H, 6-H in carboxyphenylthio), 3·50 (s, 2 H, $ArCH_2CO$). For $C_{15}H_{12}O_5S$ (304·3) calculated: 59·20% C, 3·98% H, 10·53% S; found: 59·21% C, 3·95% H, 10·49% S.

6-Oxodibenz[*b*,*e*]-1,4-oxathiepin-2-acetic Acid (*VIII*)

A) A mixture of 4·45 g *X* and 20 ml acetic anhydride was refluxed for 2 h, filtered, allowed to stand overnight, diluted with 100 ml water, allowed to stand for 4 h, the product was filtered and crystallized from acetic acid; 2·3 g (55%), m.p. 231—236°C. Analytical sample, m.p. 232 to 238°C (acetic acid). UV spectrum: infl. at 251 nm (log ε 3·83). IR spectrum: 742, 823, 894 (4 and 2 adjacent and solitary Ar—H), 920, 1 240, **1 691**, 2 595, 2 650, 2 750, infl. 3 100 (RCOOH), 1 482, 1 585, 3 020, 3 050 (Ar), **1 730** cm^{-1} (lactone ArCOOAr'). ^1H NMR spectrum (C^2H_3.SOC^2H_3): δ 7·20—7·90 (m, 7 H, ArH), 3·60 (s, 2 H, $ArCH_2CO$). For $C_{15}H_{10}O_4S$ (286·3) calculated: 62·93% C, 3·52% H, 11·20% S; found: 62·92% C, 3·59% H, 11·21% S.

B) A mixture of 14·0 g *X* and 100 ml acetic anhydride was refluxed for 4·5 h, diluted with 300 ml water and evaporated. According to TLC the residue is a mixture of *VIII* with a strongly prevailing more polar compound. It was dissolved in chloroform and chromatographed on 200 g silica gel. First to be eluted were 1·32 g (10%) *VIII*, m.p. 233—236·5°C. The elution was continued with ethyl acetate and gave 9·1 g solid melting at 152—156·5°C. Crystallization from a mixture of benzene and acetone led to the formation of a 1 : 1 benzene solvate of [4-acetoxy-2-(2-carboxyphenylthio)phenyl]acetic acid (*XI*); 9·0 g (47%), melting at 95°C and after resolidification again

at 156–158°C. Mass spectrum, *m/z* (elemental composition of the fragment and %): 346 (M^+ corresponding to $C_{17}H_{14}O_6S$), 304 ($C_{15}H_{12}O_5S$, 40), 286 ($C_{15}H_{10}O_4S$, 51), 268 ($C_{15}H_8O_3S$, 55), 240 ($C_{14}H_8O_2S$, 100), 213 ($C_{13}H_9OS$, 57), 212 (47), 184 ($C_{12}H_8$, 40). UV spectrum: λ_{max} 254 nm (log ε 3·95), 278 nm (3·69), 314 nm (3·67). IR spectrum: 740, 830, 880 (4 and 2 adjacent and solitary Ar—H), 910, 1 185, 1 240, **1 675**, **1 709**, 2 565, 2 660, infl. 3 150 (ArCOOH and R-COOH), **1 765** cm^{-1} (ArOCOR). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·89 (m, 1 H, 3-H in the carboxyphenylthio residue), 6·50–7·50 (m, remaining 12 ArH including C_6H_6), 3·60 (s, 2 H, $ArCH_2CO$), 2·02 (s, 3 H, $COCH_3$). For $C_{17}H_{14}O_6S + C_6H_6$ (424·5) calculated: 65·08% C, 4·75% H, 7·55% S; found: 64·52% C, 4·76% H, 7·73% S.

The authors thank to Mrs M. Hrubantová for an important help in the synthetic part, to Drs I. Koruna, J. Schlanger, E. Svátek and Mrs A. Hrádková (physico-chemical department of this institute) for a part of the spectral data, to Dr V. Holá (department of microbiology) for the microbiological data, to Dr J. Grimová (department of pharmacology) for the testing of the acids VIII *and* XI *for antiinflammatory activity, and finally to Mrs J. Komancová, Mrs V. Šmídová and Mr. M. Čech (analytical laboratory) for carrying out the analyses.*

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Translated by the author (M. P.).