SYNTHESIS OF NEW DIBENZO[*b*,*e*]THIEPIN DERIVATIVES RELATED TO THE ANTIDEPRESSANT AGENT PROTHIADENE*

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Received December 21st, 1978

A reaction of dibenzo[*b*,*e*]thiepin-11(6*H*)-one with cyclopropylmagnesium bromide afforded the carbinol *VII* giving by treatment with hydrogen bromide the bromo derivative *IV*. Application of the Gabriel synthesis led to the primary amine *III* postulated earlier to be a metabolite of the antidepressant agent prothiadene (*I*). Demethylation of 2-methoxy-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*X*) with boron tribromide or hydrobromic acid gave mixtures of geometric isomers of the phenol *IX* from which either the *trans*- or *cis*-form could be isolated; *trans*-*IX* is another potential metabolite of prothiadene (*I*). Attempts at preparing prothiadene N-oxide yielded as the main product the nitrogen-free diene *XI* which was apparently formed by a Cope elimination. The analogous sulfone *XII* was obtained as a by-product of the preparation of prothiadene S,S-dioxide (*XV*). Treatment of dibenzo[*b*,*e*]thiepin-11(6*H*) one with methoxymethylmagnesium chloride opened the access to the aldehyde *XVI* which was further used for the preparation of the nitrile *XVIII*, alcohol *XIX*, carboxylic acid *XX* and acrylic acid *XXI*.

In spite of the fact that prothiadene (dosulepin, dothiepin) (ref.[1-4]), *i.e.* *trans*-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*I*) hydrochloride, is one of the most successful antidepressant agents and reached practical use[5-7], the knowledge of its fate in the organism has been rather limited until now. In rats, a pharmacokinetic and metabolic study of [^{35}S]-prothiadene (*I*) was carried out[8] in which seven basic metabolites and two glucuronides were detected in the urine. On the basis of a chromatographic comparison with authentic standards, northiadene (*II*) (ref.[3,9]) and prothiadene S-oxide (*XIV*) (ref.[3,9]) were unequivocally identified as metabolites. For a further metabolite, the structure of *III* (nor$_2$-prothiadene) was suggested, and for one of products of the glucuronide fraction cleavage with β-glucuronidase, the structure of 2-hydroxy derivative of prothiadene *IX* was proposed; authentic samples of *III* and *IX* were not available at that time. More recently, metabolites of prothiadene (*I*) in the urine of patients were investigated[10,11]. In addition to northiadene (*II*) and prothiadene S-oxide (*XIV*), northiadene S-oxide was identified as a metabolite which was prepared by synthesis for comparison[3]. Prothia-

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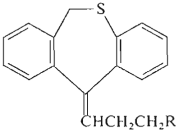
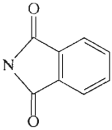
* Part CXXX in the series Neurotropic and Psychotropic Agents; Part CXXIX: This Journal *44*, 2139 (1979).

dene N-oxide (the most polar product) was further postulated to be a metabolite; for comparison, however, a properly characterized synthetic substance was not available. Finally, after the cleavage of the glucuronide fraction, two products were detected which are considered to be hydroxy derivatives of prothiadene with unknown location of the hydroxyl group.



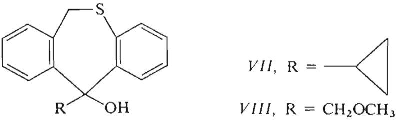
I, R = $N(CH_3)_2$
II, R = $NHCH_3$
III, R = NH_2
IV, R = Br

V, R =

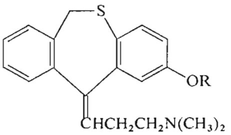


VI, R = $\overset{(+)}{N}(CH_3)_3\ I^{(-)}$

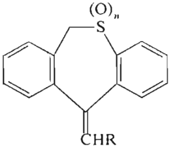
The main objects of this paper are descriptions of syntheses of nor$_2$-prothiadene (*III*), further of the 2-hydroxy derivative *IX*, and finally of the attempt at preparing prothiadene N-oxide. In the synthesis of the primary amine *III*, the starting material was the known dibenzo[*b*,*e*]thiepin-11(6*H*)-one[1,2]; an analogous procedure like in the preparation of the dibenzo[*a*,*d*]cycloheptene analogue, *i.e.* nor$_2$-amitriptyline[12] was used. Cyclopropyl bromide[13] in tetrahydrofuran was transformed to the Grignard reagent giving by treatment with the mentioned ketone the tertiary alcohol *VII*. Following reaction with a solution of hydrogen bromide in acetic acid at 15°C effected dehydration with simultaneous opening of the cyclopropane ring; 11-(3-bromopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*IV*) was obtained as the product. This crystalline substance represents an individual and homogeneous geometric isomer; its IR spectrum in the region of out-of-plane vibrations of the aromatic C—H bonds is identical with that of *trans*-prothiadene (*I*). On this basis, it is possible to ascribe *trans* configuration to compound *IV*. At this opportunity, we have to mention that the *trans* configuration of prothiadene (*I*), derived only on the basis of its IR spectrum[3], was definitely established in the meantime by an X-ray crystallographic study[14]. A reaction of the bromo derivative *IV* with potassium phthalimide in dimethylformamide yielded a crystalline and homogeneous phthalimido derivative *V* to which on the basis of a comparison of the ^{1}H-NMR spectrum with that of the bromide *IV*, *trans*-configuration could again be ascribed: the only olefinic proton present exhibits in both of the compounds a precisely identical chemical shift and coupling constant (t, 5·90 ppm, $J = 7{\cdot}0$ Hz). Hydrazinolysis of compound *V* in ethanol resulted in the primary amine *III*, the base being crystalline, and whose *trans*-configuration is supported by the IR and ^{1}H-NMR spectra. For pharmacological testing, it was converted to the maleate. For the same purpose, *trans*-prothiadene base (*I*) (ref.[3]) was transformed in the usual way to the quaternary methiodide *VI*.



The preparation of the 2-hydroxy derivative *IX* started from the corresponding 2-methoxy analogue *X* the synthesis of which was described in the literature[15]. It was obtained by the same method which was used by our group in the synthesis of the 2-methyl compound[16,17] and a series of further 2-substituted analogues[16]. All of these compounds are formed by an acid catalyzed dehydration of the corresponding tertiary alcohols; mixtures of geometrical isomers are commonly obtained. Two cases, which were investigated in detail, *i.e.* the cases of prothiadene (*I*) (ref.[3]) and of its 2-methyl derivative[17], indicated that *trans*-forms are heavily predominating in these mixtures. We thus may assume the same for the case of the methoxy compound *X*. This was described only in the form of the crystalline oxalate[15] from which we were able to prepare a crystalline base; this fact indicates the homogeneity of the substance for which *trans*-configuration is assumed. A gentle demethylation of this compound with boron tribromide in chloroform at room temperature and the following alkaline hydrolysis gave a crystalline amphoteric product, the aminophenol *IX*, the IR spectrum of which in the region of out-of-plane vibration of the aromatic C—H bonds is very similar to that of the *trans*-2-methyl derivative of prothiadene[17]. On this basis, *trans*-configuration is ascribed to this product. During demethylation of compound *X* with a boiling solution of 48% hydrobromic acid in acetic acid, protonation takes evidently (at least partly) place under formation of the corresponding carbonium cation which, after diluting with water, deprotonates under regeneration of the double bond but with a changed ratio of geometrical isomers in comparison with the starting compound. A mixture is formed which can be separated only by a repeated chromatography and crystallization; in a low yield, a product identical with the preceding one, *i.e. trans-IX*, was obtained. In the case of demethylation with 48% hydrobromic acid alone, a mixture is obtained in which the second geometric isomer forms an important constituent; it was isolated in the pure form. Its IR spectrum in the region near to 900 cm^{-1} is similar to that of the *cis*-isomer of 2-methyl derivative of prothiadene[17]; it is thus considered to be *cis-IX*.



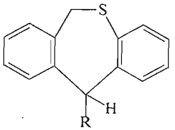
IX, $R = H$
X, $R = CH_3$



XI, $R = CH{=}CH_2$, $n = 1$
XII, $R = CH{=}CH_2$, $n = 2$
XIII, $R = OCH_3$, $n = 0$
XIV, $R = (CH_2)_2N(CH_3)_2$, $n = 1$
XV, $R = (CH_2)_2N(CH_3)_2$, $n = 2$

As a referential synthetic "prothiadene N-oxide", used for comparison with products of the prothiadene metabolism[11], there was available only an inhomogeneous product obtained by oxidation of the base *I* (ref.[3]) with hydrogen peroxide in ethanol first on standing at room temperature and finally under heating to reflux. This product, when chromatographed on a thin layer of silica gel, exhibited among others a spot corresponding to a compound being substantially more polar than prothiadene S-oxide (*XIV*). The R_F of this spot was a basis of the already mentioned "identification of prothiadene N-oxide" in the urine of patients treated with prothiadene[11]. Now, an attempt at preparing this N-oxide in pure form was undertaken. The mentioned procedure was used which proved in the case of 10-(4-alkylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepins[18] to be sufficiently selective, *i.e.* effecting only N-oxidation, whereas the sulfide sulfur atom should remain untouched. The crude product was processed by elution chromatography on a column of aluminium oxide. As the less polar constituent, a neutral sulfoxide was obtained in a yield of 35% in the form of two crystal modifications. It was identified as 11-allylidene-6,11-dihydrodibenzo[*b*,*e*]thiepin 5-oxide (*XI*). In a lower yield, a more polar oily product of basic character was isolated which gave a crystalline oxalate and was identified as the known prothiadene S-oxide (*XIV*) (ref.[3,9]). We suppose that the sulfoxide-diene *XI* resulted by a Cope elimination[19,20] from the primarily formed prothiadene N,S-dioxide. This elimination reaction is mostly described as a "thermic" reaction but for decomposing some N-oxides, heating in solvents is sufficient, which could not be avoided in the processing of our reaction mixture. It is typical that both of the isolated products are sulfoxides. This fact indicates that the selectivity of the oxidation method used[18] is limited to aminodiaryl sulfides. The sulfur atom in the prothiadene molecule, characterized by the situation $ArCH_2SAr$, is evidently much more susceptible to oxidation and under the conditions used, it is oxidized prior to the nitrogen atom. The attempt at preparing prothiadene N-oxide was thus not successful and the polar oxidation product, detected in the urine of patients[11], is considered to be prothiadene N,S-dioxide which is unstable and decomposes in the preparative experiments giving the compound *XI*.

The formation of a neutral product was also observed in the preparation of a larger amount of prothiadene 5,5-dioxide (*XV*) by the method described in principle earlier, *i.e.* by oxidation of hydrochloride of *I* with an excess of hydrogen peroxide; it was identified as the sulfone-diene *XII*. Cope elimination of the corresponding sulfone N-oxide, formed as a by-product of the oxidation reaction, is again suggested to be the mechanism of this deamination reaction. The boiling point temperature of the reaction mixture was evidently a sufficient condition for this thermic decomposition. At this opportunity, the *trans*-base *XV* was obtained for the first time in crystalline state.



XVI, R = CHO
XVII, R = CH=NOH
XVIII, R = CN
XIX, R = CH_2OH
XX, R = COOH
XXI, R = CH=CHCOOH

As an intermediate for further synthetic work in the dibenzo[*b*,*e*]thiepin series, 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carbaldehyde (*XVI*) has been prepared. The method used was analogous to that described in the dibenzo[*a*,*d*]cycloheptene series[21]. Chloromethyl methyl ether[22] was converted to the Grignard reagent in tetrahydrofuran and treatment with dibenzo[*b*,*e*]thiepin-11(6*H*)-one[1,2] gave the oily tertiary alcohol *VIII*. This was dehydrated in crude state by heating with formic acid and the product hydrolyzed with acid to give the aldehyde *XVI*. Dehydration of the alcohol *VIII* took also place in an attempt at its distillation *in vacuo*; chromatography of the distillate yielded the enol ether *XIII* as a mixture of geometrical isomers. The aldehyde *XVI* was used for preparing some further useful compounds of the dibenzo[*b*,*e*]thiepin series, mostly not yet described. The oxime *XVII* was obtained in the usual way and dehydrated by heating with acetic anhydride to the nitrile *XVIII*. This compound was synthesized earlier[23] by a reaction of 11-chloro-6,11-dihydrodibenzo[*b,e*]thiepin with silver cyanide. Reduction of the aldehyde *XVI* with sodium borohydride resulted in the primary alcohol *XIX* and the acid hydrolysis of the nitrile *XVIII* afforded the carboxylic acid *XX*. A reaction of the aldehyde *XVI* with malonic acid in the presence of pyridine at 90°C gave in a low yield 3-(6,11-dihydrodibenzo[*b,e*]thiepin-11-yl)acrylic acid (*XXI*), identified by spectra as the *trans*-isomer.

Out of the compounds prepared, nor$_2$-prothiadene (*III*) maleate (VÚFB-13.770), prothiadene methiodide (*VI*) (VÚFB-10.615) and *trans*-2-hydroxyprothiadene (*IX*) hydrochloride (VÚFB-10.535) were submitted to pharmacological testing. Compound *III* was tested as a potential antidepressant and antihistaminic agent. In an attempt at the determination of acute toxicity in mice, it has been found that even an oral dose of 400 mg/kg has not lethal effect; only some toxic effects were observed: excitation and convulsive phenomena. The compound exhibits incoordinating action in the rota-rod test only in high doses; the medium effective dose on oral administration, ED_{50} is 170 mg/kg (with a maximum of effect in 45 min after the administration). The substance practically does not antagonize the cataleptic effect of perphenazine in rats; an oral dose of 100 mg/kg exhibits anticataleptic action only in 10% animals. In the test for ulcerogenic action of reserpine in rats, antagonism could be proven only in a dose of 100 mg/kg orally; an oral dose of 10 mg/kg did not show a statistically significant effect in the test of reserpine hypothermia in mice. In the test of histamine aerosol in guinea-pigs, the substance, administered orally in a dose of 10 mg/kg, is practically inactive antihistaminically (protection in 10% animals only). It is completely inactive in the test of histamine detoxication in guinea-pigs. A complete demethylation of prothiadene (*I*) (ref.[4]) is thus connected with an almost complete loss of the main activities.

The quaternary compound *VI* was tested in a general screening programme (Dr M. Bartošová, affiliated unit of this Institute at Rosice n/L). The acute toxicity on intravenous administration is relatively high; LD_{50} = 5·1 mg/kg. After *i.v.* administration, it raised the blood pressure of normotensive rats in pentobarbital anesthesia; a dose of 0·25 mg/kg raised the pressure by 20% for more than 30 s. It inhibited intensively contractions of the isolated rat duodenum, elicited by acetylcholine; in a concentration of 0·1 μg/ml, it inhibited these contractions to 50% which is approximately 10% of the atropine activity. In a concentration of 50 μg/ml, it enhanced the frequency of the isolated rabbit-heart atrium by 25%. On the basis of preliminary experiments, the anticholinergic action of compound *VI* was investigated more in detail. The peripheral anticholinergic action was verified in the test of lacrimation in rats (elicited by methacholine chloride). After the subcutaneous administration of doses 0·5 mg and 5·0 mg/kg 15 min before the methacholine administration, no effect was found. On a *s.c.* administration of 10 mg/kg 30 min prior methacholine, however, a blockade of lacrimation was found in 50% animals; a higher dose (50 mg/kg *s.c.*) had approximately the same effect. When compared with the medium effective dose of atropine in this test (PD_{50} = 0·27 mg/kg *i.p.*), the anticholinergic action of compound *VI* is to be considered rather low. Compound *VI* was tested also for antimicrobial activity *in vitro* (Dr J. Turinová and Dr A. Čapek, bacteriological department of this Institute). The microorganisms used and the found minimum inhibitory concentrations in μg/ml are given, unless they surpass 100 μg/ml: *Staphylococcus pyogenes aureus* 100, *Saccharomyces pasterianus* 100, *Trichophyton mentagrophytes* 50, *Candida albicans* 100, *Aspergillus niger* 100.

The hydroxy derivative *IX* is less toxic than prothiadene; in mice, the LD_{50} = = 45 mg/kg *i.v.* It has a very weak central depressant and incoordinating effect in mice; ataxia appears only after sublethal doses ($ED_{50} > 30$ mg/kg *i.v.*). An intravenous dose of 9 mg/kg does not potentiate the thiopental sleeping action in mice. The reserpine ptosis in mice is significantly antagonized only by a relatively high dose (40 mg/kg *i.p.*). A subcutaneous dose of 50 mg/kg does not influence with statistical significance the ulcerogenic effects of reserpine in rats. An oral dose of 100 mg/kg does not antagonize the cataleptic effect of prochlorperazine or perphenazine. In conclusion, introduction of a hydroxyl group to position 2 of the prothiadene molecule destroys completely the pharmacological character of the parent compound.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 70 Pa over P_2O_5 at room temperature or at 100°C. The UV spectra (in CH_3OH unless stated otherwise) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer and the ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer. The mass spectrum was measured with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of silica gel.

11-Cyclopropyl-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*VII*)

Grignard reagent was prepared by a reaction of 2·9 g Mg and 16·5 g cyclopropyl bromide[13] in 60 ml tetrahydrofuran. After refluxing for 1 h, the reagent was cooled and treated over 40 min under stirring with a solution of 14·1 g dibenzo[*b*,*e*]thiepin-11(6*H*)-one[1,2] in 35 ml tetrahydrofuran, added dropwise at room temperature. The mixture was refluxed for 1 h, cooled and decomposed with 90 ml saturated NH_4Cl solution. After filtration, the filtrate was extracted with ether, the extract washed with a saturated solution of NaCl, dried with Na_2SO_4 and evaporated. The residue was crystallized from a mixture 1 : 10 of benzene and light petroleum; 11·3 g (68%), m.p. 104—106°C. Analytical sample, m.p. 105—106·5°C (benzene-light petroleum). IR spectrum: 727, 745, 764 (4 adjacent Ar—H), 874, 1021 (cyclopropyl), 1096 (R_3C—OH), 1561, 1588, 3045 (Ar), 3532 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·90—8·00 (m, 8 H, Ar—H), 4·90 and 4·24 (ABq, J = 15·0 Hz, 2 H, $ArCH_2S$), 2·30 (s, 1 H, OH), 2·00 (m, 1 H, CH of cyclopropyl), 0·40 to

1·00 (m, 4 H, CH_2CH_2 of cyclopropyl). For $C_{17}H_{16}OS$ (268·4) calculated: 76·08% C, 6·01% H, 11·95% S; found: 76·68% C, 6·14% H, 11·74% S.

trans-11-(3-Bromopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*IV*)

A solution of 5·0 g *VII* in 75 ml acetic acid was stirred and treated dropwise over 30 min with 37 ml 15% HBr solution in acetic acid at 13—15°C. After stirring for another 30 min at 15°C, the mixture was diluted with water, the precipitated product filtered, washed with water and dried *in vacuo*; 10·8 g (81%), m.p. 144—148°C. Analytical sample, m.p. 145—150°C (cyclohexane). UV spectrum (heptane): λ_{max} 233 nm (log ε 4·31), infl. 262 nm (3·91), 308 nm (3·43). IR spectrum (CS_2): 728, 746, 764 and infl. 776 cm^{-1} (Ar—H). ^{1}H-NMR spectrum: δ 6·90—7·30 (m, 8 H, Ar—H), 5·90 (t, J = 7·0 Hz, 1 H, CH=C), 4·95 and 3·35 (2 d, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·39 (t, J = 7·0 Hz, 2 H, CH_2Br), 2·52 (m, 2 H, remaining CH_2 of the propylidene). For $C_{17}H_{15}$.BrS (331·3) calculated: 61·64% C, 4·56% H, 24·12% Br, 9·68% S; found: 62·28% C, 4·63% H, 24·45% Br, 9·35% S. For this substance (configuration unknown), obtained by a different method, a m.p. of 142—143°C was reported[24].

trans-11-(3-Phthalimidopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*V*)

A mixture of 10·8 g *IV*, 13·0 g potassium phthalimide and 65 ml dimethylformamide was stirred for 3 h at 65—70°C. After standing overnight, it was diluted with 100 ml chloroform, the mixture washed with water, 5% NaOH and water, dried with K_2CO_3, filtered with charcoal and evaporated *in vacuo*. The residue crystallized after mixing with some ether; 6·4 g (49%), m.p. 172—175°C. Analytical sample, m.p. 175—177°C (benzene–light petroleum). UV spectrum: λ_{max} 227 nm (log ε 4·53), infl. 265 nm (3·98), 300 nm (3·87). IR spectrum (CS_2): 715, 746, 762, 789 (4 adjacent Ar—H), 1723, 1780 cm^{-1} (CO—N—CO). ^{1}H-NMR spectrum: δ 7·60—7·90 (m, 4 H, Ar—H of the phthalimide residue), 6·90—7·30 (m, 8 H, remaining Ar—H), 5·90 (t, 1 H, J = 7·0 Hz, CH=C), 4·80 and 3·20 (2 d, J = 14·0 Hz, 2 H, $ArCH_2S$), 3·75 (t, J = 7·0 Hz, 2 H, C=C—CH_2), 2·35 (m, 2 H, CH_2N). For $C_{25}H_{19}NO_2S$ (397·5) calculated: 75·54% C, 4·82% H, 3·52% N, 8·07% S; found: 75·42% C, 4·98% H, 3·30% N, 8·30% S.

trans-11-(3-Aminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*III*)

A mixture of 6·4 g *V*, 1·2 g 80% hydrazine hydrate and 175 ml ethanol was refluxed for 6 h. Ethanol was evaporated, the residue was diluted with 150 ml water, the mixture acidified with 2M-HCl (pH 4·5), stirred for 1 h at room temperature and for 15 min at 80°C. After standing overnight, the precipitated solid was filtered off, the filtrate was made alkaline with NH_4OH and the separated oily base was isolated by extraction with ether; 3·9 g (91%). Neutralization with 2·0 g maleic acid in 50 ml ethanol gave 4·3 g hydrogen maleate, m.p. 178—182°C (ethanol). For $C_{21}H_{21}NO_4S$ (383·5) calculated: 65·78% C, 5·52% H, 3·65% N, 8·36% S; found: 65·89% C, 5·69% H, 3·56% N, 8·50% S.

Decomposition of the maleate with NH_4OH and extraction with ether gave a homogeneous base *III*, m.p. 78—81°C (benzene–light petroleum). IR spectrum (CS_2): 730, 747, 762 cm^{-1} (Ar—H). ^{1}H-NMR spectrum: δ 6·90—7·40 (m, 8 H, Ar—H), 5·90 (t, J = 7·0 Hz, 1 H, CH=C), 5·10 and 3·32 (2 bd, J = 13·0 Hz, 2 H, $ArCH_2S$), 2·72 (t, J = 7·0 Hz, 2 H, CH_2N), 2·10 (m, 2 H, C—CH_2—C=), 1·15 (s, 2 H, NH_2). For $C_{17}H_{17}NS$ (267·4) calculated: 76·36% C, 6·41% H, 5·24% N; found: 75·64% C, 6·46% H, 4·97% N.

trans-3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-ylidene)propyl-trimethylammonium Iodide (*VI*)

A solution of 5·9 g *trans-I* (ref.[3]) in 10 ml methanol was stirred and treated over 10 min with 3·4 g methyl iodide. After standing overnight at room temperature, the product was filtered, washed with methanol and ether, and dried *in vacuo*; 8·2 g (94%), m.p. 186—188°C (methanol). For $C_{20}H_{24}INS$ (437·4) calculated: 54·92% C, 5·53% H, 29·02% I, 3·20% N, 7·33% S; found: 54·47% C, 5·50% H, 29·10% I, 3·20% N, 7·12% S.

2-Methoxy-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*X*)

A mixture of 53·3 g 2-methoxy-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (our m.p. 127—129·5°C, the literature[15] reported a m.p. of 123—125°C), 550 ml acetic acid and 220 ml hydrochloric acid was refluxed for 1 h and processed according to the literature[15]; 49·5 g oily base *X*. Neutralization of this base with 20·6 g oxalic acid dihydrate in 250 ml ethanol gave 56 g hydrogen oxalate, m.p. 177—183°C with decomposition. Repeated crystallization from water gave 36·4 g product of m.p. 191—193°C which is almost identical with the value (187—189°C) reported in the literature[15]. Decomposition of this oxalate (7·0 g) with NH_4OH and extraction with ether gave 5·5 g homogeneous base *X* which crystallized from light petroleum, m.p. 53—55°C. UV spectrum: λ_{max} 228·5 nm (log ε 4·40), 260·5 nm (3·99), 321 nm (3·53). IR spectrum: 768, 812, 863 (4 and 2 adjacent and solitary Ar—H), 1035, 1222 ($ArOCH_3$), 1552, 1590 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·00—7·40 (m, 4 H, 7,8,9,10-H_4), 6·90 (d, $J = 9·0$ Hz, 1 H, 4-H), 6·84 (mcs, $J = 2·0$ Hz, 1 H, 1-H), 6·64 (mcd, $J = 9·0$; 2·0 Hz, 1 H, 3-H,) 5·94 (t, $J = 8·0$ Hz, 1 H, C=CH), 4·85 and 3·30 (ABq, $J = 14·0$ Hz, 2 H, $ArCH_2S$), 3·71 (s, 3 H, OCH_3), 3·15 (m, 4 H, CH_2CH_2 in the side chain), 2·08 (s, 6 H, CH_3NCH_3). For $C_{20}H_{23}NOS$ (325·5) calculated: 73·80% C, 7·12% H, 4·30% N, 9·85% S; found: 73·48% C, 7·44% H, 4·39% N, 10·07% S.

2-Hydroxy-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*IX*)

A. A solution of 4·8 g crystalline base *X* in 30 ml chloroform was cooled to 10°C and under stirring treated over 10 min with a solution of 7·4 g BBr_3 in 10 ml chloroform, added dropwise. The mixture was stirred for 2 h at room temperature and decomposed with 70 ml water and 15 ml concentrated NH_4OH, added dropwise. It was stirred for 30 min, the organic layer was separated and shaken with an excess of 3% hydrochloric acid. The aqueous layer was combined with the oily hydrochloride, the mixture was made alkaline with NH_4OH and the phenolic base was extracted with chloroform. The extract was dried (K_2CO_3), filtered with charcoal and evaporated *in vacuo* giving 0·90 g (18%) homogeneous *trans-IX* base, m.p. 198—200°C (ethanol). UV spectrum: λ_{max} 228 nm (log ε 4·36), 262·5 nm (3·95), 323 nm (3·52). IR spectrum: 767, 820, 852, 894 (4 and 2 adjacent and solitary Ar—H), 1218 (Ar—OH), 1552, 1598 (Ar), 2600 cm^{-1} (NH^+ of the inner salt). IR spectrum (CS_2 with 12% dimethylformamide): 699, 716, 759, 811, infl. 883 cm^{-1} (Ar—H). For $C_{19}H_{21}NOS$ (311·4) calculated: 73·27% C, 6·80% H, 4·50% N, 10·30% S; found: 73·07% C, 7·03% H, 4·59% N, 10·32% S.

Hydrochloride, m.p. 243—245°C (aqueous ethanol). For $C_{19}H_{22}ClNOS$ (347·9) calculated: 65·59% C, 6·37% H, 10·19% Cl, 4·03% N, 9·22% S; found: 65·48% C, 6·69% H, 10·13% Cl, 3·65% N, 9·13% S.

B. A mixture of 2·3 g *X*, 5 ml acetic acid and 3 ml 48% hydrobromic acid was refluxed for 4 h. After standing overnight, it was diluted with water, made alkaline with NH_4OH, and the base isolated by extraction with chloroform; 2·3 g inhomogeneous product. Chromatography on a column of 70 g alumina (activity II) with chloroform as the eluent separated a small amount of the starting *X*. Elution with chloroform containing 2% methanol gave then 1·1 g mixture of geometric isomers of *IX*. Rechromatography of this fraction on 100 g alumina and crystallization of the most polar fraction from ethanol led to 0·1 g compound melting at 195—197°C, being almost pure *trans-IX*.

C. A mixture of 4·5 g pure oxalate of *X* and 15 ml 48% hydrobromic acid was stirred and heated for 3 h to 120°C. It was then diluted with water, made alkaline with NH_4OH and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated. The residue (2·5 g) was crystallized from 9 ml ethanol; 0·8 g (24%), m.p. 162—164°C (ethanol). This *cis- IX* base, when compared by TLC with the *trans-IX* base, appears to be a little less polar. Mass spectrum, *m/e*: 311 (M^+, corresponds to $C_{19}H_{21}NOS$), 58 (base peak). UV spectrum: λ_{max} 240 nm (log ε 4·14), 284 nm (3·76), 316 nm (3·87). IR spectrum: 699, 721, 734, 769, 778, 794, 817, 850, 856, 900 (4 and 2 adjacent and solitary Ar—H), 1254, 1262 (Ar—OH), 2590 cm^{-1} (NH^+ of the inner salt). IR spectrum (CS_2): 701, 719, 740, 762, 782, 794, 819, 853, 874, 899 cm^{-1} (Ar—H). The band corresponding to the solitary Ar—H (899 cm^{-1}) is shifted to higher frequency (in comparison with *trans-IX* exhibiting the corresponding band at 883 cm^{-1}); this is an argument for assigning the configuration[17]. For $C_{19}H_{21}NOS$ (311·4) calculated: 73·27% C, 6·80% H, 4·50% N, 10·30% S; found: 73·04% C, 6·75% H, 4·34% N, 10·25% S.

11-Allylidene-6,11-dihydrodibenzo[*b*,*e*]thiepin 5-Oxide (*XI*)

A solution of 8·9 g *trans-I* base[3] in 50 ml ethanol was treated with 6·5 ml 30% H_2O_2 at 0°C and stirred for 6 h at this temperature. After standing overnight at room temperature, the excess of H_2O_2 was destroyed with 0·2 g Pd on $BaSO_4$ (2 h stirring at room temperature and 15 min refluxing). It was then filtered, the filtrate diluted with 70 ml water and ethanol was distilled off. The aqueous solution was washed with ether and evaporated *in vacuo*. The residue (7·24 g) was dissolved in benzene and the solution chromatographed on a column of 450 g alumina (activity II). Elution with benzene gave only 0·64 g inhomogeneous least polar components. Elution with chloroform gave first 3·14 g (39%) neutral compound crystallizing from a mixture of benzene and light petroleum as needles melting at 111—114°C (form *A*), and from a mixture of ether and light petroleum as clusters melting at 120—122·5° (form *B*). Both forms are crystalline modifications of *XI*. UV spectrum of the form *A*: λ_{max} 265 nm (log ε 4·21), infl. 280 nm (4·18). IR spectrum of the form *A* (CS_2): 751, 770 (4 adjacent Ar—H), 913 ($CH{=}CH_2$), 1050, 1068 cm^{-1} (S—O). ^{1}H-NMR spectrum of the form *A*: δ 7·75 (m, 1 H, 1-H), 7·10—7·50 (m, 7 H, remaining Ar—H), 6·62 (d, $J = 10·0$ Hz, 1 H, C=CH), 6·00—6·50 (m, 1 H, CH of the terminal vinyl), 5·40 and 5·18 (2 dd, $J = 16·5$; 9·5 and 9·5; 2·0 Hz, 2 H, $=CH_2$), 4·40 (bs, at 55°C bd, $J = 13·0$ Hz, 1 H) and 4·29 (bd, at 55°C d, $J = 13·0$ Hz, 1 H) (together $ArCH_2SO$). For $C_{17}H_{14}OS$ (266·3) calculated: 76·67% C, 5·30% H, 12·02% S; found: 77·11% C, 5·61% H, 12·14% S. The UV, IR and ^{1}H-NMR spectra of the form *B* are completely identical with those of the form *A*. For $C_{17}H_{14}OS$ (266·3) calculated: 76·67% C, 5·30% H, 12·02% S; found: 76·60% C, 5·36% H, 11·78% S.

Continuation of the chromatography using still chloroform as the eluent gave 2·25 g (24%) of a basic oily substance which proved to be 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin 5-oxide (*XIV*) (ref.[3,9]). UV spectrum (ethanol): λ_{max} 275 nm infl. (log ε 3·76), infl. 247 nm (4·07). IR spectrum (CS_2): 756, 764, 774 (4 adjacent Ar—H), 1051, 1080 (S—O), 2755 (dimethylamino), 3005, 3040 cm^{-1} (Ar). The compound is reduced polarographically in 0·5M-HCl at $E_{1/2} = -0·90$ V (against a saturated calomel electrode). ^{1}H-NMR spectrum: δ 7·10—7·80 (m, 8 H, Ar—H), 6·03 (t, 1 H, C=CH), *c*. 4·50 (m, 2 H, $ArCH_2SO$), *c*. 2·30 (m, 4 H, CH_2CH_2 in the chain), 2·10 (s, 6 H, CH_3NCH_3). Neutralization with oxalic acid in ethanol gave the hydrogen oxalate, m.p. 178·5—179·5°C with decomposition (ethanol–acetone). For $C_{21}H_{23}NO_5S$ (401·5) calculated: 62·82% C, 5·77% H, 3·49% N, 7·99% S; found: 62·56% C, 5·99% H, 3·64% N, 8·26% S.

trans-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin 5,5-Dioxide (*XV*)

A mixture of 300 g *trans-I* hydrochloride[1-3], 440 ml 30% H_2O_2 and 350 ml water was stirred and heated for 2 h to 90—100°C. After cooling, it was diluted with 1 l water, made alkaline with 400 ml NH_4OH and extracted with benzene. The extract was dried (Na_2SO_4), filtered with charcoal and evaporated *in vacuo*. The residue was chromatographed on a column of 1 kg silica gel using chloroform as the eluent. The first component to be eluted was 11·5 g (5%) of a neutral substance which crystallized from 95% ethanol and melted at 183·5—185·5°C. Analysis and spectra identified the substance as 11-allylidene-6,11-dihydrodibenzo[*b*,*e*]thiepin 5,5-dioxide (*XII*). UV spectrum: λ_{max} 264·5 nm (log ε 4·34), infl. 282 nm (4·21). IR spectrum: 744, 753, 773 (4 adjacent Ar—H), 932, 999 (CH=CH_2), 1 122, 1 153, 1 300 (SO_2), 1 561, 1 572, 1 580, 1 600 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·85 (m, 1 H, 4-H), 7·00—7·50 (m, 7 H, remaining Ar—H), 6·62 (d, $J =$ = 10·5 Hz, 1 H, C=CH), 5·90—6·40 (m, 1 H, CH of vinyl), 5·40 and 5·18 (2 dd, $J =$ 16·0; 2·0 and 10·0; 2·0 Hz, 2 H, =CH_2), 5·00 and 4·18 (2 d, $J =$ 14·0 Hz, 2 H, ArCH_2SO_2). For $C_{17}H_{14}O_2S$ (282·3) calculated: 72·31% C, 5·00% H, 11·36% S; found: 72·31% C, 5·28% H, 11·36% S.

Continuation of the chromatography with chloroform as the eluent gave 186 g crude *XV* which was converted to 130 g hydrochloride, m.p. 271·5—275°C (aqueous ethanol); for the analytical product, we reported earlier[3] the m.p. of 282—284°C. Decomposition of the hydrochloride with NH_4OH and extraction with chloroform gave the base *XV*, m.p. 113·5—114·5°C (benzene–cyclohexane). UV spectrum: λ_{max} 240 nm (log ε 4·06), 276 nm (3·41). IR spectrum: 748, 766, 782, 800 (4 adjacent Ar—H), 1 121, 1 159, 1 307 (SO_2), 1 491, 1 565, 1 590 (Ar), 1 637 (C=C), 2 780, 2 820 cm^{-1} (dimethylamino). IR spectrum (CS_2): 740, 750, 762, 796 cm^{-1} (Ar—H). ^{1}H-NMR spectrum: δ 7·80 (m, 1 H, 4-H), 7·00—7·50 (m, 7 H, remaining Ar—H), 6·10 (t, $J =$ 6·0 Hz, 1 H, C=CH), 5·21 and 4·18 (2 d, $J =$ 14·0 Hz, 2 H, ArCH_2SO_2), 2·20 (m, 4 H, CH_2CH_2 in the chain), 2·05 (s, 6 H, CH_3NCH_3). For $C_{19}H_{21}NO_2S$ (327·4) calculated: 69·69% C, 6·47% H, 4·28% N, 9·79% S; found: 69·87% C, 6·69% H, 4·24% N, 9·76% S.

11-(Methoxymethyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*VIII*)

A mixture of 48 g Mg and 100 ml tetrahydrofuran was allowed to stand for 5 min with 2·5 g $HgCl_2$, it was then cooled to —5 to —10°C and under stirring treated over 1 h with a solution of 150 ml chloromethyl methyl ether[22] in 150 ml tetrahydrofuran. The mixture was stirred for another 1 h under cooling and then treated over 15 min with a solution of 226 g dibenzo[*b*,*e*]thiepin-11(6*H*)-one[1,2] in 500 ml tetrahydrofuran at the mentioned temperature. It was stirred for 1 h, the cooling bath was removed and the mixture poured into a solution of 200 g NH_4Cl in 1 500 ml H_2O. The organic layer was separated, dried with $MgSO_4$, filtered with charcoal and evaporated *in vacuo*. There were obtained 260 g (96%) crude *VIII* which was used for further work without purification.

11-(Methoxymethylene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (*XIII*)

Heating of the crude *VIII in vacuo* proceeds under decomposition and the product distills at 184°C/0·13 kPa. For analysis, the distillate was chromatographed on alumina using benzene as the eluent. The spectra (expecially the ^{1}H-NMR spectrum) identified it to be a 1 : 1 mixture of geometric isomers of *XIII*. UV spectrum: λ_{max} 231 nm (log ε 4·24), infl. 265 nm (3·94), 306 nm

(3·53). IR spectrum (CS_2): 723, 733, 744, 753, 763, 773, 783 (4 adjacent Ar—H), 1 231 (C=C—OR) 1 642 (C=C), 2820 cm^{-1} (C=C—OCH_3). ^{1}H-NMR spectrum: δ 6·70—7·60 (m, 8 H, Ar—H), 6·30 and 6·08 (2 s, 1 H, C=CH), 4·12 (bs, 2 H, $ArCH_2S$), 3·62 and 3·58 (2 s, 3 H, OCH_3). For $C_{16}H_{14}OS$ (254·3) calculated: 75·55% C, 5·54% H, 12·61% S; found: 75·28% C, 5·54% H, 12·49% S.

6,11-Dihydrodibenzo[*b,e*]thiepin-11-carbaldehyde (*XVI*)

A mixture of 250 g crude *VIII* and 720 ml 98% formic acid was stirred for 20 min at 75—90°C. It was then treated with 100 ml 1 : 9 dilute H_2SO_4 and the mixture was refluxed for 15 min. After cooling, it was poured into 2 kg ice and water and extracted with benzene. The extract was filtered with charcoal, dried with $MgSO_4$ and evaporated *in vacuo*. The residue (214 g) was crystallized from a mixture of 200 ml benzene and 190 ml light petroleum; 61·9 g, m.p. 98—101·5°C. The mother liquors were evaporated *in vacuo* and the residue distilled (b.p. 198—202°C/0·13 kPa); the distillate (65·9 g) was crystallized from a mixture of 50 ml benzene and 50 ml light petroleum giving further 43·7 g, m.p. 100·5—101·5°C. The total yield was thus 105·6 g (48%). Analytical sample, m.p. 100·5—102°C (benzene). IR spectrum: 762 (4 adjacent Ar—H), 1483, 1 503, 1 580, 1 605 (Ar), 1713, 2700, 2735, 2820 (CHO), 3015, 3053 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 9·89 (s, 1 H, CHO), 7·00—7·50 (m, 8 H, Ar—H), 4·51 (s, 1H, Ar_2CH), 4·10 and 3·82 (ABq, $J =$ $= 15·0$ Hz, 2 H, $ArCH_2S$). For $C_{15}H_{12}OS$ (240·3) calculated: 74·96% C, 5·03% H, 13·34% S; found: 75·22% C, 5·06% H, 13·20% S.

11-(Hydroximinomethyl)-6,11-dihydrodibenzo[*b,e*]thiepin (*XVII*)

A mixture of 12·0 g *XVI*, 5·0 g $NH_2OH.HCl$, 6·0 g $NaHCO_3$ and 100 ml ethanol was refluxed for 1·5 h. After standing overnight, the inorganic salts were filtered off and the filtrate evaporated *in vacuo*. The residue was dissolved in chloroform, the solution washed with H_2O, dried (Na_2SO_4), filtered with charcoal and evaporated. The residue was crystallized from ethanol; 6·9 g (54%), m.p. 153—157°C. ^{1}H-NMR spectrum (CD_3SOCD_3): δ 10·98 (s, 1 H, NOH), 7·91 (d, $J = 5·0$ Hz, 1 H, CH=N), 6·80—7·50 (m, 8 H, Ar—H), 5·10 (d, $J = 5·0$ Hz, 1 H, Ar_2CH), 4·54 and 4·00 (ABq, $J = 14·0$ Hz, 2 H, $ArCH_2S$). For $C_{15}H_{13}NOS$ (255·3) calculated: 70·56% C, 5·13% H, 5·49% N, 12·56% S; found: 70·53% C, 4·98% H, 5·49% N, 12·60% S.

6,11-Dihydrodibenzo[*b,e*]thiepin-11-carbonitrile (*XVIII*)

A mixture of 26·7 g crude *XVII* and 16 g acetic anhydride was heated for 30 min to 100°C. After cooling, it was diluted with water and extracted with chloroform. The extract was dried (Na_2SO_4) and filtered through a column of 125 g alumina. The filtrate was evaporated *in vacuo* and the residue crystallized from a mixture of benzene and light petroleum; 14·8 g (60%), m.p. 135—138°C. Analytical sample, m.p. 137—139°C (ethanol). ^{1}H-NMR spectrum: δ 7·00—7·70 (m, 8 H, Ar—H), 5·80 (s, 1 H, Ar_2CH), 4·55 and 3·96 (2 d, $J = 14·0$ Hz, 2 H, $ArCH_2S$). For $C_{15}H_{11}NS$ (237·3) calculated: 75·93% C, 4·67% H, 5·90% N, 13·49% S; found: 75·91% C, 4·67% H, 5·90% N, 13·51% S. For an impure product, prepared differently, our group[23] reported a m.p. of 130—132°C.

6,11-Dihydrodibenzo[*b,e*]thiepin-11-methanol (*XIX*)

The stirred suspension of 2·4 g *XVI* in 17 ml ethanol was treated in small portions with 0·4 g $NaBH_4$. The resulting solution was stirred for 2 h at room temperature and evaporated *in vacuo*.

The residue was decomposed with water and the product extracted with benzene. Processing of the extract gave 2·4 g residue which was crystallized from a mixture of benzene and light petroleum; 2·1 g (88%), m.p. 95—97°C. Analytical sample, m.p. 95—98°C (benzene-light petroleum). UV spectrum: λ_{max} 212 nm (log ε 4·39), 262 nm (3·92). IR spectrum: 741, 750, 768 (4 adjacent Ar—H), 1030, 1050, 1060 (CH_2OH), 1490, 1590, 3005, 3035 (Ar), 3300 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·90—7·30 (m, 8 H, Ar—H), 4·40 and 3·97 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 4·40 (m, 3 H, $Ar_2CH—CH_2O$), 1·90 (bs, disappears after D_2O, 1 H, OH). For $C_{15}H_{14}OS$ (242·3) calculated: 74·34% C, 5·82% H, 13·23% S; found: 74·30% C, 6·02% H, 13·06% S.

6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-carboxylic Acid (*XX*)

A mixture of 5·2 g *XVIII* and 35 ml 57% H_2SO_4 was refluxed for 5 h and after cooling diluted with 100 ml H_2O. The aqueous layer was removed by decantation, the residue dissolved in a mixture of 100 ml H_2O and 20 ml 20% NaOH, the solution was filtered with charcoal and the filtrate acidified with hydrochloric acid. The precipitated product was filtered, washed with water and dried *in vacuo*; 3·6 g (64%), m.p. 211—213°C. Analytical sample, m.p. 217—219°C (90% ethanol). UV spectrum: λ_{max} 260 nm (log ε 3·92), infl. 288 nm (3·12), infl. 297 nm (2·95). IR spectrum: 742, 756 (4 adjacent Ar—H), 950, 1222, 1285, 1700, 2630, 2790, 3160 (COOH), 1492, 1590 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 6·90—7·50 (m, 8 H, Ar—H), 5·12 (s, 1 H, Ar_2CH), 4·58 and 3·82 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$). For $C_{15}H_{12}O_2S$ (256·3) calculated: 70·28% C, 4·72% H, 12·51% S; found: 69·91% C, 4·86% H, 12·64% S.

trans-3-(6,11-Dihydrodibenzo[*b*,*e*]thiepin-11-yl)acrylic Acid (*XXI*)

A mixture of 7·5 g *XVI*, 3·3 g malonic acid and 5 ml pyridine was heated for 2 h to 90°C. After cooling, it was diluted with benzene and washed with dilute hydrochloric acid and water. By shaking with an excess of 5% $NaHCO_3$, the acidic product was transferred into the aqueous layer. Evaporation of the benzene layer led to recovery of 5·6 g starting *XVI*. The aqueous alkaline solution was filtered with charcoal, the filtrate was acidified with hydrochloric acid and the product isolated by extraction with chloroform. Processing gave 0·7 g (31% per conversion) crude *XXI* which was crystallized from a mixture of benzene and light petroleum, m.p. 190—194°C with decomposition. UV spectrum: λ_{max} 254 nm (log ε 3·96). IR spectrum (KBr): 735, 750, 769 (4 adjacent Ar—H), 975 (*trans*-CH=CH), 926, 1239, 1310, 1690, 2560, 2670, 3160 (COOH), 1640 (C=C), 3040 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 9 H, Ar—H and Ar_2C—CH=), 5·50 (mcd, J = 16·0; 1·0 Hz, 1 H, *trans*-C=CHCO), 5·10 (dd, J = 6·0; 1·0 Hz, 1 H, Ar_2CH), 4·51 and 3·90 (ABq, J = 15·0 Hz, 2 H, $ArCH_2S$). For $C_{17}H_{14}O_2S$ (282·4) calculated: 72·31% C, 5·00% H, 11·36% S; found: 72·44% C, 5·00% H, 11·37% S.

The authors are indebted to Dr M. Ryska, Department of physical chemistry of this Institute, for recording the mass spectrum of cis-IX*; to Mr F. Mikšík and Mrs M. Hrubantová for technical assistance with the syntheses, and finally to Mrs J. Komancová, Mrs V. Šmídová, Mrs A. Slavíková, Mr M. Čech and Mrs J. Kropáčová, Analytical department of this Institute, for carrying out the analyses.*

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Translated by the author (M. P.).