4*H*-BENZO[4,5]CYCLOHEPTA[1,2-*b*]THIOPHENES AND 9,10-DIHYDRO DERIVATIVES - SULFONIUM ANALOGUES OF PIZOTIFEN AND KETOTIFEN; CHIRALITY OF KETOTIFEN; SYNTHESIS OF THE 2-BROMO DERIVATIVE OF KETOTIFEN

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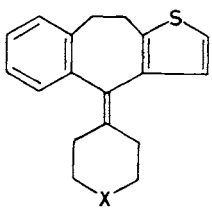
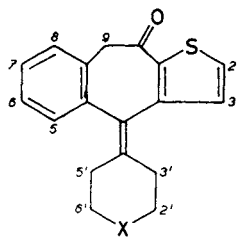
Reaction of ketone *IX* with 4-tetrahydrothiopyranylmagnesium bromide and the following dehydration with thionyl chloride afforded the sulfide *III* which was transformed to the methiodide *II* (sulfonium analogue of pizotifen). Similar sequence starting from the ketone *XXIV* and concluded by dehydration of the alcohol *XX*, cleavage of the enol ether, and by treatment with methyl iodide resulted in the formation of the sulfonium analogue of ketotifen (*V*). Three modified routes leading to ketotifen (*IV*) are being described. The chirality of ketotifen was proven by ^{1}H NMR spectroscopy with the help of the optically active NMR shift reagent. The resolution of racemic ketotifen (*IV*) was achieved by crystallization of salts with optically active O,O'-diacyltartaric acids and homogeneous enantiomers were obtained. The X-ray crystallographic analysis of (+)-*IV* (−)-O,O'-di(*p*-toluoyl)-(*R*)-tartrate led to the three-dimensional structure of the molecule of (+)-ketotifen which enabled to determine its absolute configuration to be (*R*). One of the products of bromination of the ketone *IX*, the following methanolysis and dehydrobromination, identified as *XXVII*, was transformed by reaction with 1-methyl-4-piperidylmagnesium chloride, by the following acid-catalyzed dehydration, and cleavage of the enol ether to the 2-bromo derivative of ketotifen *XXXIV*. (*R*)(+)-Ketotifen (*IV*) was found to be the more active ketotifen enantiomer but the stereoselectivity of its action is only a partial one. The 2-bromo derivative of ketotifen (*XXXIV*) is much less active than ketotifen in the line of antihistamine activity.

In a previous paper[1] we have described the synthesis of a series of sulfonium salts of tetrahydrothiopyrans in whose molecules position 4 of this heterocycle was connected by a double bond with the central carbon of some tricycles, suitable as carrier systems of molecules of a large number of neurotropic and psychotropic agents: thioxanthene, 10,11-dihydrodibenzo[*a*, *d*]cycloheptene, 6,11-dihydrodibenzo [*b*, *e*]thiepin, and 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin. This work was now

continued to include also the interesting tricyclic skeleton of 9,10- dihydro-4H-benzo [4,5]cyclohepta[1,2-*b*]thiophene (cf. refs[2,3]). In this line the leading pharmaceutical products are the antimigraine agent pizotifen (*I*) (refs[2,4]) and the antiasthmatic agent ketotifen (*IV*) (refs[3,5,6]). The first task of our investigation was thus the synthesis of sulfonium analogues of *I* and *IV*, i.e. of compounds *II* and *V* whose preparation had evidently to proceed via the sulfides *III* and *VI*.

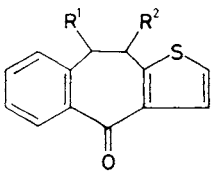


I, X = NCH_3
II, X = $\overset{(+)}{S}-CH_3\ I^{(-)}$
III, X = S

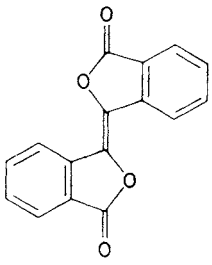


IV, X = NCH_3
V, X = $\overset{(+)}{S}-CH_3\ I^{(-)}$
VI, X = S
VII, X = NH
VIII, X = NCD_3

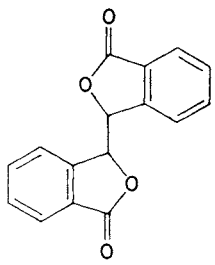
For preparing *II* we had to proceed via the ketone *IX* which was obtained, in principle, by the route described[2]. We have some remarks to the preparation of intermediates. One of the synthetic ways, leading to *IX*, utilizes phthalaldehydic acid as the intermediate. This acid is prepared by bromination of phthalide and by the following hydrolysis of the obtained 3-bromophthalide with hot water[7]. In several batches of preparation of 3-bromophthalide there was a minor distillation residue which solidified to a high-melting (358–360°C) solid $C_{16}H_8O_4$ (mass spectrum and analysis) which was identified as *XII* (obtained earlier[8–10] by different methods).



IX, $R^1 = R^2 = H$
X, $R^1 = R^2 = Br$
XI, $R^1 = Br$; $R^2 = OCH_3$



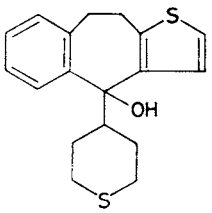
XII



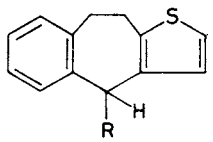
XIII

A similar substance, formulated as the dihydro compound *XIII*, was obtained in a yield of about 2% as a rather insoluble by-product of preparation of 2-(2-(2--thienyl)vinyl)benzoic acid by reaction of phthalaldehydic acid with diethyl 2-thenylphosphonate[2]. Our structure assignment is based on analysis and spectra, and the melting point of our substance is in a relatively good agreement with literature[11-13] data for *XIII*, obtained differently. A different way leading to *IX* utilizes 2-thiophenecarboxaldehyde[14] as intermediate. Its preparation by reaction of thiophene with dimethylformamide in the presence of phosphorus oxychloride[15,16] was modified which resulted in simplified processing and higher yield (see Experimental).

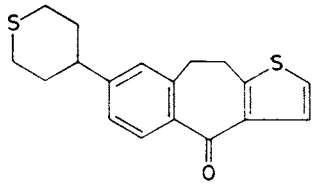
The ketone *IX* was reacted with 4-tetrahydrothiopyranylmagnesium bromide[1] in a mixture of tetrahydrofuran and ether and after hydrolysis a mixture was obtained which was separated by chromatography on silica gel. The first two compounds which were eluted with a 1 : 4 mixture of benzene and light petroleum were tetrahydrothipyran and 4,4'-bis(tetrahydrothiopyranyl), the usual by-products of similar reactions[1]. The following elution with benzene afforded the inhomogeneous product *XIV* which was purified by crystallization. Its identity was confirmed by spectra. The last to be eluted was the alcohol *XV*, product of reduction of *IX* with the Grignard reagent, which was identified by direct comparison with an authentic sample[17]. Compound *XIV* was dehydrated by heating with thionyl chloride in a mixture of pyridine and dichloromethane. The inhomogeneous product had again to be separated by chromatography on silica gel. Benzene eluted first the olefinic sulfide *III* which was characterized by spectra and transformed to the desired methiodide *II*. Continuation of the elution gave a compound $C_{18}H_{18}OS_2$ (analysis and mass spectrum) which was identified by IR and ^1H NMR spectra as *XVIII*. It is, in fact, a by-product of the preceding reaction resulting from 1,6-addition[18] of the Grignard reagent to *IX*, the following hydrolysis and elimination of two hydrogen atoms (oxidation with air oxygen). Similar products were isolated in our previous work[1].



XIV



XV, R = OH
XVI, R = H
XVII, R =



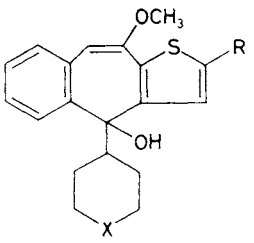
XVIII

Reduction of *IX* with zinc in refluxing acetic acid afforded 9,10-dihydro-4*H*-benzo [4,5]cyclohepta[1,2-*b*]thiophene (*XVI*), the basic substance of the whole series which

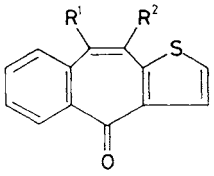
has not been described until now. The structure was corroborated by the mass and ^{1}H NMR spectra. In addition to our study on saturated side chain amines derived from condensed thiepins[19] we carried out the reduction of 4-(1-methyl-4-piperidyl)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ol (ref.[2]) to *XVII* by the known method, i.e. with hydroiodic acid in boiling acetic acid in the presence of red phosphorus[2]. Our contribution was crystallization of the base and its characterization. The same compound (*XVII*) (full spectral characterization) has now been obtained as a minor product of an attempt to reduce *XIX* (ref.[3]) with a combination of triethylsilane[20] with boron trifluoride, a reagent which was described as useful for reduction of alcohols to hydrocarbons[21,22] and for deoxygenation of ketones[23].

The synthesis of *V* made inevitable to enter the ketotifen chemistry[3]. Treatment of *IX* (ref.[2]) with N-bromosuccinimide in tetrachloromethane in the presence of dibenzoyl peroxide[3] gave the stereoisomeric mixture of dibromides *X*. Repeated crystallization led to a constantly melting dibromide (melting by 20°C higher than the literature[3] product), representing probably one homogeneous racemate. The mother liquor after the crude *X* consisted of a mixture of products and we devoted some effort to its investigation. Because of the instability of some components it proved impossible to separate the mixture by direct chromatography. For this reason it was first subjected to dehydrobromination with methanolic potassium hydroxide. The main component of the mixture now obtained was the known *XXII* which was isolated by crystallization. The mother liquor was chromatographed on silica gel. The first to be eluted with a 2 : 3 mixture of benzene and light petroleum was an isomer of *XXII*, which was identified by spectra as *XXVI*, unknown until now. TLC indicated still the presence of a component which appeared as well in the native mother liquors after *X* as in the mixture after the dehydrobromination. Its content was enriched by chromatography of the native mixture and the product was then subjected to dehydrobromination with triethylamine in dichloromethane. Chromatography gave the bromine-free product $C_{13}H_8OS$ (mass spectrum and analysis) which was identified as *XXIII*, described also by the Swiss authors[3]. In one batch of bromination of *IX* (ref.[2]), there was an unusually large „succinimide fraction", which evidently contained some brominated material. Its processing by methanolysis in the presence of potassium hydroxide gave *XI*, which was directly compared with an authentic sample[3] by TLC and by the melting point. Its further crystallization from a mixture of benzene and hexane gave a lower-melting substance which was identified as the 3 : 1 solvate of *XI* with benzene and was fully characterized. An attempt to reduce *XXII* with sodium dihydrido-bis(2-methoxyethoxo) aluminate in toluene to the corresponding secondary alcohol resulted in the formation of a mixture which was chromatographed on silica gel. The first to be eluted with a mixture of benzene and light petroleum was the bromine- and oxygen-free *XXVIII* (full spectral characterization), the product of hydrogenolysis. It was followed by compound $C_{26}H_{20}S_2$ (mass spectrum), melting at 256–258°C which was not

identified. The desired secondary alcohol (probably present in the more polar fractions) was not isolated.

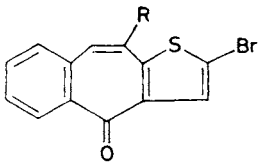


XIX, X = NCH_3; R = H
XX, X = S; R = H
XXI, X = NCH_3; R = Br

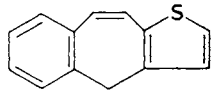


XXII, R^1 = H; R^2 = Br
XXIII, R^1 = R^2 = H
XXIV, R^1 = H; R^2 = OCH_3
XXV, R^1 = OCH_3; R^2 = H

Transformation of the crude dibromide *X* to *XXIV* was carried out by the described methanolysis and dehydrobromination[3] (yield of 70–80%). The mother liquors after *XXIV*, analyzed by TLC, show the presence of the already mentioned *XI*, *XXII*, *XXIII*, and *XXVI*. Together with a small amount of *XXIV* there appears there a more polar component, distinguishable from *XXIV* by TLC only with difficulties, easily soluble in ethanol – in contrast to *XXIV*, which is almost insoluble. Chromatography of the mother liquors after *XXIV* and rechromatography of the most polar fractions gave a mixture of *XXIV* with the unknown component. This was crystallized from a mixture of benzene and hexane which gave a sharply melting substance, identified by the ^{1}H NMR spectrum as a 68 : 32 mixture of *XXV*



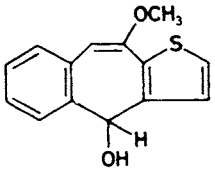
XXVI, R = H
XXVII, R = OCH_3



XXVIII

and *XXIV*. Reaction of *XXIV* with 4-tetrahydrothiopyranylmagnesium bromide[1] in a mixture of tetrahydrofuran and ether and the following hydrolysis gave a complex mixture which was chromatographed on silica gel. The first fractions (elution with mixtures of benzene and chloroform) were identified as tetrahydrothiopyran and 4,4'-bis(tetrahydrothiopyranyl) (cf. ref.[1]). They were followed by a crystalline compound $C_{14}H_{12}O_2S$ (mass spectrum and analysis) to which the structure of the secondary alcohol *XXIX*, product of reduction of *XXIV* with the Grignard reagent,

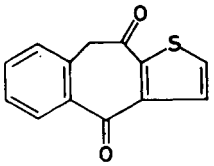
was assigned. Some starting *XXIV* was then eluted with benzene and the last to be eluted with the same solvent was the desired alcohol *XXII* which was hydrolyzed and dehydrated by the boiling solution of hydrochloric acid in dioxane. The obtained sulfide *VI* was transformed by treatment with methyl iodide in a mixture of benzene and methanol to the methiodide *V*, the sulfonium analogue of ketotifen (*IV*).



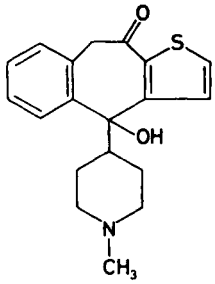
XXIX

For pharmacological comparisons we needed the substance *IV* which had thus also to be prepared (cf. ref.[3]). Reaction of *XXIV* with 1-methyl-4-piperidylmagnesium chloride in tetrahydrofuran and processing the mixture according to the Swiss authors[3] gives, indeed, the alcohol *XIX*, but if the reaction mixture was decomposed with ammonium chloride and ice, a solid $C_{20}H_{25}NO_3S$ (analysis), melting at 148–150°C, precipitated in a high yield. Its molecule corresponds to *XIX* $+H_2O$. The derivatographic thermic analysis confirmed that we are dealing here with a relatively stable monohydrate loosing the crystal water in the range between 60 and 120°C. Crystallization of this substance from ethanol leads to a compound melting at 197–198°C, having, however, still the composition of the monohydrate. We have thus to conclude that the less stable and lower melting crystal modification of the monohydrate of *XIX* crystallizes from water, and on crystallization from ethanol it is transformed to the more stable and higher melting modification. The crude monohydrate, which was not described (cf. only ref.[24]), is a suitable starting material for the final step of the synthesis of *IV*, i.e. the acid-catalyzed dehydration (boiling dilute hydrochloric acid) with simultaneous cleavage of the enol ether (cf. Experimental). A second route to *IV* started from the diketone *XXX* (ref.[3]) whose mono-enolization enables a regioselective reaction with 1-methyl-4-piperidylmagnesium chloride. Treatment of *XXIV* with three molecules of 1-methyl-4-piperidylmagnesium chloride in tetrahydrofuran and the following hydrolysis gave 68% of *XXXI* which was easily dehydrated with boiling dilute hydrochloric acid to *IV* (only mentioned in ref.[3]). A third approach to *IV* we used (in fact a formal synthesis) was the methylation of the secondary amine *VII* (ref.[3]) with methyl iodide in chloroform (a model experiment before the synthesis of the trideuteromethyl analogue of *IV*).

Our colleagues[25] indicated on the basis of a isotachophoretic study of ketotifen (*IV*) in β-cyclodextrin-modified electrolyte systems the likelihood of chirality of this compound and in microscale they carried out a partial enrichment of the enantiomers.



XXX



XXXI

We attempted to prove the chirality of *IV* and its existence in two enantiomeric forms in solution by ^{1}H NMR spectroscopy. It is known[26,27], that the optically active NMR shift reagents are able to form in solutions dynamic stereoisomeric complexes with the enantiomers whose spectra are no more identical. In the case of compound *IV*, its solution in deuterobenzene was treated with tris(3-(trifluoromethyl-hydroxymethylene)-*d*-camphorato)-europium(*III*) ($Eu(tfc)_3$) (the ratio of *IV*: $Eu(tfc)_3 \approx \approx 2 : 1$). The influence of the complexing agent was best apparent on signals of hydrogens of CH_2CO and NCH_3. At normal temperature (22°C) the spectrum showed the extreme broadening of signals (especially NCH_3) and only mild cleavage of signal of the upfield hydrogen of the CH_2CO group. After raising the temperature to 75°C, however, it was possible to observe the clear doubling of both doublets of CH_2CO and two still significantly broadened signals of NCH_3 in the intensity ratio of 1 : 1 and in this way to prove the existence of diastereomeric complexes of enantiomers of *IV*. The broadening of signals is probably increased by the fact that molecule of *IV* contains three potential binding sites for complexation with $Eu(tfc)_3$.

The chirality of ketotifen (*IV*) is not a big surprise. Its molecule, of course, does not contain any asymmetric centre but symmetry considerations show that the molecule fulfills the more general criterion of chirality, i.e. it does not have either a centre of symmetry, a plane of symmetry or an improper axis of a higher order. As the inversion of two border conformations is made difficult by the presence of the oxo group, the conformers represent two rather stable enantiomers of *IV*. A similar phenomenon was observed with the 3- and N-substituted derivatives of 5-(4-piperidylidene)dibenzo[*a*, *d*]cycloheptene where the double bond in the central ring functions as a stabilizing factor. Such compounds were resolved[28,29], the enantiomers were stable at room temperature and there was stereoselectivity of their pharmacodynamic actions.

In attempts to resolve racemic *IV* by crystallization of salts with optically active acids we first found that the use of salt with (1*S*)(+)-camphor-10-sulfonic acid, 1·5 : 1 (base to acid ratio) salt with (−)-O,O'-di(*p*-toluoyl)-(*R*)-tartaric acid, and

2 : 1 salt with (−)-dibenzoyl-(*R*)-tartaric acid did not lead to resolution. Only the 1 : 1 salts with both optically active O,O'-dibenzoyltartaric acids and with (−)-O,O'-di(*p*-toluoyl)-(*R*)-tartatic acid[30] were found suitable. Repeated crystalization of these salts from aqueous ethanol led finally to homogeneous diastereoisomers from which the optically active bases were released with aqueous ammonia[31]. The proceeding of the resolution was checked by isotachophoresis using β-cyclodextrin as an additive to the leading electrolyte[25]. From the point of view of racemization, both enantiomers of *IV* are relatively stable. The racemization proceeds quickly at the melting points of the bases (158–160°C) and in boiling aqueous solutions of the salts. Crystallization of the bases from boiling ethanol does not lead to racemization. The energetic barrier for the inversion of conformations of both enantiomers is evidently rather high.

For getting an insight to the real structural arrangement of molecules of the ketotifen enantiomers, the crystal of (+)-*IV* (−)-O,O'-di(*p*-toluoyl)-(*R*)-tartrate was subjected to X-ray crystallographic analysis. The perspective view of the molecule is given in Fig. 1. Some details of the analysis are given in the Experimental. The chemical structure of the salt investigated with a special numbering scheme (numbers of hydrogen atoms are made from numbers of their parent atoms followed by 1, 2, and 3 according to the number of hydrogens attached to the parent atom) is shown by formula *XXXII* (ref.[32]). Fractional coordinates of the salt are assembled in Table I. Selected bond lengths, angles and torsion angles of the molecule were computed by the program PARST and are assembled in Table II (ref.[33]).

The main conformational features of the salt (molecular complex) can be summarized as follows. Aromatic benzene and thiophene rings do not deviate significantly

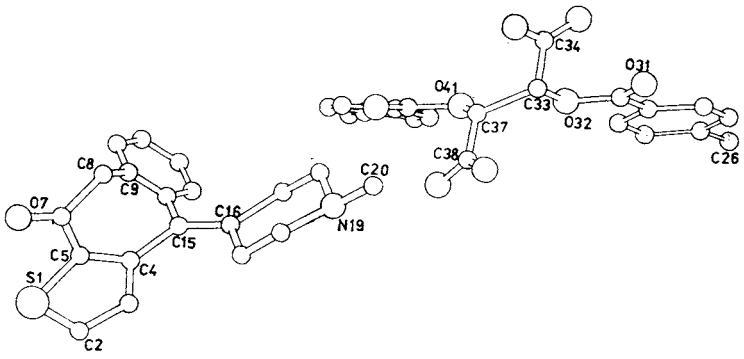


FIG. 1

Perspective view of the molecule of (*R*)(+)-ketotifen (−)-di(*p*-toluoyl)-(*R*)-tartrate (molecular complex)

TABLE I

Fractional atomic coordinates and equivalent isotropic temperature factors (A^2) with estimated standard deviations in parenthesis $U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$

Atom	*x/a*	*y/b*	*z/c*	U_{eq}
S1	1·0325(2)	1·0000(0)[a]	0·9123(2)	0·0659(9)
C2	0·9064(8)	1·0677(15)	0·8771(7)	0·0745(47)
H21	0·8826	1·1996	0·8747	
C3	0·8393(7)	0·9322(15)	0·8517(6)	0·0639(36)
H31	0·7565	0·9482	0·8271	
C4	0·8888(7)	0·7707(13)	0·8610(5)	0·0498(29)
C5	0·9957(7)	0·7887(12)	0·8944(5)	0·0509(33)
C6	1·0782(6)	0·6591(12)	0·9168(5)	0·0480(30)
O7	1·1651(5)	0·6981(10)	0·9519(4)	0·0614(23)
C8	1·0454(8)	0·4743(14)	0·8966(6)	0·0632(39)
H81	1·1147	0·3976	0·9086	
H82	1·0009	0·4343	0·9341	
C9	0·9793(7)	0·4413(14)	0·8112(5)	0·0541(34)
C10	1·0187(9)	0·3446(15)	0·7623(7)	0·0680(46)
H101	1·0983	0·3022	0·7832	
C11	0·9595(10)	0·3029(18)	0·6885(6)	0·0822(47)
H111	0·9915	0·2252	0·6519	
C12	0·8571(10)	0·3600(17)	0·6605(6)	0·0779(50)
H121	0·8102	0·3259	0·6021	
C13	0·8140(8)	0·4620(16)	0·7076(5)	0·0702(40)
H131	0·7357	0·5090	0·6847	
C14	0·8752(7)	0·5028(15)	0·7858(4)	0·0610(32)
C15	0·8337(6)	0·6073(11)	0·8356(4)	0·0437(27)
C16	0·7461(6)	0·5695(12)	0·8544(4)	0·0472(27)
C17	0·7046(7)	0·6773(14)	0·9085(5)	0·0574(33)
H171	0·6369	0·7454	0·8736	
H172	0·7636	0·7676	0·9385	
C16	0·6751(6)	0·5722(13)	0·9684(5)	0·0506(28)
H181	0·6398	0·6543	0·9987	
H182	0·7443	0·5153	0·9924	
N19	0·6002(5)	0·4329(10)	0·9311(3)	0·0450(22)
H191	0·5315	0·4897	0·8915	
C20	0·5668(7)	0·3362(14)	0·9895(5)	0·0601(34)
H201	0·5309	0·4219	1·0206	
H202	0·6334	0·2765	1·0305	
H203	0·5119	0·2394	0·9604	
C21	0·6506(6)	0·3164(12)	0·8868(5)	0·0468(26)
H211	0·5974	0·2149	0·8606	
H212	0·7199	0·2628	0·9272	
C22	0·6790(7)	0·4096(14)	0·8237(4)	0·0538(33)

TABLE I
(*Continued*)

Atom	*x/a*	*y/b*	*z/c*	U_{eq}
H221	0·7219	0·3242	0·7979	
H222	0·6087	0·4489	0·7795	
C23	0·6110(8)	0·0353(24)	0·6050(6)	0·0869(54)
H231	0·6823	0·0435	0·6528	
C24	0·6132(9)	0·0456(24)	0·5291(6)	0·0867(57)
H241	0·6869	0·0641	0·5189	
C25	0·5260(9)	0·0334(16)	0·4660(6)	0·0696(43)
C27	0·4326(10)	0·0232(25)	0·4819(6)	0·0923(58)
H271	0·3615	0·0219	0·4338	
C28	0·4278(8)	0·0131(22)	0·5602(5)	0·0773(46)
H281	0·3536	0·0063	0·5705	
C29	0·5156(7)	0·0126(14)	0·6205(5)	0·0507(30)
C26	0·5298(12)	0·0490(24)	0·3834(6)	0·1018(64)
H261	0·6092	0·0558	0·3831	
H262	0·4891	0·1632	0·3572	
H263	0·4927	−0·0610	0·3502	
C30	0·5158(6)	0·0036(14)	0·7033(5)	0·0502(28)
O31	0·5898(4)	0·0279(12)	0·7593(3)	0·0697(26)
O32	0·4230(4)	−0·0395(8)	0·7065(3)	0·0474(20)
C33	0·4052(7)	−0·0187(12)	0·7827(4)	0·0487(31)
H331	0·4749	−0·0378	0·8310	
C34	0·3716(8)	0·1606(12)	0·7926(4)	0·0510(31)
O35	0·3852(6)	0·2717(9)	0·7444(4)	0·0657(27)
H351	0·4106	0·2084	0·7001	
O36	0·3435(8)	0·1890(11)	0·8484(4)	0·0942(41)
C37	0·3238(6)	−0·1528(10)	0·7851(4)	0·0408(27)
H371	0·2991	−0·1386	0·8365	
C38	0·3677(6)	−0·3330(11)	0·7914(4)	0·0427(28)
O39	0·3169(4)	−0·4395(8)	0·7431(3)	0·0569(22)
O40	0·4503(5)	−0·3586(9)	0·8433(4)	0·0672(24)
O41	0·2386(4)	−0·1271(8)	0·7163(3)	0·0436(20)
C42	0·1459(7)	−0·1810(14)	0·7192(5)	0·0526(35)
O43	0·1336(5)	−0·2427(14)	0·7783(4)	0·0842(32)
C44	0·0623(6)	−0·1613(14)	0·6443(5)	0·0510(32)
C45	−0·0376(7)	−0·2094(18)	0·6392(6)	0·0714(41)
H451	−0·0552	−0·2604	0·6895	
C46	−0·1160(8)	−0·1909(23)	0·5668(7)	0·0925(56)
H461	−0·1940	−0·2291	0·5626	
C47	−0·0968(8)	−0·1250(18)	0·5012(6)	0·0732(46)
C48	−0·1821(10)	−0·1157(27)	0·4224(7)	0·1100(62)
H481	−0·2539	−0·1629	0·4288	
H482	−0·1605	−0·1925	0·3800	

TABLE I
(*Continued*)

Atom	*x*/*a*	*y*/*b*	*y*/*c*	U_{eq}
H483	−0·1922	0·0152	0·4027	
C49	0·0024(10)	−0·0726(20)	0·5085(6)	0·0758(44)
H491	0·0190	−0·0136	0·4594	
C50	0·0820(8)	−0·0937(17)	0·5787(6)	0·0673(37)
H501	0·1601	−0·0576	0·5821	

[a] Coordinate fixed to define the origin.

TABLE II

Selected bond lengths (Å), bond angles (°) and torsional angles (°) of the Ketotifen molecule. Estimated standard deviations are given in parenthesis

	Bond distances:		
S1–C2	1·715(11)	C11–C12	1·398(18)
S1–C5	1·731(9)	C12–C13	1·415(18)
C2–C3	1·382(15)	C13–C14	1·431(11)
C3–C4	1·419(15)	C14–C15	1·448(13)
C4–C5	1·396(12)	C15–C16	1·364(12)
C4–C15	1·482(13)	C16–C17	1·520(14)
C5–C6	1·473(13)	C16–C22	1·547(13)
C6–O7	1·193(10)	C17–C18	1·504(14)
C6–C8	1·526(14)	C18–N19	1·502(11)
C8–C9	1·542(12)	N19–C20	1·474(13)
C9–C10	1·386(17)	N19–C21	1·506(12)
C9–C14	1·428(13)	C21–C22	1·495(13)
C10–C11	1·362(15)		
	Bond angles:		
		C9–C14–C13	117·2(9)
C2–S1–C5	91·7(5)	C9–C14–C15	121·9(7)
S1–C2–C3	111·4(9)	C4–C15–C14	115·1(8)
C2–C3–C4	114·0(10)	C14–C15–C16	124·3(8)
C3–C4–C5	110·6(9)	C4–C15–C16	120·4(8)
C5–C4–C15	125·4(9)	C15–C16–C22	123·3(7)
S1–C5–C4	112·3(7)	C15–C16–C17	124·0(8)
C4–C5–C6	130·5(9)	C17–C16–C22	112·6(7)
C5–C6–C8	116.6(8)	C16–C17–C18	112·7(8)
C5–C6–O7	120·8(9)	C17–C18–N19	111·8(7)
O7–C6–C8	122·5(9)	C18–N19–C21	108·8(6)
C6–C8–C9	115·7(8)	C18–N19–C20	111·7(6)
C8–C9–C14	118·5(8)	C20–N19–C21	110·7(7)
C10–C9–C14	121·2(9)	N19–C21–C22	111·7(8)
C9–C10–C11	121·4(11)	C16–C22–C21	112·7(7)

TABLE II
(*Continued*)

Torsional angles:

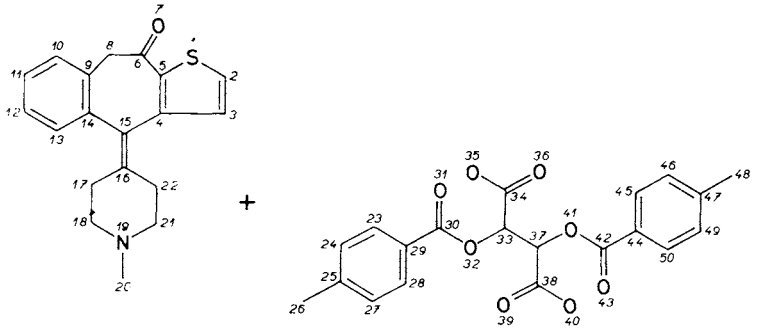
C2–S1–C5–C6	−178·3(8)	C12–C13–C14–C15	179·8(10)
C2–S1–C5–C4	0·9(8)	C9–C14–C15–C4	59·9(12)
C2–C3–C4–C15	−177·8(9)	C13–C14–C15–C4	−117·8(10)
C3–C4–C15–C16	−48·1(13)	C13–C14–C15–C16	57·4(13)
C3–C4–C15–C14	127·3(10)	C9–C14–C15–C16	−124·9(10)
C5–C4–C15–C16	134·4(10)	C14–C15–C16–C17	178·3(8)
C5–C4–C15–C14	−50·3(13)	C4–C15–C16–C17	−6·8(13)
C15–C4–C5–C6	−3·9(16)	C14–C15–C16–C22	−0·7(13)
S1–C5–C6–O7	6·3(12)	C4–C15–C16–C22	174·2(8)
C4–C5–C6–O7	−172·6(10)	C15–C16–C22–C21	133·3(9)
C4–C5–C6–C8	−3·2(15)	C15–C16–C17–C18	−133·3(9)
C5–C6–C8–C9	50·6(12)	C17–C16–C22–C21	−45·8(10)
O7–C6–C8–C9	−132·5(10)	C22–C16–C17–C18	45·8(10)
C6–C8–C9–C10	113·5(11)	C16–C17–C18–N19	−54·3(10)
C6–C8–C9–C14	−70·6(12)	C17–C18–N19–C20	−176·8(8)
C8–C9–C14–C15	5·6(14)	C17–C18–N19–C21	60·8(9)
C8–C9–C14–C13	−176·6(10)	C18–N19–C21–C22	−60·6(9)
C8–C9–C10–C11	175·1(11)	C20–N19–C21–C22	176·3(7)
C10–C9–C14–C15	178·5(10)	N19–C21–C22–C16	53·6(10)

1 Å = 10^{-10} m.

from planarity. Fragments of (−)-O,O′-di(*p*-toluoyl)-(*R*)-tartaric acid which would be formed by cleaving the C33–C37 bond are within statistical tolerance identical after superposition. An angle between the planes of the acid benzene rings is 18°. Torsion angle at the central C33–C37 bond is synclinal (see Table II). The attached carboxy groups are mutually in nearly *trans*-position and are not quite equivalent since O35 is not ionized whereas O40 is (see bond lengths in both carboxy groups). This is confirmed by an intimate contact between N19 and O40 which is – without any doubt – enabled by H-bonding (distances: N19 ... O40 = 2·70 Å, and angle N19–H191 ... O40 = 168°).

In the (+)-ketotifen molecule, an angle between mean planes of benzene and thiophene is 57° and their angles with the mean plane of the C15–C16 bond (i.e. the plane given by the atoms C4, C14, C15, C16, C17, C22) are 57° and 50°, respectively. The atoms attached to this bond deviate from planarity. Character of the C15–C16 double bond is impaired by sterical strain mainly between hydrogens H131 and H31 of the aromatic rings on one side and hydrogens H171, H172, and H221, H222 of the piperidine ring. This bond is longer than a typical C–C bond. More interesting is the

fact that lengths of both C4–C15 and C14–C15 bonds are shortened in comparison with single C–C bonds (from sterical reasons one would expect the opposite). We cannot exclude conjugation between the aromatic rings and the double bond though it is clear that the whole tricycle is not planar. A close intermolecular contact H81–H101 is probably caused by geometrical constraints of the seven-membered ring.



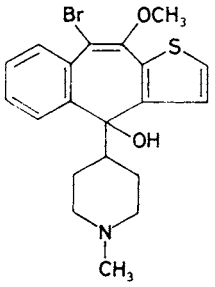
XXXII

The perspective view (see Fig. 1) and the corresponding molecular model were used for assigning the absolute configuration to (+)-ketotifen (*IV*). The following conclusions could be drawn: (i) We are dealing here with a case of planar chirality. (ii) Deformation of bonds of the mean plane formed by the C15–C16 double bond system is not important. (iii) From the point of view of planar chirality, the distortion of the seven-membered ring is important and for this reason, the plane of chirality was realized by this seven-membered ring. Using the instructions of Prelog et al.[34,35] we come to the conclusion that the absolute configuration of (+)-ketotifen is (*R*).

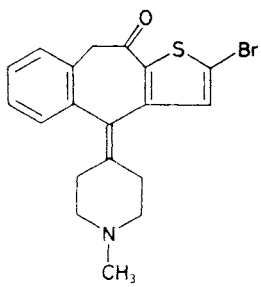
The trideutero analogue *VIII* of ketotifen was needed for bioavailability studies and was prepared by treatment of *VII* (ref.[3]) with trideuteromethyl iodide in chloroform at room temperature. The product obtained by chromatography and crystallization was evaluated by the mass spectrum and found useful for the purpose given. The substance was mentioned in the literature[36] but its preparation was not described yet.

The appearance of ketone *XXVI*, brominated in position 2 of the thiophene part of the tricycle, amongst the products of bromination of *IX*, followed by methanolysis and dehydrobromination, induced the idea of the possibility of the synthesis of the unknown 2-bromo derivative of ketotifen. A one-pot process was developed starting from *IX* and leading by the mentioned sequence of reactions (without isolation of intermediates) directly to *XXVII*. The product was identified unequivocally by analysis and spectra and subjected to reaction with 1-methyl-4-piperidylmagnesium chloride in tetrahydrofuran; processing gave *XXI*, crystallizing from a mixture of benzene and heptane as a 3 : 1 solvate with benzene. The structure was again corroborated by

spectra. An attempt to prepare *XXI* by bromination of *XIX* in chloroform in the presence of pyridine was not successful. An isomeric compound was obtained in which spectra localized the position of the bromine atom to position 9; we are thus dealing here with compound *XXXIII*. The alcohol *XXI* was refluxed with dilute hydrochloric acid which effected dehydration and cleavage of the enol ether and afforded the desired *XXXIV*. The crystalline base was fully characterized by spectra and was transformed to the hydrogen fumarate.



XXXIII



XXXIV

Some of the compounds prepared were tested as potential antiaminics.The sulfonium salts are very little toxic: *II*, LD_{50} over 500 mg/kg orally; *V*, LD_{50} = 2 500 mg/kg orally. In oral doses of 500 mg/kg both compounds had some central depressant effects. Their antihistamine activity is very poor. In the test of histamine aerosol in guinea-pigs the PD_{50} of *II* was higher than 10 mg/kg orally; *V* had the PD_{50} = = 10 mg/kg p.o. In the test of histamine detoxication in guinea-pigs, both compounds are practically inactive at oral doses of 10 mg/kg.

The ketotifen enantiomers (+)-*IV* and (−)-*IV* were compared in several tests for proving the expected stereoselectivity of actions. This was best apparent in the line of affinity to histamine-H_1 receptors in the rat brain which was asessed by inhibition of binding of 2nM [^{3}H]mepyramine; IC_{50} values in nM given: (+)-*IV*, 6·0; (−)-*IV*, 40·0; racemic *IV*, 10 (preliminary data). Lower affinity but similar relations were found when the affinity to muscarine receptors in rat brain was determined (inhibition of binding of 0·5 nM [^{3}H]quinuclidinyl benzilate); IC_{50} in nM given: (+)-*IV*, 149; (−)-*IV*, 1 217; racem. *IV*, 260. Both enantiomers have high antihistamine activity in the test of local cutaneous reaction after the administration of histamine in rats; ID_{50} values in μg/kg s.c. given: (+)-*IV*, 0·57; (−)-*IV*, 3·6. Very high antihistamine activity was also found in the test of histamine aerosol in guinea-pigs but the difference in activity of both enantiomers does not seem to be biologically important; oral PD_{50} in μg/kg are given: (+)-*IV*, 26·0; (−)-*IV*, 13·2. More important differences in activity of the enantiomers were found in the test of local reaction after

the administration of the histamine liberator, substance 48/80 in rats; ID_{50} for (+)-*IV* was 4·2 mg/kg orally. On the other hand, (−)-*IV* diminished the extent of the anaphylactoid cutaneous reaction in doses of 1 − 50 mg/kg orally with statistical significance but in no case the inhibition did reach 50% and there was no dose/action relation. (*R*)(+)*IV* (VÚFB-17 653) is evidently the more active ketotifen enantiomer but the stereoselectivity of action is only a partial one.

Compound *XXXIV* (hydrogen fumarate VÚFB-17 677) exhibited protective action in the test of histamine aerosol in guinea pigs; PD_{50} = 0·25 mg/kg orally (for *IV* 0·005 mg/kg p.o.). It also inhibited the cutaneous local reaction after the administration of the histamine liberator, substance 48/80; ID_{50} = 14·3 mg/kg orally (for *IV* 1·54 mg/kg p.o.). The 2-bromo derivative of ketotifen (*XXXIV*) is much less active than ketotifen (*IV*).

EXPERIMENTAL

The melting points of analytical samples were determined in the Kofler block (are not corrected); the samples were dried in vacuo of about 60 Pa at room temperature or at a suitably elevated temperature. UV spectra (in methanol, λ_{max} (log ε)) were recorded with a Unicam 8000 spectrophotometer, IR spectra (mostly in Nujol, ν in cm^{-1}) with a Perkin–Elmer 298 spectrophotometer, ^1H NMR spectra (in $CDCl_3$ unless stated otherwise, δ in ppm, J in Hz) mostly with the CW-NMR spectrometer Tesla BS 487C (80 MHz) and partly either with FT-NMR spectrometer Tesla BS 567A (^1H at 100 MHz, ^{13}C at 25·14 MHz) or with the FT NMR spectrometer Varian XL-200 (^1H at 200 MHz), and the mass spectra (*m/z*, fragments and/or %) with MCH 1320 and/or Varian MAT 44S (GC-MS) spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography (TLC) on silica gel (Silufol). The extracts were dried with $MgSO_4$, Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotary evaporator.

3-(3-Phthalidylidene)phthalide (*XII*)

The residue after distillation of several batches of 3-bromophthalide[7] were combined (50 g) and diluted with 30 ml chloroform. After standing overnight, the crystalline solid was filtered, washed with chloroform, and dried in vacuo; 40 g of *XII*, m.p. 347 − 355°C. Three crystallizations from dimethylformamide gave the analytical sample, m.p. 358 − 360°C. Mass spectrum: 264 (M^+, $C_{16}H_8O_4$, 95), 236 (4·5), 208 (57), 180 (70), 179 (50), 152 (63), 151 (33), 132 (10), 104 (24), 76 (100). UV spectrum (saturated solution in methanol): 356, 303, 292, 256, 225, 220. IR spectrum: 757 (4 adjacent Ar–H); 1 010, 1 020 (C–O–C); 1 590, 1 605, 3 020, 3 070, 3 090 (Ar); 1 782 (Ar–CO–O–C= in the cycle). For $C_{16}H_8O_4$ (264·2) calculated: 72·73% C, 3·05% H; found: 73·06% C, 3·04% H. Refs[8−10], m.p. values 352 − 354°C, 331 − 334°C, and 352 − 354°C, respectively.

3-(3-Phthalidyl)phthalide (*XIII*)

For crystallization, a batch of 1 090 g 2-(2-(2-thienyl)vinyl)benzoic acid[2] was dissolved in 1 550 ml of boiling toluene, the undissolved solid (18·3 g) was filtered off and crystallized from dimethylformamide; m.p. 275 − 277°C. Mass spectrum: 266 (M^+, $C_{16}H_{10}O_4$, 0·6), 133 (100), 105 (20), 77 (48), 51 (37), 50 (16). UV spectrum: 227 (4·26), 271 (3·44), 279·5 (3·44). IR spectrum:

759 (4 adjacent Ar–H); 1 050, 1 262, 1 760 (C–O–CO of the lactone); 1 595, 1 607, 3 020, 3 055, 3 082 (Ar). For $C_{16}H_{10}O_4$ (266·3) calculated: 72·17% C, 3·79% H; found: 71·85% C, 3·85% H. Refs[11–13], m.p. values 268–269°C, 290°C, and 257°C, respectively.

2-Thiophenecarboxaldehyde (refs[15,16])

A solution of 84 g thiophene in 75 g dimethylformamide was added dropwise over 20 min at 93–96°C to 150 g of stirred phosphorus oxychloride. The mixture was stirred and heated to 98–102°C for 1 h, cooled, poured into 1 kg of ice, and neutralized with 250 ml 40% NaOH. The product was extracted with chloroform and the dried extract was distilled; 87·1 g (78%), b.p. 100°C/4 kPa. Ref.[14], b.p. 97–100°C/3·5 kPa.

4-(4-Tetrahydrothiopyranyl)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ol (*XIV*)

Grignard reagent was prepared from 35·8 g 4-bromotetrahydrothiopyran[1] and 14·6 g Mg in a mixture of 70 ml ether and 30 ml tetrahydrofuran[1], diluted with 200 ml tetrahydrofuran, the solution was cooled to 3°C and was treated uoder stirring over 1 h with a solution of 21·4 g *IX* (ref.[2]) in 65 ml tetrahydrofuran, added dropwise. The mixture was stirred for 30 min at room temperature and allowed to stand overnight at 4°C. It was then poured into a stirred mixture of 75 g NH_4Cl, 200 ml water, 300 g ice, and 200 ml benzene. After melting of ice, the mixture was filtered through a glass filter, the benzene layer of the filtrate was separated and the aqueous layer was extracted with benzene. The benzene layers were combined, washed with 100 ml saturated NaCl, dried, and evaporated. The residue (38·4 g) was chromatographed on a column of 500 g silica gel. The substance, being insoluble in a mixture of benzene and light petroleum, was anchored in the column in such a way that it was first dissolved in benzene, the solution was treated with 80 g silica gel, the mixture was evaporated to dryness, and the stuff obtained was put on the top of the column. Elution with a 1 : 4 mixture of benzene and light petroleum gave first 4·8 g of tetrahydrothiopyran[1] which were followed by 6·9 g of 4,4'-bis(tetrahydrothiopyranyl), m.p. 119–121°C (benzene–hexane); ref.[1], m.p. 118–121°C. The elution was continued with benzene which gave 11·9 g (38%) of *XIV*, m.p. 189–191°C (benzene). IR spectrum: 754, 860 (4 adjacent Ar–H of the benzene ring); 855 (2 adjacent Ar–H of thiophene); 1 069 (tert. cyclic alcohol); 1 485, 3 020, 3 060 (Ar); 3 420 (OH). ^{1}H NMR spectrum: 1·20–3·80 m, 14 H (6 CH_2, CH and OH); 6·89 d, 1 H (H-2, J = 5·0); 7·18 d, 1 H (H-3, J = 5·0); 7·10–7·60 bm, 4 H (H-5, H-6, H-7, and H-8). For $C_{18}H_{20}OS_2$ (316·5) calculated: 68·31% C, 6·37% H, 20·26% S; found: 68·57% C, 6·43% H, 20·25% S.

The last to be eluted was 9,10-dihydro-4H-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ol (*XV*) (8·1 g, 38%), m.p. 110–112°C (benzene–hexane) which, in admixture with authentic *XV* (ref.[17]), melted without depression.

4-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylidene)tetrahydrothiopyran (*III*)

A solution of 8·6 g *XIV* and 14·5 g pyridine in 130 ml dichloromethane was added dropwise over 50 min to a stirred mixture of 7·3 g $SOCl_2$ and 40 ml dichloromethane which was cooled to −10°C. The mixture was stirred for 2 h at 0–5°C and treated with a solution of 30 g tartaric acid in 150 ml water. The organic layer was separated, the aqueous layer extracted with dichloromethane, and the organic layers were combined, washed with water, 2% NaOH, dried, and evaporated. The residue (9·9 g) was chromatographed on 150 g silica gel using elution with benzene. The first fractions afforded 6·3 g (78%) of *III*, m.p. 139–141°C (benzene–hexane). UV spectrum:

infl. 228·5 (4·15), 257 (3·97) .IR spectrum: 725, 750, 842 (4 and 2 adjacent Ar–H); 1 480, 3 060, 3 090 (Ar). ^{1}H NMR spectrum: 2·40—3·50 m, 12 H (6 CH_2); 6·70 d, 1 H (H-3, J = 5·0); 7·00 d, 1 H (H-2, J = 5·0); 7·15 m, 4 H (H-5, H-6, H-7, and H-8). For $C_{18}H_{18}S_2$ (298·5) calculated: 72·43% C, 6·08% H, 21·49% S; found: 72·99% C, 6·20% H, 21·29% S.

The second to be eluted was 7-(4-tetrahydrothiopyranyl)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-one (*XVIII*) (1·6 g), m.p. 178—179°C (benzene–hexane). Mass spectrum: 314 (M^+, $C_{18}H_{18}OS_2$), 267 ($C_{17}H_{15}OS$), 253 ($C_{16}H_{13}OS$), 239 ($C_{15}H_{11}OS$), 213 ($C_{13}H_9OS$), 184 ($C_{12}H_8S$). UV spectrum: 274 (4·24), infl. 310 (3·70). IR spectrum: 708, 733, 795 (Ar–H); 1 530, 1 600, 3 100, 3 115 (Ar); 1 624 (ArCOAr'). ^{1}H NMR spectrum: 1·50—3·40 m, 9 H (4 CH_2 and CH of tetrahydrothiopyranyl); 3·20 s, 4 H ($ArCH_2CH_2Ar'$); 6·90—7·30 m, 3 H (H-3, H-6, and H-8); 7·62 d, 1 H (H-2, J = 5·0); 7·90 d, 1 H (H-5, J = 8·0). For $C_{18}H_{18}OS_2$ (314·3) calculated: 68·78% C, 5·77% H, 20·36% S; found: 69·19% C, 5·94% H, 19·92% S.

4-(9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ylidene)-1--methyltetrahydrothiopyranium Iodide (*II*)

A mixture of 3·6 g *III*, 18 ml benzene, 48 ml nitromethane, and 17·1 g methyl iodide was allowed to stand for 5 days at room temperature. The precipitated product was filtered, washed with benzene and dried; 4·8 g (90%) of *II*, m.p. 167·5—170°C. Mass spectrum: 298 ($C_{18}H_{18}S_2$), 237 ($C_{16}H_{13}S$), 197 ($C_{13}H_9S$), 142 (CH_3I), 127 (I), 78 (C_6H_6). UV spectrum: infl. 252 (3·99). IR spectrum (KBr): 755, 838 (4 and 2 adjacent Ar–H); 1 480 (Ar), 1 630 (C=C in conjugation). ^{1}H NMR spectrum (CD_3SOCD_3): 2·50—4·00 m, 15 H (CH_3 and 6 CH_2); 6·90 d, 1 H (H-3, J = 5·0); 7·10—7·50 m, 5 H (remaining ArH). For $C_{19}H_{21}IS_2$ (440·4) calculated: 51·82% C, 4·81% H, 28·81% I, 14·56% S; found: 51·90% C, 4·75% H, 28·73% I, 14·39% S.

9,10-Dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (*XVI*)

A solution of 10·3 g *IX* (ref.[2]) in 370 ml acetic acid was stirred and treated at 50°C over 5 min with 31·4 g Zn. The mixture was stirred and refluxed for 5 h, cooled to 20°C, and filtered. The filtrate was evaporated in vacuo, the residue was dissolved in 100 ml benzene, the solution was washed with water, dried, and evaporated; 7·0 g (73%) of *XVI* which was purified by crystallization from a mixture of benzene and ethanol, m.p. 126—128°C. Mass spectrum: 200 (M^+, $C_{13}H_{12}S$, 100), 199 (70), 185 (25), 184 (25), 167 (55), 165 (42), 152 (25), 141 (20), 128 (10), 115 (38). ^{1}H NMR spectrum: 3·08 s, 4 H ($ArCH_2CH_2Ar'$); 3·96 s, 2 H ($ArCH_2Ar'$); 6·68 d, 1 H (H-3, J = 5·0); 6·92 d, 1 H (H-2, J = 5·0); 7·10 m, 4 H (remaining ArH). For $C_{13}H_{12}S$ (200·3 calculated: 77·95% C, 6·04% H, 16·01% S; found: 78·01% C, 6·17% H, 16·27% S.

4-(1-Methyl-4-piperidyl)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene (*XVII*)

(*A*) A solution of 9·4 g 4-(1-methyl-4-piperidyl)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]-thiophene-4-ol (ref.[2]) in 35 ml acetic acid was treated with 35 ml 57% hydroiodic acid and 4·2 g red phosphorus and the mixture was stirred and refluxed for 5 h, filtered and the filtrate was evaporated in vacuo. The residue was diluted with 100 ml water, made alkaline with 40% NaOH, and the product was extracted with dichloromethane. Processing of the extract gave 10 g of crude *XVII* which was chromatographed on 80 g silica gel. Elution with chloroform and then with chloroform containing 2% of methanol gave 6·4 g of oily *XVII* which crystallized from 90 ml hexane; 4·6 g (52%) of crystalline *XVII*, m.p. 99—101°C (hexane). For $C_{19}H_{23}NS$ (297·5) calculated: 76·72% C, 7·79% H, 4·71% N, 10·78% S; found: 76·67% C, 7·80% H, 4·67% N, 10·78% S.

(*B*) A solution of 5·8 g *XIX* (ref.[3]) in 340 ml dichloromethane was treated at −35°C with 3·95 g triethylsilane[20] and the mixture was saturated for 15 min with gaseous BF_3. It was stirred for 3·5 h at 0°C, treated with 27 g K_2CO_3 and decomposed with 270 ml water. The separated organic layer was washed with water, dried, and evaporated in vacuo. The residue (6·4 g) was dissolved in a mixture of 24 ml hydrochloric acid and 60 ml water and the solution was stirred and refluxed for 1 h. After cooling it was made alkaline with a solution of 12 g NaOH in 50 ml water and the mixture of bases was extracted with chloroform. Processing of the extract gave 6·0 g of inhomogeneous product which was chromatographed on 200 g silica gel. Chloroform and chloroform with 1% of methanol eluted the less polar components. A mixture of 90% chloroform, 5% chloroform saturated with NH_3 and 5% methanol eluted 2·3 g (46%) of crude *XVII*, which was extracted with ether, the extract was evaporated, and the residue was crystallized from ether; m.p. 102—104°C. The product is identical with the product obtained under (*A*). Mass spectrum: 297 (M^+, $C_{19}H_{23}NS$, 4), 199 (15), 165 (25), 115 (20), 98 (100), 96 (21), 70 (30), 55 (56), 44 (49). IR spectrum: 752 (Ar–H); 1 487, 1 588, 3 068, 3 105 (Ar); 2 780 (N–CH_3). ^{1}H NMR spectrum: 2·18 s, 3 H (N–CH_3); 6·70 d, 1 H (H-3, J = 5·0); 6·95 d, 1 H (H-2, J = 5·0); 7·10 m, 4 H (remaining ArH). For $C_{19}H_{23}NS$ (297·4) calculated: 76·73% C, 7·80% H, 4·71% N, 10·76% S; found: 76·44% C, 7·90% H, 4·61% N, 10·97% S.

Hydrogen oxalate, m.p. 211—212°C (ethanol–ether). For $C_{21}H_{25}NO_4S$ (387·5) calculated: 65·09% C, 6·50% H, 3·62% N, 8·27% S; found: 65·21% C, 6·68% H, 3·54% N, 8·58% S. Ref.[2] described a monohydrate melting at 175—177°C.

9,10-Dibromo-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-one (*X*)

A stirred solution of 6·45 g *IX* (ref.[2]) in 100 ml tetrachloromethane was treated with 10·7 g N-bromosuccinimide and 0·06 g dibenzyl peroxide and the mixture was refluxed for 3 h. The precipitated "succinimide fraction" (5·3 g) was filtered off while hot, the filtrate was evaporated to 35 ml and the residue was allowed to crystallize; 6·4 g (55%) of crude *X*, m.p. 143—146°C. Evaporation of the mother liquor gave 4·6 g of crystalline residue which practically does not contain any *X* (TLC). Two crystallizations of crude *X* from chloroform gave a constantly melting product considered to be one homogeneous racemate of *X*, m.p. 151—152°C. For $C_{13}H_8Br_2OS$ (372·1) calculated: 41·96% C, 2·17% H, 42·95% Br, 8·62% S; found: 41·94% C, 2·18% H, 43·16% Br, 8·80% S. Ref.[3], m.p. 134—135°C (similar procedure).

10-Bromo-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-one (*XXII*)

A suspension of 300 g of crystalline residue, obtained by evaporation of mother liquors after several larger batches of *X*, in 2 l methanol was treated with 195 g KOH and the mixture was stirred and refluxed for 3 h. It was stirred for 2 h at 5°C and the crystalline product (190 g) was filtered. It was purified by two crystallizations from boiling toluene; 80 g of almost homogeneous *XXII* (TLC), m.p. 135—136°C (benzene–hexane). Mass spectrum: 290 (M^+, $C_{13}H_7BrOS$, 55), 262 (55), 183 (77), 139 (100), 91 (40). UV spectrum: 250 (4·46), 341 (4·16), infl. 360 (4·04). IR spectrum: 738, 756 (Ar–H); 1 480, 1 582, 3 020, 3 055, 3 075, 3 095 (Ar); 1 612 (ArCOAr'). ^{1}H NMR spectrum: 7·35 d, 1 H (H-3, J = 5·5); 7·40—7·70 m, 3 H (H-6, H-7, and H-8); 7·50 s, 1 H (H-9); 7·95 d, 1 H (H-2, J = 5·5); 8·50 m, 1 H (H-5). Ref.[3], m.p. 134—135°C.

2-Bromo-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-one (*XXVI*)

The alkaline methanolic mother liquor after *XXII* was diluted with 2 l water and the mixture was extracted with dichloromethane. The extract was washed with water, dried, and evaporated.

The residue (63 g) was chromatographed on 600 g silica gel. The first fraction (3·9 g), eluted with a 2 : 3 mixture of benzene and light petroleum, was homogeneous and was identified as *XXVI*, m.p. 132–133°C (benzene). Mass spectrum: 290 (M^+, $C_{13}H_7BrOS$, 45), 262 (50), 183 (37), 139 (100), 91 (50). UV spectrum: 259 (4·52), 342 (4·22), infl. 360 (4·09). IR spectrum: 732, 800 (Ar–H); 1 481, 1 527, 1 585, 1 600, 3 055 (Ar); 1 611 (ArCOAr'). ^{1}H NMR spectrum: 6·80 d and 7·01 d (ABq), 1 + 1 H (H-9 and H-10, J = 12·0); 7·55 m, 3 H (H-6, H-7, and H-8); 7·78 s, 1 H (H-3); 8·60 m, 1 H (H-5). For $C_{13}H_7BrOS$ (291·2) calculated: 53·62% C, 2·42% H, 27·45% Br, 11·01% S; found: 53·71% C, 2·54% H, 27·66% Br, 11·20% S.

4*H*-Benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-one (*XXIII*)

TLC indicated in the mother liquor after *X* the presence of a substance which could be concentrated by chromatography on silica gel, followed by TLC. In this way 150 g of the crystalline residue, obtained by evaporation of the respective mother liquor, afforded 24·8 g of the enriched material. This was dissolved in 100 ml dichloromethane, the solution was treated with 35 g triethylamine, the mixture was stirred for 2 h at room temperature, refluxed for 20 min, and allowed to stand overnight. It was washed with 5% hydrochloric acid and water, dried, and evaporated. The residue was chromatographed on 120 g silica gel. Elution with benzene afforded 1·5 g of homogeneous material which crystallized from heptane and melted at 116·5–118°C. It was identified as *XXIII*. Mass spectrum: 212 (M^+, $C_{13}H_8OS$, 29), 184 (100), 152 (14), 139 (35). For $C_{13}H_8OS$ (212·2) calculated: 73·56% C, 3·80% H, 15·11% S; found: 73·55% C, 3·88% H, 15·28% S. Ref.[3], m.p. 109–110°C.

9-Bromo-10-methoxy-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-one (*XI*)

In one batch of bromination of *IX* (ref.[2]) (225 g), there was an unusually large "succinimide fraction" (cf. preparation of *X*) (258 g) which evidently contained some brominated material. It was processed by treatment with 4·5 l boiling methanol and 116·6 g KOH. After cooling the solution was evaporated to 500 ml and cooling resulted in crystallization of 54·6 g of crude *XI*, m.p. 105–110°C. Crystallization from a mixture of benzene and hexane gave a 3 : 1 solvate of *XI* with benzene, m.p. 99–100°C. Mass spectrum: 322 (M^+, $C_{14}H_{11}BrO_2S$, 3), 243 (100), 228 (20), 215 (25), 200 (50), 184 (70), 171 (65), 139 (59). UV spectrum: 225 (4·29), 268 (4·26), 327 (3·61). IR spectrum: 722, 752 (4 adjacent Ar–H of the benzene nucleus); 855 (2 adjacent Ar–H of the thiophene nucleus); 1 075, 1 085, 1 280 (R–O–R'); 1 529, 1 580, 1 592, 3 000, 3 080, 3 100 (Ar); 1 629 (ArCOAr'). For $C_{14}H_{11}BrO_2S + 1/3\,C_6H_6$ (349·3) calculated: 55·02% C, 3·75% H, 22·88% Br, 9·18% S; found: 54·92% C, 3·64% H, 22·63% Br, 9·48% S. Ref.[3], m.p. 103–106°C for the unsolvated substance.

4*H*-Benzo[4,5]cyclohepta[1,2-*b*]thiophene (*XXVIII*)

A suspension of 4·35 g of *XXII* in 50 ml toluene was stirred and treated over 1·5 h at 0–5°C with 12 g of a 50% solution of sodium dihydrido-bis(2-methoxyethoxo)aluminate in toluene, diluted with further 20 ml toluene. The mixture was stirred for 2 h at 5–10°C, and allowed to stand overnight at room temperature. Under external cooling it was decomposed with 40 ml 10% NaOH, the toluene layer was separated and the aqueous layer was extracted with toluene. The combined toluene solutions were dried and evaporated in vacuo. The residue (4·0 g) was chromatographed on 50 g silica gel. The first fraction, obtained by elution with a 3 : 2 mixture of benzene and light petroleum, was homogeneous *XXVIII* (0·5 g, 17%), m.p. 102–104°C (hexane). Mass spectrum: 198 (M^+, $C_{13}H_{10}S$, 35), 197 (100), 171 (10), 165 (21), 152 (19), 99 (23),

98 (24). UV spectrum: 207 (4·25), 233 (4·05), 306 (4·09), infl. 266 (3·75). IR spectrum: 750, 792 (4 and 2 adjacent Ar–H); 1 486, 1 591, 3 095 (Ar). ^{1}H NMR spectrum: 3·62 s, 2 H ($ArCH_2Ar'$); 6·78 d, 1 H (H-3, J = 5·5); 6·81 s, 2 H (H-9, H-10); 7·11 d, 1 H (H-2, J = 5·5); 7·15 m, 4 H (H-5, H-6, H-7, and H-8). For $C_{13}H_{10}S$ (198·3) calculated: 78·75% C, 5·08% H, 16·17% S; found: 78·37% C, 5·24% H, 15·90% S.

The product decribed was followed by 1·7 g of a solid melting at 256–258°C (benzene–heptane) which was only partly characterized but not identified. Mass spectrum, CI: 397 (M + 1), 396 (M^+, $C_{26}H_{20}S_2$), 199, 197; EI: 197 (100), 171 (6), 165 (10), 152 (8), 78 (17). For $C_{26}H_{20}S_2$ (396·4) calculated: 78·77% C, 5·09% H, 16·14% S; found: 77·86% C, 5·28% H, 16·03% S.

9-Methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-one (*XXV*)

Mother liquors after *XXIV* (prepared from 223 g *X* (ref.[3])) were diluted with 3 l water and extracted with dichloromethane. The extract was washed with water, dried, and evaporated. The residue (32·6 g) was chromatographed on 400 g silica gel (elution with benzene). The last fractions (10·3 g), enriched on *XXV*, were rechromatographed on 100 g silica gel. The last fraction was crystallized from a mixture of benzene and hexane, m.p. 88–89°C. The substance was identified by ^{1}H NMR spectrum as a 68 : 32 mixture of *XXV* and *XXIV*. Mass spectrum: 242 (M^+, $C_{14}H_{10}O_2S$, 81), 227 (2·5), 214 (14), 199 (100), 184 (4), 171 (55), 127 (18). UV spectrum: 240 (4·37), 262 (4·41), 339 (3·99), infl. 360 (3·87). IR spectrum: 765 (Ar–H); 1 093, 1 235 (R–O–C=C); 1 475, 1 530, 1 578, 1 600, 3 090, 3 110 (Ar); 1 620 (ArCOAr'). ^{1}H NMR spectrum: 3·90 s and 3·94 s, $\sum$ 3 H (OCH_3); 6·46 s and 6·60 s, $\sum$ 1 H (H-9 and/or H-10); 7·15 d and 7·40 d, $\sum$ 1 H (H-3, J = 5·5); 7·60 m, 2 H (H-6 and H-7); 7·70 d and 7·97 d, $\sum$ 1 H (H-2, J = 5·5); 8·30 m, 1 H (H-8); 8·55 m, 1 H (H-5). For $C_{14}H_{10}O_2S$ (242·3) calculated: 69·40% C, 4·16% H, 13·13% S; found: 69·07% C, 4·34% H, 13·23% S.

4-(4-Tetrahydrothiopyranyl)-10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ol (*XX*)

Grignard reagent[1] was prepared from 35·7 g 4-bromotetrahydrothiopyran and 14·5 g Mg in a mixture of 70 ml ether and 30 ml tetrahydrofuran, diluted with 200 ml tetrahydrofuran, the solution was cooled to 5°C and was treated under stirring over 15 min with 24·2 g *XXIV* (ref.[3]), added in portions. The mixture was stirred for 1 h at 5°C and for 3 h at room temperature. After cooling to 4°C it was poured to a stirred mixture of 75 g NH_4Cl, 300 g ice, 200 ml water, and 200 ml benzene. After melting of ice, the mixture was filtered through a glass filter, the aqueous layer of the filtrate was extracted with benzene and the organic layers were combined. After washing with water and drying, the solution was evaporated under reduced pressure. The residue (47 g) was chromatographed on 500 g silica gel. A 3 : 1 mixture of benzene and chloroform eluted first 3·8 g of tetrahydrothiopyran[1]. A 1 : 1 mixture of benzene and chloroform eluted then 6·4 g 4,4'-bis(tetrahydrothiopyranyl), m.p. 119–122°C (benzene–hexane); ref.[1], m.p. 118–121°C. The first benzene fractions eluted 3·9 g of a new compound, identified as 10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ol (*XXIX*), m.p. 222–226°C (benzene). Mass spectrum: 244 (M^+, $C_{14}H_{12}O_2S$, 100), 243 (80), 229, 228 (30), 227, 211 ($C_{13}H_7OS$), 184, 171 ($C_{11}H_7S$). UV spectrum (saturated solution in methanol): infl. 236. IR spectrum: 730, 742, 790 (4 and 2 adjacent Ar–H); 1 046 (CHOH); 1 153 (R–O–C=C); 1 479, 3 060, 3 090, 3 105 (Ar). For $C_{14}H_{12}O_2S$ (244·3) calculated: 68·33% C, 4·95% H, 13·12% S; found: 68·61% C, 4·67% H, 13·00% S.

The next fraction, eluted with benzene, was the recovered *XXIV* (5·9 g), m.p. 168–169°C (benzene); ref.[3], m.p. 164–166°C. It was followed by 9·0 g (35% per conversion) of *XX*, the most

polar component of the mixture; m.p. 208–210°C (benzéne). UV spectrum: 248·5 (4·21), 315 (4·08). IR spectrum: 770, 810 (4 and 2 adjacent Ar–H); 1 084 (Ar_2RC–OH); 1 242 (R–O–C=C); 1 560, 3 010, 3 115 (Ar); 1 612 (C=C); 3 410 (OH). ^{1}H NMR spectrum (CD_3SOCD_3): 0·80–2·50 m, 9 H (4 CH_2 and CH of tetrahydrothiopyranyl); 3·84 s, 3 H (OCH_3); 6·30 s, 1 H (H-9). 7·10–7·40 m, 4 H (H-3, H-5, H-6, and H-7); 7·50 d, 1 H (H-2, J = 5·0); 7·75 m, 1 H (H-8). For $C_{19}H_{20}O_2S_2$ (344·5) calculated: 66·24% C, 5·85% H, 18·62% S; found: 66·23% C, 5·78% H, 18·41% S.

4-(Tetrahydrothiopyran-4-ylidene)-9,10-dihydro-4*H*-
-benzo[4,5]cyclohepta[1,2-*b*]thiophene-10-one (*III*)

A mixture of 6·6 g *XX*, 60 ml dioxane, and 25 ml 37% hydrochloric acid was stirred and refluxed for 1·5 h, and allowed to stand overnight. It was diluted with 200 ml water and extracted with dichloromethane. The extract was washed with 30 ml 5% $NaHCO_3$, dried, and evaporated. The residue (6·9 g) was dissolved in 50 ml benzene. The solution was filtered through a column of 20 g silica gel. It was washed with benzene and the filtrate was evaporated. Crystallization of the residue from a mixture of 30 ml benzene and 15 ml hexane gave 3·0 g (50%) of *III*, m.p. 197–199°C. UV spectrum: infl. 225 (4·24), 299 (4·23). IR spectrum: 750, 760, 800 (4 and 2 adjacent Ar–H); 1 480, 1 509, 1 574, 3 015, 3 060 (Ar); 1 650 (RCOAr). ^{1}H NMR spectrum: 2·50–3·00 m, 8 H ($CH_2CH_2SCH_2CH_2$); 3·75 d and 4·22 d (ABq), 1 + 1 H ($ArCH_2CO$, J = 13·0); 7·02 d, 1 H (H-3, J = 5·0); 7·10–7·40 m, 4 H (H-5, H-6, H-7, and H-8); 7·55 d, 1 H (H-2, J = 5·0). For $C_{18}H_{16}OS_2$ (312·5) calculated: 69·19% C, 5·16% H, 20·52% S, found: 69·12% C, 5·25% H, 20·20% S.

1-Methyl-4-(10-oxo-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-
-4-ylidene)tetrahydrothiopyranium Iodide (*V*)

A solution of 5·5 g *III* in 55 ml benzene was treated with a solution of 12·5 g methyl iodide in 40 ml methanol and the mixture was allowed to stand for 4 days at room temperature. The crystallized product was filtered, washed with benzene, and dried in vacuo; 5·1 g (64%), m.p. 195–199°C. UV spectrum: 223 (4·37), 294 (4·12). IR spectrum: 750, 768, 797 (4 and 2 adjacent Ar–H); 1 502, 1 570 (Ar); 1 630 (ArCOR). For $C_{19}H_{19}IOS_2$ (454·4) calculated: 50·22% C, 4·22% H, 27·93% I, 14·11% S; found: 50·46% C, 4·31% H, 27·87% I, 14·14% S.

10-Methoxy-4-(1-methyl-4-piperidyl)-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ol (*XIX*)

Grignard reagent was prepared from 134 g 4-chloro-1-methylpiperidine and 24 g Mg in 350 ml tetrahydrofuran[36], was cooled and diluted with 550 ml tetrahydrofuran. The solution was stirred and treated at 15°C over 50 min with 122 g *XXIV* (ref.[3]), added in small portions. The mixture was then stirred for 1·5 h at room temperature and was poured to a stirred mixture of 107 g NH_4Cl, 800 ml water, and 900 g ice. After dilution of the mixture with 2 l water, the separated oil crystallized, the solid was filtered, washed with water, and dried at room temperature; 180 g of the less stable crystalline form of *XIX* monohydrate, m.p. 148–150°C. Crystallization from 1·55 l ethanol afforded 163 g (91%) of the stable form of *XIX* monohydrate, m.p. 196–198°C (change of crystal modification at about 150°C). Mass spectrum: 341 (M^+, $C_{20}H_{23}NO_2S$, 2), 326 (1·1), 308 (0·23), 243 (36), 228 (3·2), 211 (17), 200 (5·6), 183 (1·6), 171 (16·8), 139 (3·2), 99 (100). UV spectrum: 243 (4·14), 313 (4·03). IR spectrum: 751 (Ar–H); 1 079 (Ar_2RC–OH); 1 230 (R–O–C=C); 1 475, 1 560, 3 005, 3 055, 3 090 (Ar); 1 611 (C=C in conjugation); 2 780 (N–CH_3); 3 380, 3 480 (OH, H_2O). ^{1}H NMR spectrum: 1·50 m, 5 H (CH_2CHCH_2 of 4-piperidyl); 2·00 s,

3 H ($N-CH_3$); 2·00 bm and 2·70 bm, 2 + 2 H (CH_2NCH_2); 3·50 bs, 1 H (OH); 3·88 s, 3 H (OCH_3); 6·15 s, 1 H (H-9); 7·20 m, 5 H (H-2, H-3, H-6, H-7, and H-8); 7·80 m, 1 H (H-5). For $C_{20}H_{23}NO_2S + H_2O$ (359·5) calculated: 66·82% C, 7·01% H, 3·90% N, 8·92% S; found: 67·13% C, 7·04% H, 3·56% N, 8·87% S.

4-Hydroxy-4-(1-methyl-4-piperidyl)-9,10-dihydro-4*H*-
-benzo[4,5]cyclohepta[1,2-*b*]thiophene-10-one (*XXXI*)

Grignard reagent was prepared from 10·0 g 4-chloro-1-methylpiperidine and 1·83 g Mg in 80 ml, tetrahydrofuran[36]. At 20°C it was treated under stirring over 5 min with 3·45 g *XXX* (ref.[3]), added in portions. The mixture was stirred for 4·5 h at 20°C and allowed to stand overnight. It was refluxed for 10 min, cooled, and decomposed with a solution of 16·9 g tartaric acid in 250 ml water and the solution was washed with benzene. It was made alkaline with NH_4OH and the product was extracted with chloroform. Processing of the extract gave 6·1 g of oily base which was dissolved in chloroform and the solution was filtered through a column of 30 g silica gel. It was washed with chloroform containing 2% of methanol, the filtrate was evaporated and the residue was crystallized from 65 ml 2-propanol; 3·8 g (68%) of *XXXI*, m.p. 196—199°C (first melting at 186—188°C). UV spectrum: 285 (3·90). IR spectrum: 740, 750, 765 (Ar–H); 1 070 (Ar_2RC-OH); 1 510, 1 575 (Ar); 1 642 (RCOAr); 2 730, 2 760 ($N-CH_3$); 3 120 (OH). For $C_{19}H_{21}NO_2S$ (315·4) calculated: 68·54% C, 6·71% H, 4·44% N, 10·17% S; found: 68·77% C, 6·82% H, 4·21% N, 9·90% S. Ref.[3], m.p. 179—184°C (different method).

4-(1-Methyl-4-piperidylidene)-9,10-dihydro-4*H*-
-benzo[4,5]cyclohepta[1,2-*b*]thiophene-10-one (*IV*)

(A) Monohydrate of *XIX* (180 g) was added to a solution of 700 g hydrochloric acid in 1·5 l water and the mixture was stirred and refluxed for 1 h. Under cooling to 10°C and stirring it was treated over 10—15 min with a solution of 300 g NaOH in 1·2 l water. It was extracted with chloroform, the extract was allowed to stand for 2 h with 80 g K_2CO_3 and 25 g active carbon, the mixture was filtered through a 1 cm layer of silica gel, and the filtrate was evaporated under reduced pressure. The crystalline residue (150 g, 97%) was the practically homogeneous base *IV*, m.p. 157—159°C. After crystallization from 50% aqueous ethanol, the m.p. was 161—163°C. UV spectrum: infl. 221 (4·20), 297 (4·11). IR spectrum: 746, 756, 780 (4 and 2 adjacent Ar–H); 1 480, 1 508, 1 569, 3 005, 3 055 (Ar); 1 626 (C=C in conjugation); 1 655 (ArCOR); 2 650, 2 670, 2 720, 2 786 ($N-CH_3$). ^1H NMR spectrum (200 MHz): 2·12 m, 2 H (H-3'ax, H-5'ax); 2·29 s, 3 H ($N-CH_3$); 2·45 m, 2 H (H-3'eq, H-5'eq); 2·71 m, 4 H (H-2'ax, H-2'eq, H-6'ax, and H-6'eq); 3·75 d, 1 H (H-9a, J(9a,9b) = 13·4); 4·22, bd, 1 H (H-9b, J(9b,9a) = 13·4); 7·03 d, 1 H (H-3, J(3,2) = 5·0); 7·16—7·34 m, 4 H (H-5, H-6, H-7, and H-8); 7·52 d, 1 H (H-2, J(2,3) = = 5·0). ^1H NMR spectrum (C_6D_6, 200 MHz): 1·97 m, 2 H (H-3'ax, H-5'ax); 2·17 s, 3 H ($N-CH_3$); 2·50 m, 6 H (H-2'ax, H-2'eq, H-3'eq, H-5'eq, H-6'ax, and H-6'eq); 3·85 d, 1 H (H-9a, J(9a,9b) = 13·3); 4·24 bd, 1 H (H-9b, J = 13·3); 6·76 d, 1 H (H-3, J(3,2) = 5·0); 6·88 d, 1 H (H-2, J(2,3) = 5·0); 6·94—7·15 m, 4 H (H-5, H-6, H-7, and H-8). For $C_{19}H_{19}NOS$ (309·4) calculated: 73·75% C, 6·19% H, 4·53% N, 10·36% S; found: 73·90% C, 6·30% H, 4·53% N, 10·29% S. Ref.[8], m.p. 151—153°C.

Hydrogen fumarate, m.p. 195—199°C with decomposition (aqueous ethanol). Mass spectrum: 309 (M^+, $C_{19}H_{19}NOS$, 78), 292, 280 ($C_{18}H_{18}NS$), 276 ($C_{19}H_{18}NO$), 237 ($C_{15}H_9OS$), 98 (C_5H_6S, 45), 96 ($C_6H_{10}N$, 100), 70 (43), 58 (48), 57 (41), 44 (56), 42 (59). For $C_{23}H_{23}NO_5S$ (425·5) calculated: 64·92% C, 5·45% H, 3·29% N, 7·54% S; found: 65·18% C, 5·40% H, 3·32% N, 7·53% S. Ref.[12], m.p. 192°C.

(*B*) A mixture of 3·0 g *XXXI* and 38 ml 3M-HCl was stirred and refluxed for 1 h, after cooling it was made alkaline with 35 ml 20% NaOH, and the base was extracted with chloroform. The dried extract was filtered through a 1 cm layer of silica gel and the filtrate was evaporated. Crystallization of the residue from 45 ml aqueous ethanol gave 2·3 g (81%) of *IV*, m.p. 159—161°C. Two recrystallizations from aqueous ethanol gave the product melting at 161—163°C, identical with the substance, obtained under (*A*).

(*C*) A mixture of 0·89 g *VII* (ref.[3]), 2·5 ml chloroform and 0·213 g methyl iodide was allowed to stand for 48 h at room temperature. The separated solid (0·7 g) was filtered off, the filtrate was evaporated, and the residue was separated by preparative thin-layer chromatography on silica gel (Merck); 0·20 g, m.p. 159—161°C (aqueous ethanol).

(*D*) (1*S*)(+)-Camphor-10-sulfonate hemihydrate, m.p. 227—231°C (ethanol–ether), $[\alpha]_D^{20}$ −2·17° (*c* 1 ethanol), is a mixture of diastereoisomers which is practically not changed on repeated crystallization. For $C_{29}H_{35}NO_5S_2 + 0{\cdot}5\ H_2O$ (550·7) calculated: 63·25% C, 6·59% H, 2·54% N, 11·64% S; found: 63·43% C, 6·48% H, 2·54% N, 11·52% S.

(*E*) 1·5 : 1 (−)-O,O′-Di(*p*-toluoyl)-(*R*)-tartrate, m.p. 219—221°C (aqueous ethanol), $[\alpha]_D^{20}$ −44·78° (*c* 0·2 70% ethanol), is a mixture of diastereoisomers unsuitable for resolution. For $C_{39}H_{37}NO_9S + 0{\cdot}5\ C_{19}H_{19}NOS$ (850·5) calculated: 68·50% C, 5·51% H, 2·47% N, 5·66% S; found: 68·18% C, 5·44% H, 2·42% N, 5·64% S.

(*F*) 2 : 1 (−)-O,O′-Dibenzoyl-(*R*)-tartrate, m.p. 200—201°C (aqueous ethanol), $[\alpha]_D^{20}$ −33·23° (*c* 0·2 70% ethanol), likewise is a mixture of diastereoisomers which is unsuitable for resolution. For $C_{56}H_{52}N_2O_{10}S_2$ (977·2) calculated: 68·83% C, 5·36% H, 2·87% N, 6·56% S; found: 68·52% C, 5·29% H, 3·06% N, 6·43% S.

(*G*) 1 : 1 (−)-Di(*p*-toluoyl)-(*R*)-tartrate after four crystallizations from 75% ethanol is the homogeneous (*R*) (+)-*IV* (−)-di(*p*-toluoyl)-(*R*)-tartrate, m.p. 183—186°C, $[\alpha]_D^{20}$ −32·78° (*c* 0·2 70% ethanol). For $C_{39}H_{37}NO_9S$ (695·8) calculated: 67·32% C, 5·36% H, 2·01% N, 4·61% S; found: 66·67% C, 5·39% H, 2·44% N, 4·62% S.

Clear colorless crystals of this salt were the object of the X-ray crystallographic analysis. The X-ray diffraction of a crystal (0·36 × 0·27 × 0·18 mm) was one on a Syntex $P2_1$ diffractometer with graphite monochromated Cu Kα radiation (λ = 1·54178 Å). Lattice parameters were determined from 24 centered reflections with 2θ range 13°—27°: a = 13·566(3) Å, b = 7·838(1) Å, c = 17·960(4) Å, $\alpha = \gamma = 90°$, β = 107·92(2)° (in parentheses estimated standard deviations). Lattice parameters and a space group were independently determined by use of the Weissenberg and oscillation film techniques.

3 542 reflections were measured using $\theta - 2\theta$ scan technique within 2θ range 5°—116°. The intensities of three standard reflections decreased in a linear fashion by 2% and this decay was corrected by scaling. Intensities of 2 727 independent reflections were corrected for Lorentz and polarization effects, not for absorption (linear absorption coefficient = 12·1 cm^{-1}). 2 613 reflections had intensities greater than three times their esimated standard deviation.

The structure was solved in the $P2_1$ space group with two molecular complexes in the cell by Sheldrick's program SHELX86 (ref.[37]). The partial structure expansion of a Patterson map revealed all 50 non-hydrogen atoms of the complex (slat). The structure was refined using the program SHELX76 (ref.[38]). At an intermediate stage in the refinement, a difference Fourier map revealed about 20% of hydrogen atoms. All hydrogen atoms were included in the subsequent cycles in geometrically idealized positions and their geometries were constrained to the end of the refinement. With anisotropic temperature factors for non-hydrogen atoms, the refinement difference map showed a maximum 0·45 electron/$Å^3$ and a minimum 0·45 electron/$Å^3$.

The (*R*)(+)-base *IV* was released from the salt with dilute NH_4OH and the base was isolated by extraction with benzene, m.p. 159–162°C (ethanol), $[\alpha]_D^{20}$ +114·14° (*c* 1 ethanol).IRspectrum (KBr): 750, 767, 800 (4 and 2 adjacent Ar–H); 1 480, 1 503, 1 571, 1 596, 3 015, 3 060, 3 080, 3 100 (Ar); 1 650 (ArCOR); 2 780, 2 840 (N–CH_3). ^{1}H NMR spectrum (100 MHz): 2·32 s, (N–CH_3); 2·00–3·00 m, 8 H ($CH_2CH_2NCH_2CH_2$); 3·78 d and 4·26 d (ABq), 1 + 1 H ($ArCH_2CO$, J = 13·0); 7·06 d, 1 H (H-3, J = 5·0); 7·30 m, 4 H (H-5, H-6, H-7, and H-8); 7·57 d, 1 H (H-2, J = 5·0). For $C_{19}H_{19}NOS$ (309·4) calculated: 73·75% C, 6·19% H, 4·53% N, 10·36% S; found: 74·17% C, 6·35% H, 4·55% N, 10·40% S.

(*H*) 1 : 1 (−)-O,O′-Dibenzoyl-(*R*)-tartrate in three crystallizations gave the homogeneous (*R*)(+)-*IV*(−)-O,O′-dibenzoyl-(*R*)-tartrate, m.p. 158–160°C (aqueous ethanol), $[\alpha]_D^{20}$ −20·36° (*c* 0·2 70% ethanol). The salt is a monohydrate. For $C_{37}H_{33}NO_9S + H_2O$ (685·8) calculated: 64·80% C, 5·14% H, 2·04% N, 4·68% S; found: 65·09% C, 5·11% H, 2·11% N, 4·85% S. The released (*R*)(+)-base melted at 159–162°C (ethanol) and had an $[\alpha]_D^{20}$ +114·31° (*c* 1 ethanol).

(*I*) 1 : 1 (+)-O,O′-Dibenzoyl-(*S*)-tartrate in four crystallizations gave the homogeneous (*S*)(−)-*IV* (−)-O,O′-dibenzoyl-(*S*)-tartrate monohydrate, m.p. 158–160°C, $[\alpha]_D^{20}$ +19·55° (*c* 0·2 70% ethanol). For $C_{37}H_{33}NO_9S + H_2O$ (685·8) calculated: 64·80% C, 5·14% H, 2·04% N, 4·68% S; found: 65·13% C, 5·18% H, 2·10% N, 4·75% S.

The released (*S*)(−)-*IV* base melted at 159–160°C (ethanol) and had $[\alpha]_D^{20}$ −113·91° (*c* 1 ethanol). For $C_{19}H_{19}NOS$ (309·4) calculated: 73·75% C, 6·19% H, 4·53% N, 10·36% S; found: 73·61% C, 6·34% H, 4·56% N, 10·30% S. Its IR and ^{1}H NMR spectra were identical with those of the enantiomeric (*R*)(+)-*IV* base.

4-(1-(Trideuteromethyl)-4-piperidylidene)-9,10-dihydro-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-10-one (*VIII*)

A solution of 1·18 g *VII* (ref.[3]) in 3·5 ml chloroform was treated with 0·29 g trideuteromethyl iodide and the mixture was allowed to stand for 4 days at room temperature. The precipitated hydroiodide (0·9 g) was filtered off and the filtrate was evaporated. The residue was chromatographed on 25 g silica gel. The chloroform fractions were discarded and the fraction, obtained by elution with a mixture of 94% chloroform, 5% chloroform saturated with NH_3 and 1% methanol (0·40 g) was crystallized from aqueous ethanol; m.p. 158–159°C. Mass spectrum: 313 (M^+, $C_{19}H_{16}D_3NOS$, 20), 312 (79), 311 (21), 295 (6), 289 (9), 237 (18), 98 (100), 73 (38), 61 (43), 60 (37). The sample contained about 8% of the D_2 analogue and practically none D_0 analogue.

2-Bromo-10-methoxy-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-one (*XXVII*)

A solution of 126 g *IX* (ref.[2]) in 1·9 l tetrachloromethane was treated with 221 g 97·3% N-bromosuccinimide and 1·3 g dibenzoyl peroxide and the mixture was stirred and refluxed for 3 h. Tetrachloromethane was evaporated under reduced pressure. An exothermic reaction took then place with spontaneous heating of the residue to 75–80°C. After this was over, the residue was diluted with 2·8 l methanol and the mixture was stirred and refluxed for 5 h. After standing overnight, 120 g 85% KOH were added and the stirred mixture was refluxed for 6 h. It was then allowed to stand overnight at 4°C, the crystallized product was filtered, washed with methanol and water, and dried; 80·6 g of crude *XXVII* which was crystallized from 1·8 l ethanol; 23·6 g (13%) of almost homogeneous *XXVII*, m.p. 171–174°C. Analytical sample, m.p. 178–180°C (benzene). Mass spectrum: 322 (M^+, $C_{14}H_9BrO_2S$, 100), 320 (98), 292 (13), 279 (25), 264 (4), 249 (17), 184 (5), 170 (16), 161 (6), 139 (7), 126 (12),111 (2), 99 (6), 85 (9), 69 (10), 63 (5), 57 (10),

43 (7), 32 (4), 27 (11). IR spectrum (KBr): 715, 745 (Ar–H); 1 100, 1 245 (R–O–C=C); 1 490, 1 580 (Ar); 1 600 (ArCOAr'); 2 830 (OCH_3). ^{1}H NMR spectrum: 3·88 s, 3 H (OCH_3); 6·35 s, 1 H (H-9); 7·20—7·60 m, 3 H (H-6, H-7, and H-8); 7·82 s, 1 H (H-3); 8·40—8·65 m, 1 H (H-5). For $C_{14}H_9BrO_2S$ (321·2) calculated: 52·35% C, 2·82% H, 24·88% Br, 9·98% S; found: 52·03% C, 2·76% H, 24·39% Br, 9·88% S.

2-Bromo-10-methoxy-4-(1-methyl-4-piperidyl)-
-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ol (*XXI*)

Grignard reagent was prepared from 16·0 g 4-chloro-1-methylpiperidine and 2·9 g Mg in 45 ml tetrahydrofuran. It was cooled and at 10°C it was treated under stirring with 19·3 g *XXVII*, added in small portions over 20 min. The mixture was stirred for 3 h at 10—15°C and allowed to stand overnight at 4°C. It was then poured to a stirred mixture of 17 g NH_4Cl, 450 ml water, and 150 g ice. The product was extracted with chloroform and from this extract the base was trasnferred into a solution of 54 g tartaric acid in 270 ml water by shaking. The aqueous solution was washed with chloroform, the base was released with NH_4OH and isolated by extraction with dichloromethane. Processing of the extract gave 28·6 g of a solid residue which was chromatographed on 150 g silica gel. Elution with a mixture of 90% chloroform, 5% chloroform saturated with NH_3 and 5% methanol gave 21·6 g (86%) of *XXI* which crystallized from a mixture of benzene and heptane as a 3 : 1 solvate with benzene, m.p. 163—164°C. Mass spectrum: 419 (M^+, $C_{20}H_{22}BrNO_2S$, 1), 414 (0·4), 321 (6), 242 (5), 199 (2), 171 (3), 99 (100), 98 (52), 96 (14), 55 (11), 44 (13). 42 (8). The presence of benzene was verified. UV spectrum: 248 (4·16), 322 (4·13). IR spectrum: 753, 889 (Ar–H); 1 098, 1 237 (R–O–C=C); 1 080 (Ar_2RC–OH); 1 480, 1 560, 3 000, 3 040, 3 050 (Ar); 1 615 (C=C in conjugation); 2 675, 2 733, 2 780 (N–CH_3); infl. 3 240 (OH). ^{1}H NMR spectrum (100 MHz): 3·12 bs, 1 H (OH); 2·16 s, 3 H (N–CH_3); 3·88 s, 3 H (OCH_3); 6·19 s, 1 H (H-9); 7·30 m, 4 H (H-3, H-6, H-7, and H-8); 7·80 m, 1 H (H-5). For $C_{20}H_{22}$ . . $BrNO_2S$ + 1/3 C_6H_6 (446·4) calculated: 59·19% C, 5·42% H, 17·90% Br, 3·14% N, 7·18% S; found: 59·43% C, 5·64% H, 17·73% Br, 3·00% N, 7·53% S.

9-Bromo-10-methoxy-4-(1-methyl-4-piperidyl)-
-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-4-ol (*XXXIII*)

A suspension of 7·2 g *XIX* monohydrate in 80 ml chloroform was treated with 1·66 g pyridine and then under stirring with a solution of 3·19 g Br in 50 ml chloroform, added dropwise over 1·5 h at 20°C. The mixture was stirred for 1 h at room temperature and made alkaline with a solution of 2·5 g Na_2CO_3 in 70 ml water. The chloroform layer was washed with water and 3% $Na_2S_2O_3$. Chloroform was evaporated and the residue, dissolved in 80 ml chloroform containing 1·66 g pyridine, was similarly brominated with 3·19 g Br in 50 ml chloroform and refluxed. After cooling, the mixture was similarly processed and the residue (10·7 g) was chromatographed on 130 g silica gel. Elution with chloroform gave 4·1 g (49%) of *XXXIII*, m.p. 223—225°C (ethanol). Mass spectrum: 419 (M^+, $C_{20}H_{22}BrNO_2S$, 0·2), 340, 321, 242, 99 (100). UV spectrum: 305 (4·09), infl. 255 (3·87), 230 (4·00). IR spectrum: 727, 742, 769, 890 (Ar–H); 1 143, 1 273 (R–O–C=C); 1 594, 3 060, 3 090 (Ar); 2 740, 2 795 (N–CH_3, O–CH_3); 3 300 (OH). ^{1}H NMR spectrum (100 MHz, CD_3SOCD_3): 0·80—3·00 m, 9 H (4 CH_2 and CH of piperidyl); 2·06 s, 3 H (N–CH_3); 3·70 s, 3 H (OCH_3); 5·94 bs, 1 H (OH); 7·24 d, 1 H (H-3, J = 5·0); 7·40 m, 2 H (H-6, H-7); 7·72 d, 1 H (H-2, J = 5·0); 7·82 m, 2 H (H-5 and H-8). ^{13}C NMR spectrum (CD_3SOCD_3): 25·25 t and 25·84 t (C-3' and C-5'); 45·86 q (C of NCH_3); 55·80 t (2 C: C-2' and C-6'); 58·23 q (C of OCH_3); 77·46 s (C-4); 11·45 s (C-9); 126·09 s (C-10a); 124·37, 126·31 d, 127·21 d, 127·60 d, 128·70 d, and 131·02 d (C—2, C-3, C-5, C-6, C-7, and C-8); 130·49 s (C-8a); 144·46 s (C-3a); 147·60 s (C-4a); 150·14 s (C-10); signal of C-4' probably covered by the multiplet

of the solvent. For $C_{20}H_{22}BrNO_2S$ (420·4) calculated: 57·14% C, 5·28% H, 19·01% Br, 3·33% N, 7·62% S; found: 57·09% C, 5·31% H, 19·35% Br, 3·22% N, 7·86% S.

2-Bromo-4-(1-methyl-4-piperidylidene)-9,10-dihydro-
-4*H*-benzo[4,5]cyclohepta[1,2-*b*]thiophene-10-one (*XXXIV*)

A mixture of 60 ml hydrochloric acid, 150 ml water, and 17·0 g *XXI* was stirred and refluxed for 1 h. After cooling the mixture was made alkaline with dilute NaOH and extracted with chloroform. Processing of the extract gave 15·8 g of oily residue which was chromatographed on 230 g silica gel. A mixture of benzene and chloroform (1 : 1) eluted 6·9 g (43%) of *XXXIV* which crystallized from a mixture of toluene and heptane; m.p. 156·5—158°C (2-propanol). UV spectrum: 227 (4·21), 333 (4·19). IR spectrum: 750, 757 (4 adjacent Ar–H of the benzene nucleus); 846, 857 (solitary Ar–H in position 3 of thiophene); 1 481, 1 509, 1 573, 1 599, 3 055, 3 060, 3 070 (Ar); 1 649 (ArCOR); 2 680, 2 732, 2 760, 2 780 (NCH_3). ^{1}H NMR spectrum (100 MHz): 1·90—3·00 m, 8 H (4 CH_2 of piperidylidene); 2·29 s, 3 H ($N-CH_3$); 3·70 d and 4·14 d, (ABq), 1 + 1 H ($ArCH_2CO$, J = 13·0); 7·03 s, 1 H (H-3); 7·10—7·30 m, 4 H (H-5, H-6, H-7 and H-8). For $C_{19}H_{18}BrNOS$ (388.3) calculated: 58·76% C, 4·67% H, 20·58% Br, 3·61% N, 8·26% S; found: 58·98% C, 4·93% H, 20·42% Br, 3·51% N, 8·32% S.

Hydrogen fumarate, m.p. 235—237°C with decomposition (ethanol–ether). For $C_{23}H_{22}$ . . $BrNO_5S$ (504·4) calculated: 54·77% C, 4·40% H, 15·84% Br, 2·78% N, 6·36% S; found: 54·81% C, 4·48% H, 15·92% Br, 2·72% N, 6·53% S.

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