# NEUROTROPIC AND PSYCHOTROPIC COMPOUNDS. LI.*

## 8-ACETAMIDO- AND 8-METHYLSELENO DERIVATIVES OF 10-(4-METHYLPIPERAZINO)DIBENZO[*b,f*]THIEPIN

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A synthesis of dibenzo[*b,f*]thiepin derivatives using 2-iodophenylacetic acid (*X*) as the precursor of the A ring is described. Condensation of this acid with potassium salts of 4-aminothiophenol and 4-methylselenothiophenol (*XXII*) produced acids *XI* and *XXV* which were cyclized by polyphosphoric acid to 8-amino (*XIV*) and 8-methylseleno-11*H*-dibenzo[*b,f*]thiepin-10-one (*XXVI*). The usual reaction sequences then led to the synthesis of 8-acetamido- (*III*) and 8-methylseleno-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*IV*) as well as of the corresponding enamine *VI*. While the acetamido derivative *III* is only a weak neuroleptic, the methylseleno derivatives *IV* and *VI* are highly active.

In connection with studying neuroleptics derived from 10-piperazinodibenzo[*b,f*]-thiepin we devoted some attention to 8-amino-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin[1] (*I*) and to the analogous 8-methylthio derivative[2] (*II*). Compound *I* was found to be an active neuroleptic although it differed from the previously prepared most active compounds of this series[2,3] in the presence of a strong polar substituent in position 8. It could be expected that the presence of a free primary amino group will alter to a considerable degree the overall physico-chemical character of the compound, in comparison with compounds of the same series with a nonpolar substituent in position 8, which might unfavourably affect the transport of the compound to its site of action. For this reason we thought it to be useful to prepare a derivative of *I* with the amino group blocked by acylation. In the present communication we describe the synthesis and the properties of the acetamido derivative *III*. Similarly, the methylthio derivative *II* is a potent neuroleptic. As it had been shown before[4] that the sulfur atom in position 5 of the skeleton in this series of compounds may be replaced with an atom of selenium without an adverse effect on its activity the question arose as to the possibility of replacing the sulfur atom in the substituent at position 8 with an atom of selenium. In this way we set out to study the 8-methylseleno derivative *IV*. In view of the fact that introduction of the 10(11)-double bond into the molecule of *II* the neuroleptic activity is further increased[5] we included here also the 8-methylseleno-enamine derivative *VI*.

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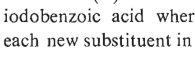
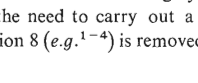
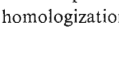
For the preparation of the acetamido derivative *III* two approaches came into consideration: the first was a direct acetylation of amine *I*, the second an independent synthesis during which the acetamide group would be formed at the intermediate stage. Since we did not have sufficient amounts of *I* at our disposal we chose the second alternative and developed a synthesis during which we depended only partly on intermediates described previously.[1]. The first modification was the use of 2-iodophenylacetic acid (*X*) as an universal intermediate during synthesis of *I*–*IV* in place of 2-iodobenzoic acid whereby the need to carry out a four-step homologization for each new substituent in position 8 (*e.g.*[1–4]) is removed.



*I*, R = $NH_2$
*II*, R = $SCH_3$
*III*, R = $NHCOCH_3$
*IV*, R = $SeCH_3$

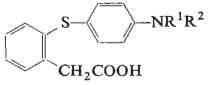


*V*, R = $SCH_3$
*VI*, R = $SeCH_3$

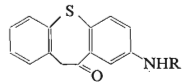


*VII*, R = OH
*VIII*, R = Br
*IX*, R = CN
*X*, R = COOH

In the literature, two preparations of 2-iodophenylacetic acid (*X*) have been described. In the first[6–8], 2-iodotoluene is brominated to 2-iodobenzyl bromide (*VIII*) which is treated with potassium cyanide and the crude nitrile *IX* is subjected to acid hydrolysis. In the second procedure[9] the starting compound is 2-iodobenzoyl chloride and use is made of Wolff's rearrangement of 2-iodophenyl diazomethyl ketone. In our work we selected 2-iodobenzyl alcohol (*VII*) (refs[9–15]) as our starting compound. In view of the fact that reduction of 2-iodobenzoic acid with lithium aluminium hydride in tetrahydrofuran[10] was not found to be suitable (at a slight excess of the reagent a great part of the starting acid remains unreduced but, at the same time, a partial hydrogenolysis of the C—I bond occurs; at a greater excess hydrogenolysis predominates) we looked for a more selective method of reduction. Such was found to be *e.g.* the reduction of a mixed anhydride formed by reaction of 2-iodobenzoic acid with ethyl chloroformate, with sodium borohydride (for analogy see[16]). In terms of yields, it is even more suitable to reduce 2-iodobenzoic acid with diborane generated in the reaction of sodium borohydride with boron trifluoride etherate in tetrahydrofuran. One may also use the reaction of potassium iodide with the diazonium salt prepared from 2-aminobenzyl alcohol[17].

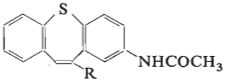


*XI*, $R^1 = R^2 = H$
*XII*, $R^1 = COCH_3$, $R^2 = H$
*XIII*, $R^1 = R^2 = COCH_3$

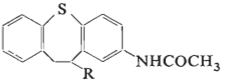


*XIV*, R = H
*XV*, R = $COCH_3$

Alcohol *VII* was converted to 2-iodobenzyl bromide (*VIII*) (refs[6,8,12,13]) with the aid of phosphorus tribromide in the presence of pyridine, the further transformation to 2-iodophenylacetonitrile (*IX*) was carried out by a modification of the described procedure[6,8] whereupon an alkaline hydrolysis to 2-iodophenylacetic acid (*X*) followed.



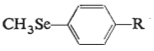

*XVI*, R = $OCOCH_3$
*XVII*, R = H



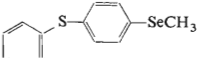

*XVIII*, R = OH
*XIX*, R = Cl

The iodine atom in acid *X* is sufficiently reactive since the compound reacts with thiophenols under the same conditions as 2-iodobenzoic acid: reaction with 4-aminothiophenol[18] in boiling aqueous potassium hydroxide and in the presence of powdered copper gives 2-(4-aminophenylthio)phenylacetic acid[1] (*XI*) in a practically quantitative yield. Even at this stage we attempted a transition to the acetamido series: by heating the amino acid *XI* with acetic anhydride to 100°C we obtained a mixture of the desired acetamido acid *XII* and of the N,N-diacetylamino acid *XIII*. N-Acetylation at this stage is thus not uniform and we postponed it to a next step.

Cyclization of acid *XI* to 8-amino-11*H*-dibenzo[*b*,*f*]thiepin-10-one[1] (*XIV*) was modified by reducing the reaction temperature to 130°C and by increasing the excess of polyphosphoric acid; in this way, we attained an increase of the yield to 80%. For the N-acetylation at this stage we found it most practicable to heat the mixture with acetic anhydride[1]. After acetylation of the amino ketone *XIV* with acetic anhydride in pyridine at room temperature the yield of the acetamido ketone *XV* is somewhat lower and the diacetyl derivative is formed as a by-product. As was shown by the spectra, the compound is not the N,N-diacetyl derivative but rather acetamidofenol acetate *XVI*.




*XX*, R = Br
*XXI*, R = $SeCH_3$
*XXII*, R = SH

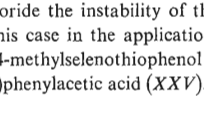



*XXIII*, R = COOH
*XXIV*, R = $CH_2OH$
*XXV*, R = $CH_2COOH$

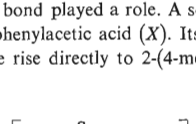
By a modification of the described procedure[1] the ketone *XV* was transformed to acetamido alcohol *XVIII* which, with the aid of anhydrous hydrogen chloride in chloroform, produced a high yield of 8-acetamido-10-chloro-10,11-dihydrodibenzo[*b*,*f*]-thiepin (*XIX*). A substitution reaction of the compound with 1-methylpiperazine in chloroform yielded 76% of base *III* and 20% of the elimination product *XVII*.

During synthesis of *IV* and *VI* we attempted in the first place to make use of the readily available phenyl methyl selenide[19] as the starting compound. Attempts at introducing a suitable substituent into the *p*-position were not successful. An attempt at bromination of phenyl methyl selenide with elementary bromine in boiling tetrachloromethane resulted in demethylation and diphenyl diselenide was the only product isolated from the reaction mixture[20–22]. Demethylation leading to diphenyl diselenide also played a role in the action of chlorosulfonic acid on phenyl methyl selenide in cold chloroform. A by-product isolated there was a compound (m.p. 129–132°C) containing chlorine but not oxygen. This compound, the analysis of which corresponds to the empirical formula $C_7H_8Cl_2Se$, is assumed to be methylphenylselenium dichloride $C_6H_5.SeCl_2.CH_3$ described in the literature[23] as a product of treating phenylmethyl selenide with chlorine.

During synthesis of *IV* and *VI* we concentrated therefore on 4-bromoselenophenol[24,25]. The product prepared by a reaction of selenium with 4-bromophenylmagnesium bromide was converted with dimethyl sulfate in an alkaline solution to 4-bromophenyl methyl selenide (*XX*). The by-product isolated here was 1,4-bis(methylseleno)-benzene (*XXI*) (ref.[26]) apparently formed by a reaction of selenium with 1,4-phenylene-bis(magnesium bromide) which results from the reaction of magnesium with 1,4-dibromobenzene[27] in addition to the desired 4-bromophenylmagnesium bromide. Reaction of 4-bromophenyl methyl selenide (*XX*) with magnesium produced a Grignard reagent which, by treatment with sulfur, yielded the desired 4-methylselenothiophenol (*XXII*). In the following we attempted to apply our older procedure[1–4] to *XXII*. Reaction with 2-iodobenzoic acid in boiling potassium hydroxide in the presence of copper resulted in 2-(4-methylselenophenylthio)benzoic acid (*XXIII*) which was reduced with sodium bis(2-methoxyethoxy)dihydroaluminate[28] in benzene to 2-(4-methylselenophenylthio)benzyl alcohol (*XXIV*). Attempts at further treatment of the compound according to an earlier scheme[1–4] resulted in noncrystalline and polymeric products; it is possible that during the treatment of alcohol *XXIV* with thionyl chloride the instability of the Se—$CH_3$ bond played a role. A solution was found in this case in the application of 2-iodophenylacetic acid (*X*). Its condensation with 4-methylselenothiophenol (*XXII*) gave rise directly to 2-(4-methylselenophenylthio)phenylacetic acid (*XXV*).




*XXVI*




*XXVII*

The acid *XXV* was then cyclized with polyphosphoric acid in toluene; the reaction did not proceed as smoothly as in the case of the analogous methylthio derivative[2]. According to thin-layer chromatography on silica gel the neutral product was a mixture of five compounds where the desired 8-methylseleno-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*XXVI*) represented some 60%, and another compound some 30%. After dilution of the oily mixture of products with benzene a compound melting at 200 to

204°C was produced, which, by its $R_F$, corresponded to the second major product and which, according to analyses and IR spectrum, is a dimeric diselenide *XXVII*. Even in this case the Se-demethylation with subsequent oxidation of the intermediately formed selenophenol derivative plays a role. The ketone *XXVI* was then obtained by column chromatography of the mother liquor after *XXVII* on alumina.

TABLE I

Pharmacological Properties (in mg/kg) of 10-Piperazinodibenzo[*b*,*f*]thiepin Derivatives *III*, *IV*, *VI* and Reference Compounds

| Compound | Application | Toxicity $LD_{50}$ | Rotating rod $ED_{50}$ | Locomotor activity $D_{50}$ | Catalepsy $ED_{50}$ |
|---|---|---|---|---|---|
| *III* | *i.v.* | 29 | 2·3 | — | 6·0 |
| *IV* | *i.v.* | 46 | 0·18 | 0·12 | 0·47 |
| *VI* | *p.o.* | 94 | 2·1 | 0·65 | 0·5 |
| *I* (ref.[1]) | *i.v.* | 9·6 | 0·21 | — | 3·4 |
| *II* (ref.[5]) | *i.v.* | 51 | 0·094 | 0·09 | 1·95 |
| *V* (ref.[5]) | *i.v.* | 40 | 0·045 | — | 0·18 |
| Octoclothepin[3] | *i.v.* | 46 | 0·06 | 0·09 | 2·4 |
| | *p.o.* | 78 | 2·2 | 1·6 | 4·3 |
| Chlorpromazine | *i.v.* | 52 | 0·58 | 0·7 | 8·6 |
| | *p.o.* | 198 | 8·2 | 4·8 | 16·0 |

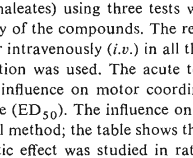
TABLE II

Minimum Inhibitory Concentration (in μg/ml) of 10-Piperazinodibenzo[*b*,*f*]thiepin Derivatives *III*, *IV* and *VI in vitro*

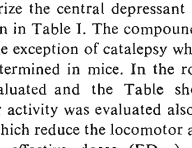
| Microorganism[a] | *III* | *IV* | *VI* |
|---|---|---|---|
| *Streptococcus β-haemolyticus* | 50 | 50 | 12·5 |
| *Streptococcus β-haemolyticus* WARD | 50 | 25 | 12·5 |
| *Staphylococcus pyogenes aureus*[b] | 100 | 50 | 12·5 |
| *Klebsiella pneumoniae* | 100 | — | — |
| *Pseudomonas aeruginosa* | 100 | — | — |
| *Mycobacterium tuberculosis* H37Rv | 25 | 25 | — |
| *Saccharomyces pasterianus* | — | 125 | 62·5 |
| *Trichophyton mentagrophytes* | — | 125 | 62·5 |

[a] Unless a numerical value is given, the compound was ineffective. [b] A penicillin-resistant strain gave the same values.

Reduction of ketone *XXVI* with sodium borohydride yielded the alcohol *XXVIII* which gave rise to the chloro derivative *XXIX* on treatment with hydrogen chloride in benzene at room temperature. Reaction with 1-methylpiperazine in chloroform yielded finally the required amine *IV* besides the elimination product, 2-methylselenodibenzo[*b*,*f*]thiepin (*XXX*). Reaction of ketone *XXVI* with 1-methylpiperazine and titanium tetrachloride in benzene led to the enamine[5] *VI*.




*XXVIII*, R = OH
*XXIX*, R = Cl




*XXX*

Derivatives *III*, *IV*, and *VI* were pharmacologically tested (*III* as dimethanesulfonate, *IV* and *VI* as maleates) using three tests which characterize the central depressant and the neuroleptic activity of the compounds. The results are shown in Table I. The compounds were applied either *p.o.* or intravenously (*i.v.*) in all the tests with the exception of catalepsy where intraperitoneal application was used. The acute toxicity was determined in mice. In the rotating-rod rest in mice the influence on motor coordination was evaluated and the Table shows the mean effective dose ($ED_{50}$). The influence on the locomotor activity was evaluated also in mice, using the photocell method; the table shows the $D_{50}$ doses which reduce the locomotor activity by 50%. The cataleptic effect was studied in rats[29], the mean effective doses ($ED_{50}$) causing a cataleptic state in 50% animals being reported. All the values refer to the respective bases.

For the sake of comparison, Table I contains also compounds *I* (ref.[1]), *II* (ref.[2]) and *V* (ref.[5]) which are direct analogues of the newly synthesized compounds, and also "octoclothepin"[3] and "chlorpromazine" as standards. Several new conclusions for evaluating the relationships between structure and activity in the series of 10-piperazinodibenzo[*b*,*f*]thiepins follow from the Table. Thus, blocking of the free amino group in position 8 by acylation did not bring the expected increase of activity. The acetamido derivative *III* is in both tests less effective than the primary amine *I*: in the rotating-rod test 10 times and in the catalepsy test about twice. The substance is comparable with chlorpromazine in the catalepsy test and is about 4 times less potent in the rotating-rod test.

It is further shown that the methylseleno group as a substituent in position 8 belongs to the most favourable from the point of view of neuroleptic activity. A comparison of the methylseleno derivative *IV* with the methylthio derivative *II* shows that the two substances are about equally toxic, the selenium derivative being twice weaker in the rotating-rod test than the sulfur derivative but on the contrary about 4 times more effective in the catalepsy test. Compound *IV* is also highly effective in the test of potentiation of thiopental sleep in mice (threshold dose 0·025 mg/kg *i.v.*) and further in the antiapomorphine test in rats[30] on subcutaneous application in both the parameters studied (chewing $D_{50}$ 0·53 mg/kg; agitation $D_{50}$ 0·58 mg/kg). The comparison

of methylselenoenamine *VI* with methylthioenamine *V* is complicated by the fact that the selenium derivative is so poorly soluble that it had to be administered per os while the sulfur derivative was tested by parenteral application[5]. In any case, the methylseleno derivative *VI* is an extraordinarily powerful compound in the catalepsy test in which it exceeds "octoclothepin" about 10 times while in the rotating-rod test it is about equally effective as this standard. It thus displays an interesting shift of the equilibrium of the depressant and the cataleptic effect, of a kind similar to that found for dehydroclothepin on parenteral application[5].

Compounds *III*, *IV* and *VI* are inhibitory for growth of several microorganisms *in vitro*. Table II gives the minimum inhibitory concentrations for the various species in μg/ml.

## EXPERIMENTAL

The melting points of the compounds were determined in Kofler's block; the samples were dried in the usual way. The NMR spectra (in deuteriochloroform) were recorded on a ZKR 60 (Zeiss, Jena) spectrometer, the IR spectra (in Nujol or in a KBr pellet) were recorded on a Unicam SP 200 G spectrophotometer or on a Hilger and Watts Infrascan. The UV spectra (in methanol) were recorded on a Unicam SP 700 spectrophotometer.

2-Iodobenzyl Alcohol (*VII*)

*A.* Via *a mixed anhydride*: 119 g ethyl chloroformate were added to a solution of 248 g 2-iodobenzoic acid in 400 ml dioxane and the mixture was refluxed for 5 h. After cooling to 40°C, the mixture was stirred for 2 h while 83 g sodium borohydride were being added, and for another hour at 40—50°C. After standing overnight at room temperature it were heated for 90 min on a boiling-water bath. After cooling, it was decomposed with water and the product was extracted with chloroform. After evaporation of the extract, a total of 218 g residue was obtained which, after mixing with light petroleum, yielded 150 g of a crystalline product. Distillation of the mother liquor gave further 15 g product boiling at 145°C/10 Torr. The total yield was 165 g (71%), m.p. 88—90°C. Ref.[10] reports for a product obtained by reduction with lithium aluminium hydride a m.p. of 87—89°C.

*B. With diborane*: 0·76 g sodium borohydride was added to a solution of 5·0 g 2-iodobenzoic acid in 10 ml tetrahydrofuran and this was followed by 2·5 ml boron trifluoride etherate in 5 ml tetrahydrofuran so that the temperature would not exceed 30°C. The mixture was stirred for 3·5 h at room temperature, then left to stand overnight and decomposed by adding dropwise 10 ml 5% hydrochloric acid and 50 ml water, and extracted with benzene. The extract was washed with 5% sodium hydroxide and water, dried with magnesium sulfate and evaporated. A total of 4·4 g (93%) crystalline product melting at 91°C was obtained.

*C. From 2-aminobenzyl alcohol*: 30·0 g 2-aminobenzyl alcohol[17] were dissolved in a mixture of 250 ml water and 39 ml hydrochloric acid, the solution was cooled below 5°C and, over an hour, a solution of 18·6 g sodium nitrite in 40 ml water was added under stirring. The mixture was stirred for 1 h under cooling and then, over a period of 15 min, added dropwise to a stirred solution of 61 g potassium iodide and 13·5 ml sulfuric acid in 100 ml water. The mixture formed was heated under stirring for 2 h on a boiling-water bath and then left to stand overnight at room temperature. The precipitated product was isolated by extraction with 500 ml benzene, the extract was washed with 20% sodium thiosulfate and evaporated. A total of 44·5 g (78%) crystalline product melting at 80—82°C was obtained, which, by a single crystallization from benzene, yielded an analytical product melting at 86—88°C. For $C_7H_7IO$ (234·0) calculated: 35·92% C, 3·01% H, 54·24% I; found: 36·30% C, 3·07% H, 54·30% I.

2-Iodobenzyl Bromide (*VIII*)

A mixture of 14·5 g pyridine and 17 ml benzene was added dropwise to a solution of 73 g phosphorus tribromide in 27 ml benzene at −5°C. To the mixture formed, 172 g crystalline 2-iodobenzyl alcohol was added over 90 min under stirring and cooling (temperature below 10°C). The mixture was then left for 2 days at room temperature, was heated for 1 h to 50°C, coolled and decomposed with 200 ml 5% hydrochloric acid and extracted with 300 ml chloroform. The extract was quickly washed with ice-cold 5% solution of sodium hydroxide and water. Its evaporation produced 218 g (99%) colourless product melting at 56—57°C. Ref.[12,13] give a m.p. of 55—55·5°C for a product obtained differently.

2-Iodophenylacetic Acid (*X*)

58 g sodium cyanide were added to a solution of 209 g 2-iodobenzyl bromide in 350 ml dimethylformamide under stirring over a 30 min period, the mixture was stirred for another hour and left to stand overnight. On the next day, it was heated for 2 h on a boiling-water bath, dimethylformamide was distilled off at reduced pressure, the residue was decomposed with water and extracted with benzene. Evaporation of the extract yielded 168 g crude 2-iodophenylacetonitrile (*IX*) (refs[6,8]). The residue was dissolved in 500 ml ethanol, a solution of 150 g potassium hydroxide in 270 ml $H_2O$ was added and the mixture was refluxed for 4 h. After cooling, ethanol was evaporated for the most part at reduced pressure, the residue was dissolved in 350 ml water, the solution was washed with benzene and made acid with concentrated hydrochloric acid. Filtration yielded 164·4 g (91%) product melting at 114—116°C (aqueous ethanol). Ref.[6–9] give melting points between 110 and 117°C.

2-(4-Aminophenylthio)phenylacetic Acid (*XI*)

23 g 4-aminothiophenol[18] (b.p. 152°C/24 Torr, m.p. 39—42°C), 47 g acid *X* and 2 g copper powder added to a solution of 30·8 g potassium hydroxide in 310 ml water. The mixture was refluxed under stirring for 7 h (130°C bath), filtered while hot and the filtrate was made acid with dilute hydrochloric acid to a slightly acid reaction. A total of 45·5 g (98%) product melting at 177—182°C precipitated; this was recrystallized from aqueous ethanol to the analytical product melting at 183—185°C. For $C_{14}H_{13}NO_2S$ (259·3) calculated: 64·85% C, 5·05% H, 5·40% N, 12·36% S; found: 64·57% C, 5·06% H, 5·16% N, 12·12% S. For a product prepared before by a different procedure, a m.p. of 182—184°C was found[1].

2-(4-Acetamidophenylthio)phenylacetic Acid (*XII*)

A mixture of 1·58 g acid *XI* and 10 ml acetic anhydride was heated for 4 h to 100°C, acetic anhydride was distilled off *in vacuo* and the residue was boiled with aqueous dioxane. After evaporation of the volatile products at reduced pressure to dryness the residue was boiled with benzene and the insoluble fraction was recrystallized from aqueous ethanol: 1·2 g (65%), m.p. 170 to 171°C. For $C_{16}H_{15}NO_3S$ (301·3) calculated: 63·78% C, 5·02% H, 4·65% N, 10·62% S; found 63·78% C, 5·04% H, 4·53% N, 10·43% S.

Evaporation of the benzene mother liquor yielded 0·65 g substance crystallizing from aqueous methanol; m.p. 140—142°C. UV spectrum: $\lambda_{max}$ 219 nm (inflex) (log ε 3·947), 254 nm (4·171), inflex 274 nm (3·896). IR spectrum (Nujol): 751 (1,2-$C_6H_4$), 820 (1,4-$C_6H_4$), 1240 and 1728 (COOH), 1696 and 1703 $cm^{-1}$ (N—CO). We are dealing here with 2-(*4-diacetylaminophenylthio)phenylacetic acid* (XIII). For $C_{18}H_{17}NO_4S$ (343·3) calculated: 62·95% C, 4·99% H, 4·08% N, 9·34% S; found: 63·13% C, 5·15% H, 4·22% N, 9·32% S.

8-Amino-11*H*-dibenzo[*b,f*]thiepin-10-one (*XIV*)

Acid *XI* (99 g) was added under stirring over 20 min at 130°C to polyphosphoric acid prepared from 900 g phosphorus pentoxide and 500 ml 80% phosphoric acid. The mixture was maintained at that temperature for 90 min. After partial cooling, it was poured into 6 liters of water. After standing overnight, the precipitated product was filtered, washed with 10% sodium carbonate and water and recrystallized from benzene; 74·2 g (81%), m.p. 185—188°C. IR spectrum is identical with the spectrum of the previously described product[1] for which a m.p. of 186—188°C was reported.

8-Acetamido-11*H*-dibenzo[*b,f*]thiepin-10-one (*XV*)

Acetic anhydride (1·33 g) was added to a solution of 2·75 g aminoketone *XIV* in 25 ml pyridine, the mixture was left to stand for 24 h at room temperature and then poured into water. The precipitated compound was recrystallized from ethanol: 2·25 g (70%), m.p. 214—217°C. It is identical with the product previously obtained by acetylation without pyridine.

According to thin-layer chromatography on silica gel the mother liquor contained another compound which was isolated by evaporation and crystallization from a mixture of benzene and cyclohexane: m.p. 155—156°C. The compound in question is 8-*acetamido*-10-*acetoxydibenzo*[*b,f*]*thiepin* (XVI) as demonstrated by spectra as well as analysis. UV spectrum: $\lambda_{max}$ 225 nm (log $\varepsilon$ 4·478), 267 nm (4·613), inflex 290 nm (3·848). IR spectrum (Nujol): 762 (1,2-$C_6H_4$), 830 and 900 (1,2,4-$C_6H_3$), 1227 (C═C—OCO), 1685 (NCOR), 1767 (C═C—OCOR), 3500 $cm^{-1}$ (NH). NMR spectrum: $\delta$ 7·77 (singlet, 2 H, one of them disappearing after deuterization, aromatic proton in position 9 and NH), 7·00—7·60 (multiplet, 6 H, the remaining aromatic protons), 6·91 (singlet, 1 H in —CH═C—), 2·28 (singlet, 3 H in $CH_3CON$), 2·06 (singlet, 3 H in $CH_3$.COO). For $C_{18}H_{15}NO_3S$ (325·3) calculated: 66·45% C, 4·65% H, 4·31% N, 9·84% S; found: 66·75% C, 4·67% H, 4·18% N, 9·76% S.

8-Acetamido-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*XVIII*)

A solution of 0·76 g sodium borohydride in 10 ml water and 0·2 ml 20% sodium hydroxide was added dropwise to a warm solution of 5·2 g ketone *XV* in 130 ml ethanol and the mixture was refluxed for 2 h. After evaporation of ethanol the residue was mixed with 80 ml water, made acid with 5 ml hydrochloric acid and the precipitated substance was filtered; 5·0 g (96%), m.p 221—228°C. For the reduction performed in a mixture of ethanol and dioxane, a yield of 66% was reported[1] with a m.p. of the pure product of 227—229°C.

8-Acetamido-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin (*XIX*)

Anhydrous hydrogen chloride was introduced under stirring into a suspension of 4·9 g crude alcohol *XVIII* in 200 ml chloroform. After 30 min, 1·3 g anhydrous calcium chloride was added to the solution and saturation with hydrogen chloride continued for 90 min. After standing overnight, the reaction mixture was heated to 50°C and filtered, the filtrate was evaporated *in vacuo* and the residue recrystallized from a mixture of chloroform and benzene; 4·0 g (77%), m.p. 146—147°C. For $C_{16}H_{14}ClNOS$ (303·8) calculated: 63·25% C, 4·64% H, 11·67% Cl, 4·62% N, 10·55% S; found: 62·87% C, 4·65% H, 12·01% Cl, 4·44% N, 10·38% S.

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

A mixture of 3·8 g chloride *XIX*, 10 ml 1-methylpiperazine and 10 ml chloroform was refluxed for 7 h. After standing overnight, chloroform was evaporated, the residue mixed with 50 ml

water and extracted with 50 ml benzene. The benzene layer was washed with water and the basic fraction was extracted from it into 5% hydrochloric acid (twice 50 ml). The combined acid solutions were made alkaline with 20% sodium hydroxide and the released base was re-extracted with benzene. Evaporation of the extract yielded 3·5 g (76%) amorphous base *III*. IR spectrum (KBr): 755, 822 and 895 (1,2-$C_6H_4$ and 1,2,4-$C_6H_3$), 1533, 1586, 1604, 1670 (Ar, CONH), 2805, 2942 (CH), 3070, 3190, 3300 and 3410 $cm^{-1}$ (NH).

*Dimethanesulfonate* crystallizes as monohydrate, m.p. 172—177°C (changes from 150°C up; ethanol–ether). For $C_{23}H_{35}N_3O_8S_3$ (577·7) calculated: 47·81% C, 6·11% H, 7·27% N, 16·65% S; found: 47·74% C, 6·10% H, 7·09% N, 16·06% S.

*Di(hydrogensulfate)* crystallizes with 1 molecule of water and 1 molecule of ethanol, m.p. 185—187°C (aqueous ethanol–ether). For $C_{23}H_{37}N_3O_{11}S_3$ (627·8) calculated: 44·01% C, 5·94% H, 6·69% N, 15·32% S; found: 44·16% C, 5·80% H, 6·46% N, 15·11% S.

After extraction of the basic fractions with dilute hydrochloric acid, the benzene fraction yielded by evaporation 0·67 g (20%) *2-acetamidodibenzo*[b,f]*thiepin* (XVII), m.p. 201—202°C (aqueous ethanol). UV spectrum: $\lambda_{max}$ 225 nm (log ε 4·150), 266·5 nm (4·320). IR spectrum (Nujol): 753 (1,2-$C_6H_4$), 829 and 894 (1,2,4-$C_6H_3$), 1533, 1577 and 1663 (CONH), 3273 $cm^{-1}$ (NH). For $C_{16}H_{13}NOS$ (267·3) calculated: 71·90% C, 4·90% H, 5·24% N, 11·98% S; found: 71·34% C, 4·95% H, 5·19% N, 12·16% S.

Diphenyl Diselenide

A. *From phenylmethyl selenide when attempting a bromination*: A solution of 89 g bromine in 50 ml tetrachloromethane was added dropwise to a boiling solution of 95 g phenyl methyl selenide (b.p. 98—102°C/22 Torr)[19] in 40 ml tetrachloromethane and the mixture was refluxed for 15 h. After cooling, the reaction mixture was washed with water, with a solution of sodium thiosulfate and again with water; the tetrachloromethane was evaporated and the residue (65 g) was identified as diphenyldiselenide, m.p. 62°C (yellow needles from ethanol). For $C_{12}H_{10}Se_2$ (312·1) calculated: 46·17% C, 3·23% H, 50·60% Se; found: 45·98% C, 3·13% H, 50·64% Se. Ref.[20—22] give for this compound m.p. from 62 to 63·5°C.

B. *From phenylmethyl selenide when attempting a chlorosulfonation*: Chlorosulfonic acid (90 g) was added dropwise under stirring to a solution of 60 g phenylmethyl selenide in 250 ml chloroform, the mixture was stirred for another hour at room temperature and poured over ice. Filtration resulted in 8·0 g colourless substance which crystallized from benzene and had a m.p. of 131 to 132·5°C. The compound in question is probably *methylphenylselenium dichloride* $C_6H_5.SeCl_2.CH_3$ for which ref.[23] gives a m.p. of 122°C. For $C_7H_8Cl_2Se$ (242·0) calculated: 34·74% C, 3·33% H, 29·30% Cl, 32·63% Se; found: 35·22% C, 3·47% H, 29·39% Cl, 32·53% Se. From the filtrate after the preceding compound the chloroform layer was separated, dried ($MgSO_4$) and subjected to distillation. 20·25 g of the starting compound was recovered, b.p. 81°C/11 Torr and further 10·85 g fraction boiling at 150°C/1 Torr and melting at 60—62°C was obtained. Here again the compound is diphenyl diselenide.

4-Bromophenylmethyl Selenide (*XX*)

Grignard's reagent was prepared from 18·95 g magnesium and 184 g 1,4-dibromobenzene[27] in 800 ml ether. Over a period of 45 min, 52·5 g grey selenium was added under stirring and the mixture was stirred and refluxed for further 30 min. After standing overnight, the mixture was poured into 0·75 kg ice and 150 ml hydrochloric acid, the ether layer was separated and shaken with 600 ml (in two parts) of 10% sodium hydroxide. The solution of the sodium salt of crude

4-bromoselenophenol[24,25] obtained was methylated at 20—40°C under stirring by adding dropwise 130 g dimethyl sulfate. Finally, the reaction mixture was heated on a boiling-water bath. The product precipitated upon cooling was isolated by extraction with chloroform and by evaporation of the extract: 108 g. Its distillation on a column yielded 93g product boiling at 125°C° 10 Torr which crystallizes from ethanol and, according to thin-layer chromatography on silica gel, is homogeneous: m.p. 48—49°C. For $C_7H_7BrSe$ (250·0) calculated: 33·63% C, 2·82% H, 31·97% Br, 31·58% Se; found: 33·62% C, 2·84% H, 31·60% Br, 32·06% Se.

Crystallization of the distillation residue from ethanol gave rise to another substance, melting at 78°C which was identified as 1,4-*bis(methylseleno)benzene* (XXI) (ref.[26] gives a m.p. of 81°C). NMR spectrum: $\delta$ 7·32 (singlet, 4 H, protons of the aromatic ring), 2·30 (singlet, 6 H of $CH_3$ groups). For $C_8H_{10}Se_2$ (264·1) calculated: 36·38% C, 3·82% H, 59·80% Se; found: 36·44% C, 3·89% H, 59·30% Se.

4-(Methylseleno)thiophenol (*XXII*)

Reaction of 7·2 g magnesium with 71·5 g compound *XX* in 150 ml tetrahydrofuran yielded a Grignard reagent. After dissolving most of the magnesium the mixture was refluxed for further 30 min under stirring and then 9·0 g sulfur powder was added over 1 h. The mixture was stirred for 1 h, decomposed by pouring over 300 g ice and 70 ml hydrochloric acid, the ether layer was separated and shaken with 200 ml 10% sodium hydroxide. The alkaline solution was made acid with hydrochloric acid and the product was extracted with ether. The extract was dried with calcium chloride and evaporated. A total of 37·5 g (66%) crude product usable for further work was obtained. The sample was redistilled for analysis: b.p. 105°C/2 Torr. For $C_7H_8SSe$ (203·2) calculated: 41·38% C, 3·97% H, 38·87% Se; found: 41·61% C, 4·01% H, 39·66% Se.

2-(4-Methylselenophenylthio)benzoic Acid (*XXIII*)

36·5 g crude *XXII*, 44·6 g 2-iodobenzoic acid and 2 g copper powder were gradually added to a solution of 30·8 potassium hydroxide in 310 ml water and the mixture was refluxed for 6 h. After adding charcoal, it was filtered while hot and the filtrate was cooled and made acid with hydrochloric acid: 46·8 g (81%), m.p. 192—192·5°C (ethanol). For $C_{14}H_{12}O_2SSe$ (323·3) calculated: 52·01% C, 3·74% H, 24·43% Se; found: 52·14% C, 3·85% H, 24·73% Se.

2-(4-Methylselenophenylthio)benzyl Alcohol (*XXIV*)

Sodium bis(2-methoxyethoxy)dihydroaluminate[28] (107·5 ml 53% benzene solution) was added dropwise over 45 min under stirring to a suspension of 45·5 g acid *XXIII* in 250 ml benzene. The mixture was stirred at room temperature for 3 h, decomposed with 150 ml 20% sodium hydroxide, the benzene layer was washed with water, dried with $Na_2SO_4$ and evaporated. A total of 39·0 g (90%) oily product was obtained, a small part of which was redistilled for analysis: b.p. 192 to 194°C/0·7 Torr, m.p. 46—48°C. For $C_{14}H_{14}OSSe$ (309·3) calculated: 54·37% C, 4·56% H, 25·53% Se; found: 54·26% C, 4·60% H, 25·34% Se.

2-(4-Methylselenophenylthio)phenylacetic Acid (*XXV*)

Compound *XXII*, 24·7 g, 28·8 g 2-iodophenylacetic acid (*X*) and 1·0 g copper powder were added to a solution of 18·5 g potassium hydroxide in 190 ml water and the mixture was refluxed 8 h under stirring. After filtration, the filtrate was made acid with hydrochloric acid and the precipitated crude product was recrystallized first from aqueous ethanol with charcoal and then from a mix-

ture of benzene and light petroleum; 21·2 g (58%), m.p. 109—112°C. For $C_{15}H_{14}O_2SSe$ (337·3) calculated: 53·41% C, 4·18% H, 23·41% Se: found: 53·38% C, 4·24% H, 23·44% Se.

8-Methylseleno-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*XXVI*)

Toluene 40 ml and 12·9 g acid *XXV* were added to polyphosphoric acid prepared from 40 ml 80% phosphoric acid and 80 g phosphorus pentoxide, and the mixture was vigorously stirred and heated for 2 h to 120°C. After partial cooling, it was poured into 400 ml water, the toluene layer was separated and the aqueous layer was extracted with benzene. The combined organic layers were washed with water, 5% sodium hydroxide and agains with water. The solvents were distilled off at reduced pressure. A total of 8·9 g oily residue was obtained which was found to contain five components (thin-layer chromatography on silica gel). After addition of benzene, 1·15 g compound melting at 200—204°C (benzene) precipitated. The compound is probably *di*(10-*oxo*-11*H*-*dibenzo*[*b*,*f*]*thiepin*-8-*yl*) *diselenide* (XXVII). IR spectrum (KBr): 747, 765, 832 and 880 (1,2-$C_6H_4$ and 1,2,4-$C_6H_3$), 1 533 (Ar), 1 668 (ArCO), 2 890 and 2 960 ($CH_2$), 3 045 $cm^{-1}$ (Ar—H). For $C_{28}H_{18}O_2S_2Se_2$ (608·5) calculated: 55·27% C, 2·98% H, 25·95% Se; found: 55·23% C, 3·18% H, 25·75% Se. The oil (7·75 g) obtained by evaporation of the filtrate was chromatographed on a column of alumina (activity II). A mixture of benzene and light petroleum was then used to wash out 0·85 g strongly pungent mixture of three compounds which were not further separated and identified. Elution with benzene then yielded 5·4 g (44%) *ketone* XXVI melting at 105·5—107°C (cyclohexane). For $C_{15}H_{12}OSSe$ (319·3) calculated: 56·43% C, 3·79% H, 24·73% Se; found: 56·59% C, 3·87% H, 25·03% Se.

8-Methylseleno-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol (*XXVIII*)

Several drops of 20% sodium hydroxide, followed by 1·18 g sodium borohydride were added to a solution of 5·0 g ketone *XXVI* in 80 ml ethanol and the mixture was refluxed for 3 h. After cooling, it was poured into 150 ml 5% hydrochloric acid and the product was extracted with benzene. Usual treatment of the extract yielded 5·0 g crude alcohol *XXVIII* which was recrystallized from a mixture of benzene and light petroleum: 3·7 g (73·5%), m.p. 115°C. For $C_{15}H_{14}OSSe$ (321·3) calculated: 56·07% C, 4·39% H, 24·58% Se; found: 56·79% C, 4·48% H, 24·65% Se.

8-Methylseleno-10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXIX*)

Anhydrous calcium chloride 2 g was added to a solution of 3·6 g alcohol *XXVIII* in 30 ml benzene and the stirred suspension was saturated for 2·5 h with anhydrous hydrogen chloride. After standing overnight, the hydrogen chloride was introduced for 2 h at 40—50°C, the mixture was filtered and the filtrate evaporated at reduced pressure. A total of 3·8 g (100%) product was obtained: m.p. 109°C (cyclohexane). For $C_{15}H_{13}ClSSe$ (339·7) calculated: 53·02% C, 3·86% H, 10·44% Cl, 23·24% Se; found: 53·28% C, 3·97% H, 10·38% Cl, 23·00% Se.

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

A mixture of 3·8 g chloride *XXIX*, 10 ml 1-methylpiperazine and 10 ml chloroform was refluxed for 7 h, chloroform was then evaporated and the residue was separated between 50 ml water and 50 ml benzene. The benzene layer was washed with water and shaken with 50 ml 10% hydrochloric acid. The precipitate was filtered and suspended in the acid aqueous phase of the filtrate. Alkalinization with 20% solution of sodium hydroxide and extraction with chloroform yielded

3·6 g (80%) base *IV* from which a *maleate* was prepared in the usual way: m.p. 137—138°C (ethanol–ether). For $C_{24}H_{28}N_2O_4SSe$ (519·5) calculated: 55·49% C, 5·43% H, 5·39% N, 15·20% Se; found: 55·56% C, 5·59% H, 5·22% N, 15·04% Se.

From the benzene layer from which base *IV* had been washed out, evaporation yielded 0·65 g (19%) 2-*methylselenodibenzo*[*b,f*]*thiepin* (XXX), m.p. 67·5—68°C (ethanol). UV spectrum: $\lambda_{max}$ 220·5 nm (log ε 4·378), 264 nm (4·450). IR spectrum (Nujol): 741 (1,2-$C_6H_4$), 801, 878 (1,2,4-$C_6H_3$), 900, 920, 1 094, 1 379 $cm^{-1}$. For $C_{15}H_{12}SSe$ (303·3) calculated: 59·40% C, 3·99% H, 26·04% Se; found: 59·76% C, 4·21% H, 25·89% Se.

8-Methylseleno-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*VI*)

A solution of 1·0 g titanium tetrachloride in 10 ml benzene was added dropwise to a solution of 3·3 g ketone *XXVI* and 10 g 1-methylpiperazine in 30 ml benzene and the mixture was stirred for 1 h at room temperature and then refluxed for 26 h. After cooling, it was decomposed with 50 ml water, after 1 h of stirring it was filtered, the benzene fraction was washed with water and evaporated. The crude base (3·82 g) was dissolved in ethanol and neutralized by an addition of 1·05 g maleic acid in ethanol. A total of 3·15 g *maleate*, melting at 198—200°C (ethanol) under decomposition, was obtained. For $C_{24}H_{26}N_2O_4SSe$ (517·5) calculated: 55·70% C, 5·06% H; found: 56·22% C, 5·44% H.

Decomposition of the maleate with 10% sodium hydroxide and extraction with chloroform yielded the crystalline base, m.p. 149—150°C (ethanol). NMR spectrum: δ 7·72 (singlet, 1 H in position 9 of the skeleton), 7·65—7·00 (multiplet, 6 H, other protons of the aromatic rings), 6·36 (singlet, 1 H of —CH=C—), 3·00 (multiplet, 4 H of $CH_2$ groups in positions 2 and 6 of the piperazine ring), 2·55 (multiplet, 4 H of remaining $CH_2$ groups of piperazine), 2·35 (singlet, 3 H in N—$CH_3$), 2·31 (singlet, 3 H in Se—$CH_3$). For $C_{20}H_{22}N_2SSe$ (401·4) calculated: 59·84% C, 5·52% H, 6·98% N, 19·67% Se; found: 59·30% C, 5·69% H, 6·68% N, 19·73% Se.

*The antiapomorphine activity of* IV *was tested by Dr J. Metyš of the pharmacological department. The antimicrobial activity was tested by Dr J. Turinová at the bacteriological department. The NMR spectra were recorded and interpreted by Dr B. Kakáč and Dr J. Holubek, the IR spectra and UV spectra by Dr E. Svátek and Mrs P. Vejdělková of the physico-chemical laboratories. The analytical determinations were done in the analytical department by Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová, Mr M. Čech and Mrs A. Slavíková. Technical cooperation with the preparative section of the work by Mr Z. Šedivý, Mrs E. Princová, Mrs H. Nováková, Mr L. Tůma, Mrs P. Vejdělková and Mrs M. Hrubantová is acknowledged.*

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