ANTIAMINIC AGENTS DERIVED FROM THIENO[2,3-*c*]-2-BENZOTHIEPIN: 4-(1-METHYL-4-PIPERIDYLIDENE)--4,9-DIHYDROTHIENO[2,3-*c*]-2-BENZOTHIEPIN AND SOME RELATED COMPOUNDS*

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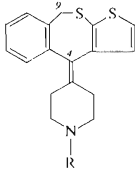
Received June 25th, 1982

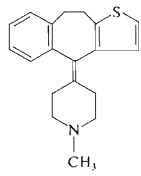
In the reaction of thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one (*VI*) with 1-methyl-4-piperidylmagnesium chloride 7-(1-methyl-4-piperidyl)thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one (*VIII*) is formed in addition to the expected amino alcohol *VII*. The title compound *I* was obtained by the acid catalyzed dehydration of the pure alcohol *VII*. Compound *I* ("pipethiadene") has outstanding antihistamine, antiserotonin, antireserpine and anticataleptic activity and was recommended to clinical trials as a potential antimigraine agent. For pharmacokinetic and metabolic studies there were prepared the NC^2H_3 analogue of pipethiadene *IV* and further, as potential metabolites, the demethyl analogue *III*, S-oxide *X*, demethyl S-oxide *XI*, N-oxide *XIII* and N,S-dioxide *XIV*. The Wittig reaction of the ketone *VI* with 3-dimethylaminopropylidenetriphenylphosphorane resulted in a mixture of geometric isomers of 4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin with the strongly predominating *Z*-isomer *XVI* which was isolated from the mixture by crystallization of the hydrogen maleate. The mixture with the predominating *Z*-isomer *XVI* was converted by treatment with 80% sulfuric acid and dilution with water to a mixture with the predominating *E*-isomer *XV* (dithiadene) which was isolated by crystallization of the hydrogen sulfate. Some further new thieno[2,3-*c*]-2-benzothiepin derivatives were synthesized as potential intermediates.

In one of the previous communications of this series[1] the reaction of thieno[2,3-*c*]--2-benzothiepin-4(9*H*)-one (*VI*) (ref.[1-3]) with 1-methyl-4-piperidylmagnesium chloride[4] in tetrahydrofuran and the following acid catalyzed dehydration of the amino alcohol *VII* to the title compound *I* was described. This compound proved interesting by its outstanding antihistamine and antiserotonin activity but as an antihistamine agent there was developed the *E*-isomer of its 4-(3-dimethylaminopropylidene) analogue (dithiadene[1-3,5,6]). Further pharmacological testing of compound *I*, its structural similarity with 4-(1-methyl-4-piperidylidene)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (*V*) (ref.[7,8]), which found practical use in the

* Part CLXXVI in the series Neurotropic and Psychotropic Agents; Part CLXXV: This Journal *48*, 163 (1983).

treatment of migraine (pizothifen, Sandomigran^R, ref.[9]), and finally, a direct comparison of compounds *I* and *V* (ref.[10–14]) led to preclinical investigation of compound *I* [hydrogen (+)-tartrate "VÚFB-12.384", pipethiadene] and to suggestion of its clinical trials in the indication of an antimigraine agent. This development resulted in a new interest in the chemistry of *I*, in the necessity of investigating more carefully its synthesis and of preparing a series of its potential metabolites which is described in the present communication.



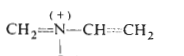


I. R = CH_3
II. R = $COOC_2H_5$
III. R = H
IV. R = C_2H_5

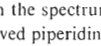
V

The starting ketone *VI* was obtained by published method[3] and its characterization was perfected by recording the spectra. Its reaction with 1-methyl-4-piperidylmagnesium chloride[4] proceeds best in tetrahydrofuran; the basic products were transferred to the aqueous layer by a solution of tartaric acid and the neutral components were removed by extraction with toluene. The solution of tartrates was made alkaline with ammonia and the bases were isolated by extraction with chloroform. The crude product was extracted with ethanol. The insoluble solid is the practically pure amino alcohol *VII* in a yield of about 50% whose characterization was also completed by recording of the spectra. Evaporation of the mother liquor gave an inhomogeneous product which was purified by crystallization and chromatography on silica gel to yield about 5% of a substance melting at the same temperature as did the alcohol *VII* but differing by a substantially lower polarity. The UV spectrum of this compound indicates a rather high degree of conjugation corresponding to a diaryl ketone. The IR spectrum proves the absence of the hydroxyl group and the band at 1 611 cm^{-1} may be interpreted as corresponding to a diaryl ketone. Whilst the ^1H NMR spectrum of the carbinol *VII* indicates the presence of 6 aromatic protons, out of which the signals of five are fused in an unresolvable multiplet and only the proton in position 5 may be differentiated, the ^1H NMR spectrum of the less polar product shows only five aromatic protons whose signals are clearly differentiated and they may be localized in the individual positions of the skeleton; the proton in position 7 of the skeleton is missing. Further the proton which may be substituted

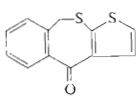
by deuterium, is absent; this confirms the absence of the hydroxyl group. The mass spectrum of the new compound shows the molecular ion with m/z of 329 and with a high intensity (40%); the amino alcohol *VII*, on the other hand, has the molecular weight of 331 and the corresponding ion has a very low intensity (0·5%). The base peak of the new compound has m/z of 70 which corresponds to an ion formed by cleavage of the piperidine nucleus, *i.e.*



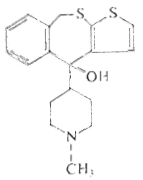
on the other hand, the base peak in the spectrum of the alcohol *VII* has m/z of 98, corresponding to an ion with preserved piperidine nucleus, *e.g.*



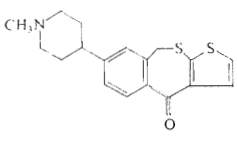
This difference indicates that whilst in the first case the piperidine residue is bound directly to an aromatic carbon, in the other case it is bound to an aliphatic carbon (*cf.*[15,16]). All the data mentioned lead to the formulation of the new compound as 7-(1-methyl-4-piperidyl)thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one (*VIII*). This substance is evidently the result of a 1,6-addition[17] of the Grignard reagent, the following hydrolysis and elimination of two hydrogen atoms (apparently by oxidation with the air oxygen). Similar products were identified in reactions of the sterically hindered aromatic ketones, especially of 2,3,5,6-tetramethyl- and 2,3,5,6-tetramethyl--2′-methoxybenzophenone, with Grignard reagents[18–20]. The final step was the dehydration of the amino alcohol *VII* with boiling dilute sulfuric acid; the crude base *I* was purified by crystallization from ethanol which removed the last traces of the by-product *VIII* which remained unchanged under the conditions of the dehydration. With the previously prepared and tested product[1] we cannot exclude a contamination with some amount of compound *VIII*. For pharmacological tests the hydrogen (+)-tartrate proved more advantageous than the previously used hydrogen maleate[1].



VI

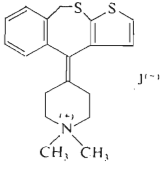


VII



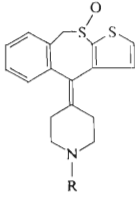
VIII

The purpose of further work was to help the pharmacokinetic and metabolic studies with pipethiadene (*I*) by the preparation of some substances, especially of the potential metabolites as standards. In the choice of these compounds we especially used the knowledge of metabolism of dithiadene (*XV*) (ref.[21,22]). The demethyl derivative *III* was prepared in the first line; it may be almost with certainty considered a metabolite of pipethiadene (*I*). Compound *I* was transformed by treatment with ethyl chloroformate in boiling benzene to the carbamate *II* which was hydrolyzed with ethanolic potassium hydroxide to the secondary amine *III*. Its hydrogen maleate was prepared for pharmacological testing. The other substance needed was the analogue of pipethiadene *IV* which is completely deuterated in the N-methyl group. As model experiments in this line there were carried out attempts at methylating the secondary amine *III* with dimethyl sulfate under various conditions on the one hand, and with methyl iodide on the other. In the first case there resulted mixtures which appeared after chromatography to be an almost homogeneous compound *I* but it did not crystallize. Methylation of compound *III* with a slight excess of methyl iodide in a mixture of methanol and chloroform resulted in a mixture in which the thin layer chromatography on silica gel proved the presence of the starting compound *III*, of the desired product *I* and of a highly polar substance which proved to be the quaternary salt *IX* and which was the only one which crystallized. This salt was prepared for comparison by treatment of the base *I* with methyl iodide in methanol. Methylation of compound *III* with an insufficient amount of methyl iodide in chloroform eliminated the formation of the quarternary salt *IX* but the obtained mixture of compounds *I* and *III* needed the column chromatography on silica gel. Finally, the reduction of the carbamate *II* with lithium aluminium hydride in boiling ether proved the best method; the chromatographically homogeneous and crystalline base *I* was obtained in a yield of 70% and afforded the hydrogen (+)-tartrate. The analogously performed reduction with lithium aluminium deuteride gave the crystalline base *IV* which was evaluated by mass spectrometry and found to be practically free of the N—CH_3 and N—$CH_2{}^2H$ analogues and only moderately contaminated with the N—CH^2H_2 compound which was completely satisfying for the purpose given.

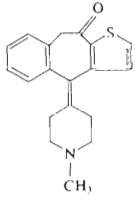


IX

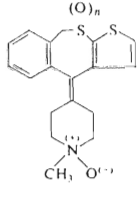
The main type of metabolites of the aminosulfides are compounds oxidized on the sulfur atom to sulfoxide and on the nitrogen atom to N-oxide. For this reason the sulfoxides *X* and *XI* were first prepared by oxidation of the solutions of bases *I* and *III* in acetic acid at room temperature by an excess of hydrogen peroxide. Their identity was confirmed not only by analyses and spectra but also by the typical course of the polarographic reduction. Compound *X*, whose structure resembles the structure of the antianaphylactically and antiasthmatically active ketothifen (*XII*) (refs[23-26]), was prepared for pharmacological evaluation in the form of the hydrogen maleate. Oxidation of a solution of the base *I* with hydrogen peroxide in ethanol first at room temperature and finally at the boiling point of the mixture resulted in a mixture of oxidation products which was separated by chromatography on a column of silica gel. Two crystalline bases were obtained which were considered already on the basis of their polarity to be the N-oxide *XIII* and the N,S-dioxide *XIV*. Their identity was corroborated by analyses, spectra and polarographic reduction.



X, R = CH_3
XI, R = H



XII



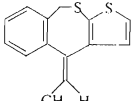
XIII, $n = 0$
XIV, $n = 1$

In the next part of this paper we are presenting a contribution to the chemistry of the antihistamine agent 4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]--2-benzothiepin whose *E*-isomer *XV* is in practical use as dithiadene (Dithiaden--Spofa®). The compound was previously prepared by the acid catalyzed dehydration of 4-(3-dimethylaminopropyl)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol[2,27]; some time later it has been found that a product prepared in this way is a mixture of geometric isomers in which the *E*-isomer heavilly predominates[3,28]. The identification of the geometric isomers of dithiadene as the *E*-isomer *XV* and the Z-isomer *XVI* was derived exclusively from the argumentation originating in differences between the IR spectra of both isomers in the region corresponding to extraplanar C—H vibrations of the 1,2-disubstituted benzene ring, as well as of the 2,3-disubstituted thiophene nucleus[3]; this type of assignment of configuration on the double bond must not be considered completely satisfying. In the communication mentioned[3]

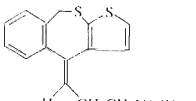
we described the ^{1}H NMR spectra of both isomers which showed likewise some differences but we did not attempt in interpreting these spectra for the assignment of configuration on the double bond. Such an interpretation, however, is possible and is in full agreement with the conclusion made on the basis of the IR spectra. In the first line it is clear that the coalescence temperature of the *E*-isomer *XV* must be higher than for the *Z*-isomer *XVI*; the bulky substituent aggravates the inversion between the both possible nonplanar conformers on the carbon in position 9. The signals of the protons of the methylene group in position 9 are a diagnostic tool: In the spectra, registered at 20°C, the signal of protons of this methylene group with the predominating isomer appears as the broad singlet at 3·10–4·80 ppm (in the communication under discussion[3] the medium value of 4·10 was given), whilst with the minor isomer it appears as a sharp singlet at 4·25 ppm. This proves that the coalescence temperature is higher with the predominating isomer which thus must have the *E*-configuration *XV*. This finding is confirmed by the appearance of signals of the aromatic protons of the thiophene nucleus. In the molecule of the predominating *E*-isomer *XV* they are equivalent and appear in the form of a two-proton singlet at 7·04 ppm. On the other hand, with the minor *Z*-isomer *XVI*, an interaction with the aliphatic side chain takes place resulting in the nonequivalency of protons in positions 2 and 3 of the skeleton whose signals appear as an AB quartet at 7·14 (d) and 6·94 ppm (d).

For differentiating the geometric isomers of dithiadene, a gas chromatographic method was elaborated[29] and more recently the high-performance liquid chromatography has been used for the same purpose[30]. By means of gas chromatography it could be established that the crude product contains approximately 90% of the *E*-isomer *XV* and 10% of the *Z*-isomer *XVI*. The *E*-isomer *XV* is isolated from the mixture as the crystalline hydrogen sulfate, whilst the minor *Z*-isomer *XVI* is only tediously obtained from the mother liquors as the crystalline hydrogen maleate. For more detailed pharmacological investigation there appeared the need of a larger quantity of the *Z*-isomer *XVI* which led to attempts at finding a new synthetic method. On the basis of analogy with 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepin (doxepin), whose *Z*-isomer was obtained from the corresponding ketone by the Wittig reaction, *i.e.* by treatment with 3-dimethylaminopropylidenetriphenylphosphorane[31], the same approach was used in our case[32]. 3-Dimethylaminopropylidenetriphenylphosphorane was prepared from 3-dimethylaminopropyltriphenylphosphonium bromide by means of butyllithium in a mixture of tetrahydrofuran and hexane[31] and *in situ* it was subjected to treatment with the ketone *VI*. After decomposition of the reaction mixture with water, the basic product was isolated and purified by chromatography on aluminium oxide. In a yield of 75% there was obtained a mixture of bases which was characterized by gas chromatography as containing 80% of the *Z*-isomer *XVI* and 20% *E*-isomer *XV*. Neutralization of this mixture with maleic acid and a single crystallization of the salt led

to the homogeneous hydrogen maleate of the base *XVI*. Subjecting the mixture obtained to a brief treatment with 80% sulfuric acid at room temperature and stabilizing the transitionally formed carbonium cation by diluting the mixture with water, a mixture of bases *XV* and *XVI* is obtained, in which again the *E*-isomer is the main component (86%) and can be easily isolated in pure form as the hydrogen sulfate. The Wittig method with this subsequent isomerization is thus useful also for the preparation of the *E*-isomer *XV*. The mentioned isomerization procedure may also be used for obtaining further quantities of the *E*-isomer from the mother liquor enriched with the *Z*-isomer.

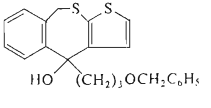


XV

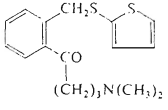


XVI

Two attempts directed to new syntheses of compounds *XV* and *XVI* were carried out but were not successful. 3-Benzyloxypropyl chloride[33] was transformed to the Grignard reagent which was subjected to a reaction with the ketone *VI* and gave the oily tertiary alcohol *XVII*. Its reaction with hydrobromic acid in acetic acid with the purpose of dehydration and substitution of the benzyloxy group with the atom of bromine resulted in destruction of the molecule under the formation of hydrogen sulfide, apparently by extrusion of the sulfur atom from the central ring. In the other attempt, a reaction of 2-(2-thienylthiomethyl)benzoic acid[2,3] with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran afforded the amino ketone *XVIII* which was considered a suitable starting compound for a dehydrocyclization reaction, which was successful in the case of synthesis of 2-chloro-9-(3-dimethylaminopropylidene)thioxanthene (chlorprothixene) (ref.[34]). The treatment of compound *XVIII* with polyphosphoric ester at 130°C did not lead to the reaction; raising the temperature to 160°C resulted in a mixture from which we could not succeed in isolating any characterized product.



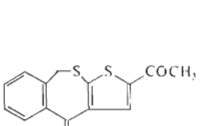
XVII



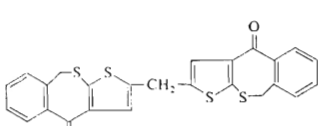
XVIII

Several new 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin derivatives were prepared as potential intermediates for further synthetic studies. Previously we have described[1] the preparation of 2-acetylthieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one (*XIX*) by a reaction of the ketone *VI* with acetic anhydride and phoshoric acid. When repeating this reaction we found that the yield on the pure product is very poor (about 17%). For this reason the procedure was modified by using a boiling mixture of acetic anhydride and boron trifluoride etherate; in this way it was possible to synthesize the desired ketone *XIX* in a yield of 48%. An attempt at its transformation to the corresponding thiomorpholide by treatment with sulfur and boiling morpholine was unsuccessful because the hydrolysis of the inhomogeneous product obtained with ethanolic potassium hydroxide did not lead to any characterized product. The reaction of the diketone *XIX* with zinc in acetic acid resulted only in the reduction of the keto group in position 4 and 2-acetyl-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*XX*) was obtained in a moderate yield. The same compound was produced by a reaction of 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin[1] with a boiling mixture of acetic anhydride and boron trifluoride etherate. An attempt at chloromethylation of the ketone *VI* with aqueous formaldehyde in hydrochloric acid under saturation with gaseous hydrogen chloride proceeded as a strongly exothermic reaction and intensive cooling was necessary. A mixture was obtained the chromatography of which on silica gel afforded as the less polar component a major part of the starting ketone *VI*. It was followed by a more polar component which does not contain chlorine and whose analysis and mass spectrum indicate its identity as that of methylenebis(4-oxo-9*H*-thieno[2,3-*c*]-2-benzothiepin-2-yl) (*XXI*). The UV and IR spectra are not at variance with this assignment. Finally, an attempt was carried out at preparing the corresponding 4-carboxaldehyde from the ketone *VI* using a method which led in a similar series to 6,11-dihydrodibenzo[*b*,*e*]thiepin-11-carboxaldehyde[35]. The ketone *VI* was subjected to treatment with the Grignard reagent, which was prepared from chloromethyl methyl ether[36] in tetrahydrofuran, and the inhomogeneous product obtained, which was considered a crude alcohol *XXII*, was heated with formic acid to 60°C. The product was chromatographed on a column of silica gel and the oil, obtained as the least polar component, was identified by the ^{1}H NMR spectrum as the enol ether *XXIV*. The more polar component, which was in fact the main product and partly crystallized, was the alcohol *XXII* contaminated by the starting ketone *VI*. An attempt at hydrolysis of the enol ether *XXIV* with a mixture of formic acid and dilute sulfuric acid gave only polymeric products. From an attempt at dehydration of the crude alcohol *XXII* with a solution of formic acid in dioxane there was obtained in a yield of about 25% as the only crystalline product a substance $C_{28}H_{24}O_3S_4$ (mass spectrum and analysis) to which the structure of the ether *XXIII* was assigned. The tendency of the alcohols of the benzhydrol type to yield ethers in acid media is well known[37].

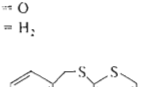
The pharmacological properties of the hydrogen (+)-tartrate of compound *I*

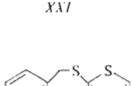


XIX, Z = O
XX, Z = H_2



XXI





XXII, R = H
XXIII, R =

XXIV

were described in a series of five short communications[10-14]. The potential metabolites *III* and *X* were also evaluated, both of them as hydrogen maleates; the doses were calculated for the bases. Compound *III* had a mild protective effect in the test of histamine aerosol in guinea-pigs, PD_{50} = 0·6 mg/kg orally (for *I* and *V*, PD_{50} = = 0·046, and 0·054 mg/kg *p.o.*, respectively). It has also a mild antiserotonin effect in the test of oedema of the rat paws, ED = 3 mg/kg *i.p.* (for *I* and *V*, ED = 0·3 mg/kg *i.p.*). The sulfoxide *X*, on the other hand, has a high protective activity in the test of histamine aerosol PD_{50} = 0·02 mg/kg *p.o.*, but only a weak antiserotonin effect (ED = 1–10 mg/kg *p.o.*). In an intraperitoneal dose of 1 mg/kg in rats, the compound *X* has a full protective effect towards the lethal action of the histamine liberator „48/80" (ref.[38]) (a similar effect was found with compounds *I* and *V*). In subcutaneous doses of 1 and 10 mg/kg the compound was devoid of antianaphylactic activity in mice (towards human serum albumin), whilst compound *V* revealed the effect starting from a dose of 1 mg/kg. The structural analogy of compounds *X* and *XII* is thus only partly accompanied by a similarity of pharmacological properties.

Compounds *III* and *X* showed some antimicrobial activity in the tests *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus* β-*haemolyticus*, *III* 50; *Streptococcus faecalis*, *III* 100; *Escherichia coli*, *III* 100; *Proteus vulgaris*, *III* 25; *Mycobacterium tuberculosis* H37Rv, *III* 25, *X* 100; *Saccharomyces pasterianus*, *III* 50, *X* 50; *Trichophyton mentagropytes*, *III* 50, *X* 50.

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 60 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with Unicam SP 200G and 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 MCH-1320 and Varian MAT 44S spectrometers. The homogeneity of the compounds and composition of the reaction mixtures was checked by chromatography on thin layers of silica gel (Silufol).

Thieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one (*VI*)

Was prepared using our previously published method[1] and recrystallized from ethanol; m.p. 64—66°C. UV spectrum: λ_{max} 261 nm (log ε 4·23), 354 nm (3·63), inflex at 234 nm (4·00). IR spectrum: 700, 735, 761 (4 adjacent Ar—H), 825, 855 (2 adjacent thiophene Ar—H), 1 500, 1 570, 1 590, 3 090 (Ar), 1 620 cm^{-1} (ArCOAr). ^{1}H NMR spectrum: δ 7·75 (m, 1 H, 5-H), 7·65 (d, J = 5·0 Hz, 1 H, 2-H), 7·00—7·50 (m, 3 H, 6,7,8-H_3), 6·98 (d, J = 5·0 Hz, 1 H, 3-H), 4·10 (s, 2 H, $ArCH_2S$). Lit.[1], m.p. 61—62·5°C.

4-(1-Methyl-4-piperidyl) 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol (*VII*)

A solution of 1-methyl-4-piperidylmagnesium chloride was prepared by treatment of 3·65 g Mg with 20·0 g 4-chloro-1-methylpiperidine in 60 ml tetrahydrofuran[1,4] and after cooling to 15°C it was stirred and treated dropwise over 30 min with a solution of 23·2 g *VI* in 50 ml tetrahydrofuran. The mixture was stirred for 30 min at room temperature and under cooling to 20—28°C decomposed with a solution of 67·5 g (+)-tartaric acid in 300 ml water. The solution was washed with toluene, made alkaline with NH_4OH and the base was extracted with chloroform. The extract was washed with water, dried with K_2CO_3, filtered with charcoal and the filtrate was evaporated under reduced pressure. The residue was boiled for a short time with 50 ml ethanol, the suspension was kept overnight in a refrigerator and the product was filtered, washed with light petroleum and dried; 17·8 g (54%) homogeneous *VII*, m.p. 207—210°C. For recording the spectra, the product was crystallized from ethanol, m.p. 212—213°C. Mass spectrum, m/z (%): 331 (M^+ corresponding to $C_{18}H_{21}NOS_2$, 0·5%), 233 (12), 200 (10), 171 (7), 99 (80), 98 (100), 96 (15), 91 (12), 70 (18), 55 (22). IR spectrum: 763 (4 adjacent Ar—H), 838 (2 adjacent thiophene Ar—H), 1 070 (R_3COH), 1 557, 1 602 (Ar), 2 798 (N—CH_3), infl. 3 160 cm^{-1} (OH). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·75 (m, 1 H, 5-H), 7·25 (m, 5 H, remaining ArH), 5·75 (s, 1 H, OH), 4·80 and 3·90 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 2·10 (s, 3 H, NCH_3), 1·40—3·00 (m, 9 H, 4 CH_2 and CH of piperidine). Lit[1], m.p. 211—213°C.

Hydrogen sulfate, m.p. 210—215°C (changes starting from 170°C) with decomposition (tetrahydrofuran–ether). For $C_{18}H_{23}NO_5S_3$ (430·6) calculated: 50·21% C, 5·62% H, 3·25% N, 22·34% S; found: 50·23% C, 5·21% H, 2·81% N, 22·00% S.

The ethanolic mother liquor was evaporated under reduced pressure and the residue (11·5 g) was crystallized from a mixture of 10 ml ethanol and 10 ml hexane; 1·8 g (6%) of a compound melting at 210—212°C but differing from *VII* by lower polarity. It was chromatographed on a column of 60 g silica gel (Silpearl). Elution with a mixture of 60% chloroform, 35% chloroform saturated with NH_3 and 5% methanol gave in the first fractions 1·0 g *VIII*, m.p. 211·5—213°C. The analytical sample was obtained by crystallization from a mixture of cyclohexane and ethanol

and then chloroform and ethanol, m.p. 212—213 °C. The product was identified as 7-(1-*methyl*-4-*piperidyl*)*thieno*[2,3-*c*]-2-*benzothiepin*-4(9*H*)-*one* (*VIII*). Mass spectrum, *m/z* (%): 329 (M^+ corresponding to $C_{18}H_{19}NOS_2$, 40%), 314 ($C_{17}H_{16}NOS_2$, 3%), 300 ($C_{17}H_{18}NS_2$, 1%), 296 ($C_{18}H_{18}NOS$, 2%), 259 ($C_{14}H_{11}OS_2$, 1%), 97 (44), 83 (22), 70 (C_4H_8N, 100%), 57 (23). UV spectrum: λ_{max} 265 nm (log ε 4·24), 356 nm (3·62). IR spectrum: 836, 845 (2 adjacent Ar—H including the thiophene C—H), 899 (solitary Ar—H), 1 270, 1 361 (CO), 1 500, 1 598, 3 085, 3 110 (Ar), 1 611 (ArCOAr), 2 670, 2 730, 2 770 cm^{-1} (N—CH_3, N—CH_2). ^1H NMR spectrum: δ 7·80 (d, J = 8·0 Hz, 1 H, 5-H), 7·71 (d, J = 5·5 Hz, 1 H, 2-H), 7·28 (dd, J = 8·0; 1·5 Hz, 1 H, 6-H), 7·05 (d, J = 1·5 Hz, 1 H, 8-H), 7·04 (d, J = 5·5 Hz, 1 H, 3-H), 4·15 (s, 2 H, $ArCH_2S$), 2·35 (s, 3 H, NCH_3), 1·70—3·10 (m, 9 H, 4 CH_2 and CH of piperidine). For $C_{18}H_{19}NOS_2$ (329·3) calculated: 65·64% C, 5·82% H, 4·25% N, 19·44% S; found: 65·10% C, 5·80% H, 4·08% N, 19·25% S. The low-melting products (m.p. 119—120 and 125°C) mentioned in our previous paper[1], which were considered to be solvates of *VII*, were probably mixtures of *VII* and *VIII*.

Hydrogen maleate, m.p. 206—208°C with decomposition (aqueous ethanol). For $C_{22}H_{23}NO_5S_2$ (445·6) calculated: 59·31% C, 5·20% H, 3·14% N, 14·39% S; found: 59·59% C, 5·30% H, 3·15% N, 14·42% S.

4-(1-Ethoxycarbonyl-4-piperidylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*II*)

A solution of 12·5 g *I* (ref.[1]) in 100 ml benzene was added dropwise over 1 h to a stirred and refluxing solution of 8·7 g ethyl chloroformate in 25 ml benzene. The mixture was stirred and refluxed for another 1·5 h, cooled and washed with a solution of 10 g (+)-tartaric acid in 100 ml water. The benzene layer was dried with K_2CO_3 and evaporated under reduced pressure. The residue was dissolved in 100 ml benzene and the solution was filtered through a column of 50 g silica gel (Silpearl). Washing with 300 ml benzene and evaporation of the filtrate gave 12·0 g (81%) product which crystallized on standing, m.p. 98—104°C. Analytical sample, m.p. 103 to 105°C (cyclohexane–hexane). UV spectrum: λ_{max} 283 nm (log ε 3·86), inflex at 305 nm (3·69). IR spectrum: 740 (4 adjacent Ar—H), 770, 780 (2 adjacent Ar—H of thiophene), 1 220 (CO of ester), 1 630, 1 655, 1 664 (C=C), 1 700 (NCOOR), 3 080 and 3 110 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·20 (m, 4 H, 5,6,7,8-H_4), 6·99 (d, J = 5·0 Hz, 1 H, 2-H), 6·68 (d, J = 5·0 Hz, 1 H, 3-H), 4·85 and 3·49 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 4·12 (q, J = 7·0 Hz, 2 H, OCH_2), 3·70 and 3·12 (2 m, 4 H, CH_2NCH_2), 2·50 and 2·18 (2 bt, 3 H, remaining 2 CH_2 of piperidylidene), 1·25 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{20}H_{21}NO_2S_2$ (371·5) calculated: 64·66% C, 5·70% H, 3·77% N, 17·26% S; found: 64·56% C, 5·61% H, 3·57% N, 17·11% S.

4-(4-Piperidylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*III*)

A solution of 40·1 g crude *II* in 36 ml ethanol was treated with 30 g KOH and the mixture was stirred and refluxed for 2 h. After cooling it was diluted with 200 ml water and the base was extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated under reduced pressure. The residue (according to TLC it is free of the starting *II*) was crystallized from a mixture of 250 ml cyclohexane and 100 ml benzene; 25·4 g (79%), m.p. 154—156°C. Analytical sample, m.p. 157—158°C (benzene). Mass spectrum, *m/z* (%): 299·0787 (M^+ corresponding to $C_{17}H_{17}NS_2$, 60%), 266·1003 ($C_{17}H_{16}NS$, 100%), 241 (23), 237 (28), 223 (33), 221 (35), 165 (43). UV spectrum: λ_{max} 283 nm (log ε 3·81). IR spectrum: 740, 766 (4 adjacent Ar—H), 808 (2 adjacent Ar—H of thiophene), 1 490, 3 065, 3 105 (Ar), 2 723, 2 790 (N—CH_2), 3 310 cm^{-1} (NH). ^1H NMR spectrum: δ *c.* 7·20 (m, 4 H, 5,6,7,8-H_4), 6·98 (d, J = 5·0 Hz, 1 H, 2-H), 6·70 (d, J = 5·0 Hz, 1 H, 3-H), 4·90 and 3·50 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 2·00 to

3·10 (m, 8 H, 4 CH_2 of piperidylidene), 1·70 (bs, 1 H, NH). For $C_{17}H_{17}NS_2$ (299·5) calculated: 68·18% C, 5·72% H, 4·68% N, 21·42% S; found: 68·40% C, 5·97% H, 4·38% N, 20·96% S.

Hydrogen maleate, m.p. 198·5—199·5°C (aqueous ethanol). For $C_{21}H_{21}NO_4S_2$ (415·5) calculated: 60·70% C, 5·09% H, 3·37% N, 15·44% S; found: 60·79% C, 5·12% H, 3·49% N, 15·58% S.

4-(1-Methyl-4-piperidylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*I*)

A) *VII* (16·6 g) was refluxed with a solution of 24 g H_2SO_4 in 120 ml water for 15 min and the mixture was processed by treatment with 24 ml NH_4OH and extraction with chloroform[1]. The extract was dried with K_2CO_3 and evaporated. The residue was crystallized from 90 ml ethanol with filtration of the hot solution with charcoal; 13·8 g (88%), m.p. 160—161°C. Analytical sample, m.p. 162—164°C (ethanol). Lit.[1], m.p. 155—157°C. Mass spectrum, *m/z* (%): 313 (M^+ corresponding to $C_{18}H_{19}NS_2$, 20%), 280 (100), 241 (9), 222 (11), 221 (12), 209 (9), 70 (51), 44 (40), 43 (12), 42 (28). UV spectrum: λ_{max} 232 nm (log ε 4·27), 284 nm (3·80), infl. 306 nm (3·62). IR spectrum (KBr): 740, 769 (4 adjacent Ar—H), 840 (2 adjacent Ar—H of thiophene), 1 488, 3 013, 3 065, 3 100 (Ar), 1 636 (C=C), 2 728, 2 775 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ *c.* 7·15 (m, 4 H, 5,6,7,8-H_4), 6·94 (d, J = 5·0 Hz, 1 H, 2-H), 6·68 (d, J = 5·0 Hz, 1 H, 3-H), 4·88 and 3·45 (ABq, J = 13·0 Hz, 2 H, $ArCH_2S$), 2·50 and 2·20 (2 m, 8 H, 4 CH_2 of piperidylidene), 2·20 (s, 3 H, NCH_3).

Hydrogen (+)-tartrate, m.p. 228—231°C with decomposition (aqueous ethanol). For C_{22}. $.H_{25}NO_6S_2$ (463·6) calculated: 57·00% C, 5·44% H, 3·02% N, 13·84% S; found: 56·76% C, 5·70% H, 2·91% N, 13·90% S.

B) A solution of 3·6 g (0·012 mol) *III* in 10 ml chloroform was treated with 0·43 g (0·003 mol) methyl iodide and the mixture was allowed to stand overnight at room temperature. It was then shaken with 20 ml 5% NH_4OH, the chloroform layer was dried with K_2CO_3 and evaporated under reduced pressure. The residue was dissolved in chloroform and chromatographed on a column of 100 g silica gel (Silpearl). Elution with a mixture of 74·5% chloroform, 25% chloroform saturated with NH_3 and 0·5% methanol gave 0·8 g (76% per conversion) *I*, m.p. 160—161°C, identical with the product described under *A*). Hydrogen (+)-tartrate, m.p. 226—228°C with decomposition (ethanol). Continuation of the chromatography with elution with a mixture of 50% chloroform, 48% chloroform saturated with NH_3 and 2% methanol led to recovery of 2·6 g starting *III*, m.p. 156—158°C.

C) A solution of 1·9 g *II* in 40 ml ether was added dropwise over 15 min to a stirred suspension of 0·38 g $LiAlH_4$ in 15 ml ether and the mixture was refluxed for 1·5 h. After cooling it was decomposed under stirring by a slow addition of 0·4 ml water, 0·4 ml 15% NaOH and 1·2 ml water, it was stirred for 1 h, the solid was filtered off and washed with chloroform. The filtrate was dried with K_2CO_3, filtered through a column of 5 g silica gel (Merck) and the column was washed with 50 ml mixture of 99% chloroform saturated with NH_3 and 1% methanol. Evaporation of the filtrate under reduced pressure yielded 1·1 g (70%) chromatographically homogeneous *I*, m.p. 160—161°C. Hydrogen (+)-tartrate, m.p. 227—229°C with decomposition (aqueous ethanol).

4-[1-($^2H_3$)-Methyl-4-piperidylidene]-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*IV*)

A solution of 5·5 g *II* in 120 ml ether was added dropwise over 45 min to a stirred solution of 1·39 g 90% $LiAl^2H_4$ (isotopical purity of 99%) in 50 ml ether under nitrogen and the mixture

was stirred and refluxed for 5 h. After standing overnight at room temperature the mixture was decomposed under stirring by a successive addition of 1·5 ml 15% NaO^2H and 4·5 ml ^2H_2O. After stirring for 15 min the solid was filtered off, the filtrate was evaporated and the residue crystallized from 35 ml ethanol; 3·3 g (70%), m.p. 160·5–162·5 C. According to the mass spectrometric determination the product is free of the CH_3 analogue, contains only traces of the $CH_2{}^2H$ analogue and approximately 10% of the CH^2H_2 analogue.

1,1-Dimethyl-4-(4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ylidene)piperidinium Iodide (*IX*)

A solution of 6·3 g *I* in 120 ml methanol was treated with 3·0 g methyl iodide. The mixture was allowed to stand for 5 h at room temperature, then refluxed for 5 min and allowed to stand at room temperature for another 16 h. The separated oil was dissolved by heating and by addition of 30 ml methanol, the warm solution was filtered with charcoal and the filtrate was diluted with 30 ml ether. Crystallization in a refrigerator gave 8·2 g (90%) *IX*, m.p. 282–288°C. Analytical sample, m.p. 295–298°C (aqueous methanol–ether). For $C_{19}H_{22}INS_2$ (455·4) calculated: 50·11% C, 4·87% H, 27·86% I, 3·08% N, 14·08% S; found: 50·21% C, 4·86% H, 28·11% I, 3·04% N, 14·31% S.

4-(1-Methyl-4-piperidylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin 10-Oxide (*X*)

A solution of 4·5 g *I* in 20 ml acetic acid was stirred and slowly treated with 2·3 g 30% H_2O_2. The mixture was allowed to stand overnight at room temperature, diluted with 200 ml water, made alkaline with NH_4OH and the oily product was extracted with chloroform. The extract was dried with K_2CO_3 and evaporated under reduced pressure. The residue was dissolved in 11 ml boiling benzene, the solution was cooled and treated with light petroleum. After standing for several hours the base was filtered and dried *in vacuo*; 3·4 g (72%), m.p. 149–154°C. Analytical sample, m.p. 155–158°C (benzene–light petroleum). IR spectrum: 742, 773, 790 (4 adjacent Ar–H), 854 (2 adjacent Ar–H of thiophene), 1 053 (S–O), 1 468, 1 529, 3 080 (Ar), 1 629 cm^{-1} (C=C). The polarographic reduction in 0·5M-HCl (towards a saturated calomel electrode) showed two reduction waves at $E_{1/2}$ −0·92 V corresponding to the sulfoxide and at −0·735 V corresponding to a probable contamination by the N-oxide. For $C_{18}H_{19}NOS_2$ (329·5) calculated: 65·61% C, 5·81% H, 4·25% N, 19·47% S; found: 65·60% C, 5·86% H, 4·10% N, 19·56% S.

Hydrogen maleate, m.p. 205–207°C with decomposition (aqueous ethanol). For $C_{22}H_{23}NO_5S_2$ (445·6) calculated: 59·30% C, 5·20% H, 3·14% N, 14·40% S; found: 59·13% C, 5·26% H, 3·01% N, 14·30% S.

4-(4-Piperidylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin 10-Oxide (*XI*)

A solution of 9·0 g *III* in 45 ml acetic acid was cooled to 10°C and treated under stirring with 4·8 g 30% H_2O_2, added dropwise. The mixture was allowed for 20 h at room temperature, diluted with 120 ml water, made alkaline with 80 ml NH_4OH and the base was extracted with chloroform. The extract was washed with water, dried with K_2CO_3 and evaporated under reduced pressure. The residue was crystallized from a mixture of 40 ml benzene and 30 ml hexane; 7·6 g (80%), m.p. 175–179°C. Analytical sample, m.p. 182–184°C (benzene–ethanol–hexane). UV spectrum: λ_{max} 271 nm (log ε 4·11). IR spectrum: 771, 794 (4 adjacent Ar–H and 2 adjacent thiophene Ar–H), 1 030 (S–O), 1 483, 1 498, 1 571, 3 050 (Ar), 1 618 (C=C), 3 290 cm^{-1} (NH). Polarography in 0·25M-H_2SO_4 (saturated calomel electrode), reduction wave at $E_{1/2}$ = −0·85 V (S–O). The ^1H NMR spectrum indicates that we are dealing here with a mixture of two rather

stable stereoisomers: δ 7·00—7·60 (m, 4 H, 5,6,7,8-H_4), 6·98 and 6·91 (2 d, 2 H, 2,3-H_2), 5·01; 4·32 and 4·48; 4·18 (2 ABq, 2 H, $ArCH_2S$), 2·00—3·20 (m, 8 H, 4 CH_2 of piperidylidene), 1·80 (bs, 1 H, NH). For $C_{17}H_{17}NOS_2$ (315·5) calculated: 64·73% C, 5·43% H, 4·44% N, 20·33% S; found: 64·69% C, 5·62% H, 3·88% N, 19·78% S.

Hydrochloride, m.p. 289—292°C with decomposition (aqueous ethanol–ether). For $C_{17}H_{18}$.$ClNOS_2$ (351·9) calculated: 58·02% C, 5·16% H, 10·08% Cl, 3·98% N, 18·22% S; found: 57·86% C, 4·98% H, 10·16% Cl, 3·98% N, 18·00% S.

4-(1-Methyl-4-piperidylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin N-Oxide (*XIII*) and N,10-Dioxide (*XIV*)

A solution of 6·4 g *I* in 100 ml ethanol was treated with 3·5 ml 30% H_2O_2, the mixture was allowed to stand for 12 h at room temperature and then refluxed for 3 h. The excess of H_2O_2 was decomposed by refluxing with a small tin of Pt for 1 h and the mixture was evaporated *in vacuo*. The residue was dissolved in chloroform and the solution was chromatographed on a column of 120 g silica gel (Silpearl). Elution with a mixture of 80% chloroform, 17·5% chloroform saturated with NH_3 and 2·5% methanol recovered 0·9 g starting *I* (m.p. 160·5—164°C) as the least polar component. The elution was then continued with a mixture of 60% chloroform, 35% chloroform saturated with NH_3 and 5% methanol which led to obtaining 2·9 g (50% per conversion) homogeneous *XIII* (the ^1H NMR spectrum indicates again that we are dealing with a mixture of two rather stable steroisomers but they cannot be differentiated by TLC). It was dissolved in ethanol and the solution was acidified with a solution of HCl in ether. The mixture was evaporated *in vacuo* and the hydrochloride was crystallized from aqueous ethanol, m.p. 225—228°C with decomposition. For $C_{18}H_{20}ClNOS_2$ (366·0) calculated: 59·05% C, 5·51% H, 9·69% Cl, 3·83% N, 17·52% S; found: 59·07% C, 5·53% H, 9·71% Cl, 3·68% N, 17·38% S.

The base *XIII* was obtained by treatment of the hydrochloride with NH_4OH, extraction with chloroform and after drying and evaporation of the extract by crystallization from a mixture of benzene and chloroform; m.p. 209—210°C. UV spectrum: λ_{max} 284 nm (log ε 3·81), infl. 304 nm (3·66). IR spectrum: 720, 752, 760 (4 adjacent Ar—H), 840 (2 adjacent Ar—H of thiophene), 950 (N—O), 1 480, 1 593, 3 055, 3 095 (Ar), 1 632 cm^{-1} (C=C). Polarographic reduction in 0·25M-H_2SO_4 (saturated calomel electrode) showed a wave at $E_{1/2}$ —0·70 V (N—O). ^1H NMR spectrum: δ *c.* 7·20 (m, 4 H, 5,6,7,8-H_4), 7·00 (d, J = 5·0 Hz, 1 H, 2-H), 6·75 and 6·65 (2 d, J = 5·0 Hz, 1 H, 3-H), 4·84; 3·55 and 4·80; 3·52 (2 ABq, 2 H, $ArCH_2S$), 3·25 and 3·12 (2 s, 3 H, NCH_3), 2·00—3·40 (m, 8 H, 4 CH_2 of piperidylidene). For $C_{18}H_{19}NOS_2$ (329·5) calculated: 65·62% C, 5·81% H, 4·25% N, 19·46% S; found: 65·99% C, 6·01% H, 3·77% N, 18·92% S.

The chromatography was continued by elution with a mixture of 55% chloroform, 35% chloroform saturated with NH_3 and 10% methanol and gave 2·9 g (48% per conversion) homogeneous *XIV* which crystallized from a mixture of benzene, chloroform and ethanol, m.p. 197—200·5°C. Mass spectrum, *m/z*: 345 (M^+ corresponding to $C_{18}H_{19}NO_2S_2$, low intensity), 327, 312. UV spectrum: λ_{max} 269 nm (log ε 4·14). IR spectrum: 759, 849 (4 adjacent Ar—H and 2 adjacent thiophene Ar—H), 950 (N—O), 1 050 (S—O), 1 505 (Ar), 1 635 cm^{-1} (C=C). Polarography in 0·25M-H_2SO_4 (saturated calomel electrode), two reduction waves at $E_{1/2}$ of —0·48 V (N—O) and —0·89 V (S—O). For $C_{18}H_{19}NO_2S_2$ (345·5) calculated: 62·58% C, 5·54% H, 4·06% N, 18·56% S; found: 62·77% C, 5·61% H, 3·77% N, 18·10% S.

Hydrochloride, m.p. 233—237°C (aqueous–ethanol–ether). For $C_{18}H_{20}ClNO_2S_2$ (382·0) calculated: 56·60% C, 5·28% H, 9·28% Cl, 3·67% N, 16·79% S; found: 56·84% C, 5·37% H, 9·27% Cl, 3·31% N, 16·38% S.

(*Z*)-4-(3-Dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*XVI*)

A suspension of 19·8 g 3-dimethylaminopropyltriphenylphosphonium bromide[31] in 60 ml tetrahydrofuran was stirred and treated over 20 min with a solution of 5·0 g n-butyllithium in 40 ml hexane. The mixture was stirred for 30 min at room temperature and then treated with a solution of 7·0 g *VI* in 15 ml tetrahydrofuran. It was allowed to stand for 24 h at room temperature and decomposed by addition of 10 ml water. The solvents were evaporated under reduced pressure and the residue separated by shaking between 200 ml benzene and 250 ml 10% hydrochloric acid. The aqueous acid layer with the oily hydrochloride were made alkaline with NH_4OH and the crude bases were extracted with chloroform. The extract was washed with water, dried with K_2CO_3, filtered with charcoal and evaporated. The oily residue was dissolved in a small quantity of benzene and the solution was chromatographed on a column of 320 g neutral aluminium oxide (activity II). Benzene and its mixture with chloroform (3 : 1) eluted 6·8 g (75%) mixture of bases *XV* and *XVI* containing (gas chromatographic evaluation) 80% *XVI* and 20% *XV*. Neutralization of this mixture with maleic acid in ethanol and a single crystallization of the hydrogen maleate of *XVI* from ethanol gave the pure compound melting at 167—170°C. Lit.[3], m.p. 163—165°C.

(*E*)-4-(3-Dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*XV*)

The oily mixture of bases (10·2 g), obtained in the foregoing experiment, was dissolved in 30 ml benzene and the solution was added with stirring to 80 ml 80% H_2SO_4. It was stirred for 8 min at room temperature, poured into 800 ml water, heated for a short time to 80°C, after cooling made alkaline with NH_4OH and the oily bases were extracted with benzene. The extract was dried with K_2CO_3 and evaporated under reduced pressure. The residue was distilled *in vacuo* to give 6·7 g (66%) fraction boiling at 188—190°C/116 Pa; it is a mixture of bases *XV* and *XVI* containing 86% *XV* and 14% *XVI* (gas chromatographic evaluation). Neutralization of this mixture with 50% H_2SO_4 in ethanol and a single crystallization of the hydrogen sulfate from 90% ethanol gave the pure salt of *XV* melting at 189—191°C. Lit.[3], m.p. 189—191°C.

4-(3-Benzyloxypropyl)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol (*XVII*)

Mg (2·3 g) in 20 ml ether was slowly treated with a solution of 17·7 g 3-benzyloxypropyl chloride[33] in 40 ml ether (the reaction was started with a little amount of iodine and several drops of 1,2-dibromoethane) and the mixture was stirred and refluxed for 2 h to obtain the solution of the Grignard reagent. After cooling it was treated under stirring with a suspension of 13·9 g *VI* in 100 ml ether over 5 min and the mixture was stirred for 3 h. It was allowed to stand overnight at room temperature, decomposed by addition of a solution of 20 g NH_4Cl in 100 ml water, the organic layer was separated, dried with K_2CO_3, filtered with charcoal and evaporated. The residue was chromatographed on a column of 750 g neutral Al_2O_3 (activity II). Benzene eluted 8·5 g (37%) homogeneous oil which resisted to all attempts at its crystallization. A sample of the oily product was used for recording the spectrum and for analysis. ^1H NMR spectrum: δ 7·80 (m, 1 H, 5-H), 7·30 (s, 5 H, C_6H_5), 7·10—7·40 (m, 4 H, 2,6,7,8-H_4), 6·98 (d, J = 5·0 Hz, 1 H, 3-H), 4·58 and 3·85 (ABq, J = 14·0 Hz, 2 H, $ArCH_2S$), 4·42 (s, 2 H, OCH_2Ar), 3·60 (s, 1 H, OH), 3·38 (t, 2 H, CH_2O of propyloxy), 2·40 and 1·55 (2 m, 4 H, remaining 2 CH_2 of propyl). For $C_{22}H_{22}O_2S_2$ (382·5) calculated: 69·07% C, 5·80% H, 16·77% S; found: 68·92% C, 6·02% H, 16·49% S.

4-Dimethylamino-1-[2-(2-thienylthiomethyl)phenyl]butan-1-one (*XVIII*)

Treatment of 6·0 g Mg with 30·4 g 3-dimethylaminopropyl chloride in 75 ml tetrahydrofuran

(the reaction was started with a grain of iodine and 0·1 ml 1,2-dibromoethane) and refluxing the mixture for 1 h gave the Grignard reagent. It was cooled with water and a solution of 21·8 g 2-(2-thienylthiomethyl)benzoic acid[2,3] in 50 ml tetrahydrofuran was added under stirring. After standing overnight the mixture was decomposed by a slow addition of a solution of 25 g NH_4Cl in 250 ml water and extracted with chloroform. The extract was washed with 5% NaOH and water, dried with K_2CO_3 and evaporated under reduced pressure. The residue was chromatographed on 500 g neutral Al_2O_3 (activity II). Elution with chloroform gave 5·4 g (19%) homogeneous oil which did not crystallize but gave by neutralization with HCl in a mixture of ethanol and ether a hydrochloride, m.p. 136—137°C (ethanol–ether). UV spectrum: λ_{max} 239 nm (log ε 4·15), infl. 280 nm (3·57). IR spectrum: 739, 750, 768, 850, 860, 892 (4 adjacent Ar—H and 3 adjacent thiophene Ar—H), 1 210 (CO), 1 573, 1 607, 3 050, 3 068, 3 085 (Ar), 1 684 (COAr), 2 480, 2 570, 2 600, 2 670 cm^{-1} (NH^+). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·78 (m, 1 H, 6-H of benzoyl), 7·50 (q, J = 5·0; 1·5 Hz, 1 H, 5-H of thienylthio), 7·30 (m, 2 H, 4,5-H_2 of benzoyl), 7·00 (m, 1 H, 3-H of benzoyl), 6·85 (m, 2 H, 3,4-H_2 of thienylthio), 4·15 (s, 2 H, $ArCH_2S$), 3·00 (m, 4 H, $COCH_2$ and CH_2N), 2·65 (s, 6 H, CH_3NCH_3), 1·90 (m, 2 H, CH_2 in the middle of the chain). For $C_{17}H_{22}ClNOS_2$ (356·0) calculated: 57·36% C, 6·23% H, 9·96% Cl, 3·94% N, 18·02% S; found: 57·61% C, 6·45% H, 9·78% Cl, 3·83% N, 18·00% S.

2-Acetylthieno[2,3-*c*]-2-benzothiepin-4(9*H*)-one (*XIX*)

Boron trifluoride etherate (1·42 g) was added to a stirred mixture of 23·2 g *VI* and 20·4 g acetic anhydride and the mixture was refluxed for 5 min. Over 30 min it was cooled to room temperature and poured into 100 ml water. It was extracted with chloroform, the extract was washed with 5% NaOH and water, dried with Na_2SO_4, filtered with charcoal and evaporated. The residue was dissolved in 50 ml benzene and the solution was chromatographed on 600 g neutral Al_2O_3 (activity II). Benzene eluted first 5·3 g starting *VI* as the least polar component and then 10·1 g (48% per conversion) homogeneous product which crystallized from ethanol and melted at 139·5—142°C. Ref.[1], m.p. 140—141°C.

2-Acetyl-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin (*XX*)

A) Boron trifluoride etherate (0·71 g) was added to a stirred mixture of 10·9 g 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin[1] and 10·2 g acetic anhydride. The mixture was heated to 130°C and stirred for 10 min at this temperature, cooled over 30 min to room temperature, poured into 100 ml water and extracted with chloroform. The extract was washed with 5% NaOH and water, dried with Na_2SO_4 and evaporated under reduced pressure. The residue was dissolved in 100 ml benzene and chromatographed on a column of silica gel (15 cm, diameter of 2·5 cm). Elution with benzene gave a homogeneous product which was dissolved in 25 ml chloroform, the hot solution was filtered with charcoal and the filtrate treated with 40 ml ethanol. Crystallization gave 4·7 g (36%) *XX*, m.p. 175—176°C (chloroform–ethanol). UV spectrum: λ_{max} 217 nm (log ε 4·15), 272 nm (3·65), 356 nm (4·23). IR spectrum: 754, 767, 884, 900 (4 adjacent Ar—H and solitary thiophene Ar—H), 1 282 (CO), 1 490, 1 542, 1 580, 1 600, 3 020, 3 068 (Ar), 1 642 cm^{-1} (COAr). ^1H NMR spectrum: δ 7·30 (s, 1 H, 3-H), 7·22 (bs, 4 H, 5,6,7,8-H_4), 4·30 and 4·08 (2 s, 4 H, $ArCH_2S$ and $ArCH_2Ar$), 2·42 (s, 3 H, $COCH_3$). For $C_{14}H_{12}OS_2$ (260·4) calculated: 64·58% C, 4·65% H, 24·63% S; found: 64·66% C, 4·68% H, 24·42% S.

B) A mixture of 2·75 g *XIX*, 50 ml acetic acid and 6·55 g Zn was stirred and refluxed for 1·5 h, cooled to 50°C and filtered with suction (washing with 25 ml acetic acid). The filtrate was diluted with 200 ml water and the mixture was extracted with benzene. The extract was washed with

water, dried with $MgSO_4$ and evaporated. The residue was crystallized from a mixture of benzene and ethanol; 1·6 g (61%) crude product which was recrystallized from a mixture of benzene and hexane, m.p. 174–176°C. Chromatographic comparison and the mixed melting point confirmed the identity wiht the product obtained under *A*).

Methylenebis(4-oxo-9*H*-thieno[2,3-*c*]-2-benzothiepin-2-yl) (*XXI*)

A suspension of 11·6 g powdered *VI* in 10 ml hydrochloric acid was stirred and treated at 0°C over 30 min with 5 ml 40% formaldehyde. The stirring and cooling was continued and the mixture was saturated for 3 h with HCl. It was then diluted with 50 ml dichloromethane and decomposed with 100 g ice. The organic layer was separated, the aqueous one extracted with dichloromethane and the organic layers were combined, washed with a solution of $NaHCO_3$ and water, dried with K_2CO_3 and evaporated. The mixture obtained was dissolved in 80 ml benzene and chromatographed on 350 g silica gel (Merck). Elution with benzene recovered 6·1 g starting *VI*, m.p. 58–61°C. The chromatography was continued by elution with chloroform which yielded 4·5 g (80% per conversion) homogeneous *XXI*, m.p. 225–227°C (ethyl acetate–chloroform). Mass spectrum, *m/z* (%): 476 (M^+ corresponding to $C_{25}H_{16}O_2S_4$, 27%), 245 ($C_{13}H_9OS_2$, 100%), 216 (51), 213 (63), 184 (34), 171 (31), 115 (62), 90 (94), 89 (84), 69 (32), 63 (30). UV spectrum (saturated solution in methanol): λ_{max} 269 and 354 nm. IR spectrum (KBr): 721, 728, 767 (Ar—H), 1 590, 3 010, 3 030, 3 050 (Ar), 1 617 cm^{-1} (ArCOAr). For $C_{25}H_{16}O_2S_4$ (476·7) calculated: 62·99% C, 3·38% H, 26·91% S; found: 62·47% C, 3·37% H, 26·55% S.

4-Methoxymethyl-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-ol (*XXII*)

Mg (6·1 g) in 12 ml tetrahydrofuran was activated with 0·3 g $HgCl_2$ and treated over 1 h at −5 to 0°C with a solution of 20 g chloromethyl methyl ether[36] in 20 ml tetrahydrofuran. The mixture was stirred for 3 h with cooling, treated with a solution of 23·2 g *VI* in 50 ml tetrahydrofuran at 0°C, stirred for 1 h and allowed to stand overnight at room temperature. It was decomposed by pouring into 200 ml 15% NH_4Cl and extracted with ether. Evaporation of the extract gave a residue which was treated with 100 ml formic acid, the mixture was heated for 10 min to 50 to 60°C, diluted with water and extracted with benzene. The residue (26·5 g) was chromatographed on 500 g silica gel (Silpearl). A mixture of benzene and light petroleum eluted 3·8 g homogeneous oil which was shown to be 4-*methoxymethylene*-4,9-*dihydrothieno*[2,3-*c*]-2-*benzothiepin* (*XXIV*). ^1H NMR spectrum: δ 7·30 (d, 1 H, 2-H), 7·18 (bs, 4 H, 5,6,7,8-H_4), 6·97 (d, 1 H, 3-H), 6·11 (s, 1 H, C=CH), 4·18 (s, 2 H, $ArCH_2S$), 3·72 (s, 3 H, OCH_3).

The chromatography was continued by elution with benzene giving 11·5 g (41%) impure *XXII* (containing some starting *VI* which could not be removed), m.p. 140–150°C (cyclohexane). ^1H NMR spectrum: δ 4·98 (s, 2 H, OCH_2), 3·40 (s, 3 H, OCH_3). For $C_{14}H_{12}OS_2$ (260·2) calculated: 64·61% C, 4·65% H, 24·60% S; found: 65·52% C, 4·87% H, 23·52% S.

Bis(4-methoxymethyl-4,9-dihydrothieno[2,3-*c*]-2-benzotheipin-4-yl) Ether (*XXIII*)

A mixture of 1·9 g crude *XXII*, 10 ml formic acid and 10 ml dioxane was heated to dissolution, allowed to stand for one week at room temperature, and then diluted with water, 1 drop hydrochloric acid was added and the mixture allowed to stand for one month. Then it was further diluted with water, the solid was filtered, dried and crystallized from a mixture of benzene and cyclohexane; 0·45 g (25%), m.p. 212–215°C (benzene). Mass spectrum does not show the expected molecular peak but the structure suggested is supported by the presence of peaks with *m/z* 492 ($C_{26}H_{20}O_2S_4$, cleavage of H and CH_2OCH_3) and 446 ($C_{25}H_{18}O_2S_3$, cleavage of SCH_2);

the base peak has an m/z of 45 (CH_2OCH_3). For $C_{28}H_{26}O_3S_4$ (538·8) calculated: 62·42% C, 4·86% H, 23·80% S; found: 62·56% C, 4·16% H, 24·70% S.

The authors are indebted to Dr J. Schlanger and Mrs A. Hrádková for recording some of the spectra, to Mr F. Mikšík for the assistance with the syntheses, to Dr J. Turinová for the microbiological screening and to Mrs J. Komancová, Mrs V. Šmídová and Mr M. Čech for carrying out the analyses. Dr. K. Šindelář carried out the preparation of comdounds XXII—XXIV (*all of the mentioned belong to the research staff of this institute*).

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Translated by the author (M. P.).