GEOMETRIC ISOMERISM OF 4-(3-DIMETHYLAMINO-PROPYLIDENE)-9*H*-THIENO [2,3-*b*]BENZO[*e*]THIEPIN

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Acid-catalyzed dehydration of 4-(3-dimethylaminopropyl)-4*H*,9*H*-thieno[2,3-*b*]benzo[*e*]thiepin--4-ol (*VI*) yielded the olefinic base *I* which is not homogeneous. Crystallization of the hydrogen sulfate yielded in the pure state the prevailing geometric isomer *Ia* which, on the basis of the IR spectrum, appears to have a *trans*-configuration. A pure *cis*-isomer *Ib* was isolated from the mother liquor. Both isomers were converted to the sulfoxides *VIIa*, *VIIb* and the *trans*-isomer *Ia* was converted to the secondary amine *III*. Improved synthesis of the intermediates *IV*—*VI* is described. For pharmacological purposes, the analogues *IX* and *XII* were prepared. The geometric isomers of *I* ("dithiadene") practically do not differ in the degree of antihistamine activity.

4-(3-Dimethylaminopropylidene)-9*H*-thieno[2,3-*b*]benzo[*e*] thiepin (*I*) (dithiadene) described in previous communications of this series[1,2] (see also ref.[3,4]) was proved in a later pharmacological study[5] to possess a high degree of selective antihistamine effect and to be therapeutically active at very low doses (6—12 mg per day) in allergic conditions[5] as well as in some pathological conditions of the respiratory tract[6,7]. Its spectrophotometric estimation was worked out[8] and a study of its biotransformation in rats was published[9].

When working with greater quantities and using an improved paper chromatography it was found that *I*, as it is formed[1,3] through an acid-catalyzed dehydration of carbinol *VI*, is not homogeneous; besides the principal component a small amount of a less polar admixture was detected. It was assumed, in analogy with the derivatives of the dibenzo[*b*, *e*]thiepin series[10,11] that we are dealing here with a mixture of geometric isomers of *I*, with one of the isomers predominating. While crystallization of the hydrochloride has no separation effect, crystallization of hydrogen sulfate leads to a rapid purification of the major component (*Ia*) which was then prepared as a crystalline base and in the form of other salts. The mother liquor after removal of the crystalline hydrogen sulfate was the source for isolating the oily isomeric base *Ib* which was purified by crystallization of hydrogen maleate. To define the configur-

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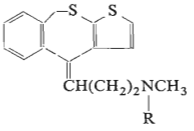
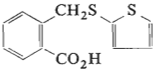
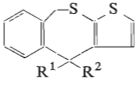
ation, IR spectra were used, similarly to the cases quoted above[10,11]. The region of the IR spectrum corresponding to extraplanar C—H vibrations of the 1,2-disubstituted benzene ring contains the usual band at 761 cm^{-1} but also an additional satellite band at 789 cm^{-1}. This satellite band is lacking in the spectrum of *Ib*. Since it is known that the occurrence of satellite bands is due to interaction of the CH groups of the aromatic ring with a side chain, *Ia* was taken to be *trans* and the *Ib* isomer to be *cis*. This is in agreement with the course of absorption in the region of 800–900 cm^{-1}, ascribed to extraplanar vibrations of two vicinal C—H bonds in the thiophene ring. On the contrary, in this region the isomer *Ib* shows a spectrum which is richer in the satellite bands (809, 861 and 879 cm^{-1}) which is in accord with the assumed *cis*-configuration. This again may be explained by an interaction of the side chain with the corresponding C—H groups.



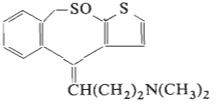
I, R = CH_3
II, R = $COOC_2H_5$
III, R = H



V



V, $R^1R^2 = =O$
VI, R^1 = OH, $R^2 = (CH_2)_3N(CH_3)_2$

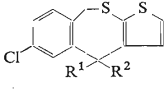


VII

Of the improved preparation procedures for the intermediates *IV*–*VI* mention should be made of the preparation of ketone *V* by cyclization of acid *IV* with the aid of a phosphoric acid ester[12] in a 75% yield; the existing methods were based on cyclization with polyphosphoric acid[1] (24%) and on cyclization with phosphorus pentoxide in toluene[2] (61%). Both isomeric bases *Ia* and *Ib* were oxidized with hydrogen peroxide in acetic acid at room temperature[2], giving rise to the corresponding geometric isomers of sulfoxide *VII* (*trans VIIa*, *cis VIIb*). Analysis of IR spectra leads to the same conclusions as shown for the sulfide bases *Ia* and *Ib*. Partial demethylation of *Ia* (for procedure see ref.[1,11]) led to the secondary amine *III*, apparently belonging also to the *trans*-series: heating of the benzene solution of base *Ia* with ethyl chloroformate yielded the oily carbamate *II* which was hydrolyzed with a very concentrated solution of potassium hydroxide to the desired product which appears

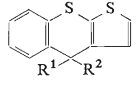
to be chromatographically homogeneous. Both the sulfoxide *VIIa* and the secondary amine *III* were identified as dithiadene metabolites in rats[9].

In view of the fact that the basically substituted derivatives of 6-chloro and 6-bromo-9*H*-thieno[2,3-*b*]benzo[*e*]thiepin showed signs of activity of the chlorpromazine type[2] compound *IX* was synthesized containing in its side chain a methylpiperazine fragment known to intensify the neuroleptic character[13]. Reaction of 6-chlorothieno-[2,3-*b*]benzo[*e*]thiepin-4(9*H*)-one[2] with 3-(4-methylpiperazino)propylmagnesium chloride[14] (for the starting chloride see ref.[15–17]) yielded the tertiary alcohol *VIII* which was dehydrated by heating with dilute hydrochloric acid. The olefinic product *IX*, which is apparently a mixture of geometric isomers, was obtained in the form of an poorly crystallizing and water-solvated hydrochloride. Patents[18] described the synthesis and the high degree of antihistamine activity of thieno[2,3-*b*]-1-benzothiopyran derivative *XII*, *i.e.* a lower homologue of dithiadene (*I*). For the sake of comparison, we prepared *XII* which is also a mixture of geometric isomers, from thieno[2,3-*b*]-1-benzothiopyran-4-one[19] (*X*) *via* the tertiary alcohol[18] *XI*; in the experimental section we show more accurate data than reported in the patents[18] and an improved preparation procedure for ketone *X*, based on cyclization of 2-(2-thienylthio)benzoic acid[19] with phosphoric ester[12] in toluene.



VIII, $R^1 = OH$, $R^2 = (CH_2)_3N(CH_2CH_2)_2NCH_3$

IX, $R^1R^2 = =CH(CH_2)_2N(CH_2CH_2)_2NCH_3$



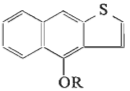
X, $R^1R^2 = =O$

XI, $R^1 = OH$, $R^2 = (CH_2)_3N(CH_3)_2$

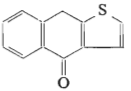
XII, $R^1R^2 = =CH(CH_2)_2N(CH_3)_2$

In an attempt to prepare the 4,9-dihydronaphtho[2,3-*b*]thiophene analogue of dithiadene (*I*) we synthesized ketone *XV*. After the failure of a cyclization attempt on 2-(2-thenyl)benzoic acid[20] with phosphorus pentoxide in boiling toluene we set out to prepare *XV via* the described 4-acetoxynaphtho [2,3-*b*]thiophene[21] (*XIII*) formed by cyclization of the acid mentioned with the aid of anhydrous zinc chloride in a boiling mixture of acetic anhydride and acetic acid. Alkaline hydrolysis of this ester led to a yellow crystalline compound, unstable in air and in light and analytically corresponding to phenol *XIV*, or to ketone *XV*. Its IR spectrum shows absorption bands of the phenolic hydroxyl (3410 and 3605 cm^{-1} in tetrachloromethane, 1199 cm^{-1} in Nujol), as well as the doubly conjugated keto group (1663 cm^{-1} in CCl_4) which suggests the presence of the two tautomers *XIV* and *XV* in the substance. NMR spectrum (in hexadeuteriodimethylsulfoxide) rather suggests the phenolic structure *XIV*. The results discouraged us from attempting the reaction with 3-di-

methylaminopropylmagnesium chloride. Only after this work had been concluded, preparation of phenol *XIV* by cyclization of 2-(2-thenyl)benzoic acid with stannic chloride was described[22] and the keto-enol tautomerism of the pair *XIV*–*XV* was studied (see also ref.[23]).



XIII, R = $COCH_3$
XIV, R = H



XV

The compounds prepared were evaluated pharmacologically first of all with a view to their antihistamine effect. The usual *in vivo* tests in guinea pigs were used, as well as the aerosol test after intraperitoneal administration and the detoxication test after subcutaneous administration. The central depressant effect of the compounds was tested in a preliminary way using the rotating-rod test in mice after intravenous administration. The results of these tests, together with the values of acute toxicity for mice after intravenous application are shown in Table I (in mg/kg, toxicity as the mean lethal dose LD_{50}, antihistamine effect as the mean protective dose PD_{50} and disturbance of coordination on the rotating rod as the mean effective dose ED_{50}). The compounds were applied in the form of solutions of the salts shown. Some of the results were reported before[2,5,9]. The methods used in the tests were described elsewhere[5,24]. The table includes for comparison three standard antihistamine preparations: promethazine[25,26], cyproheptadine[27,28] and embramine (*i.e.* mebrophenhydramine)[29,30].

When discussing the results of Table I one should compare critically the properties of geometric isomers of dithiadene (*Ia*, *Ib*). It may be seen that the *cis*-isomer *Ib* is somewhat less toxic; the difference is even more marked on oral application (for *Ia* LD_{50} = 275 mg/kg, for *Ib* 1020 mg/kg). In agreement with this, the *cis*-isomer *Ib* exhibits a lower depressant activity in the rotating-rod test. In the test of potentiation of thiopental sleep in mice there is practically no difference between the two isomers: a dose of the *trans* isomer (*Ia*) equal to 5% of the LD_{50} (*i.v.*) prolongs thiopental sleep 1·6 times; a similarly defined dose of the *cis*-isomer (*Ib*) prolongs it 1·8 times. A dose equal to 10% LD_{50} prolongs thiopental sleep 2·5 times with both isomers. In their antihistamine effect the two isomers differ only insignificantly. Only in the aerosol test the activity seems to be slightly higher with the *trans*-isomer *Ia*. Both isomers surpass the standards by at least one order of magnitude in the aerosol test, they are more effective in the detoxication test and, as compared with promethazine and cyproheptadine, they are more suitable even from the point of view of the depressant effect. The secondary amine *III* is similarly toxic as compounds *Ia* and *Ib*, its antihistamine activity is insignificant, which is true also for the antianaphylactoid and antiserotonin activities. Its depressant effect in the rotating-rod test is low and brief, dying away after 15 min. Duration of thiopental sleep in mice is not prolonged

TABLE I

Pharmacological Properties of Thieno[2,3-*b*]benzo[*e*]thiepin Derivatives (mg/kg)

Compound	Acute toxicity *i.v.* LD_{50}	Antihistamine effect: aerosol *i.p.* PD_{50}	Antihistamine effect: detoxication *s.c.* PD_{50}	Rotating rod *i.v.* ED_{50}
Ia-HCl	25·1	0·02	0·03	6·1
Ib-HM[a]	35·9	0·04	0·03	9·8
III-HCl	31·0	>5·0[b]	0·5	13·5
VIIa-HCl	52·1	0·14	0·08	>40[c]
VIIb-HCl	88·0	0·10	0·18	>60[d]
IX-2 HCl (1·5 H_2O)	72·0			13·0
XII-HT[e]	72·0	0·30	1·25	15·0
Promethazine	55·0	0·47	0·06	2·6
Cyproheptadine	18·5	0·23	0·04	1·7
Embramine	80·0	1·4	0·17	27·0

[a] HM hydrogen maleate; [b] a dose of 5·0 mg/kg protects only 20% animals; [c] the sublethal dose shown (40 mg/kg) does not cause ataxia in mice; [d] the sublethal dose shown (60 mg/kg) brings about a brief ataxia in 30% animals; [e] HT hydrogen tartrate (dihydrate).

even by a dose equal to 20% LD_{50} (*i.v.*). Its antireserpine activity is very low and may be detected only in the test of affecting the ulcerogenic activity of reserpine in rats (only a dose of 60 mg/kg *s.c.* shows a statistically significant effect); in the test of reserpine ptosis in mice it has no effect.

The sulfoxides *VIIa* and *VIIb* show a markedly lower toxicity as compared with *Ia* and *Ib*. They are characterized by a practically complete absence of central depressant activity. This is displayed even in the test of potentiation of thiopental sleep in mice where only a dose corresponding to 20% LD_{50} (*i.v.*) slightly potentiates. A higher degree of antihistamine activity is preserved, the *trans*-isomer *VIIa* being 2–3 times more effective than the *cis*-isomer *VIIb* in the detoxication test. The *trans*-sulfoxide *VIIa* may be defined on the basis of the results achieved as a relatively nontoxic, highly effective antihistamine, practically devoid of the undesirable depressant effect.

Compound *IX* was synthesized as a potential neuroleptic; hence no data on its antihistamine activity are available. In the rotating-rod test it is only slightly effective and it is ineffective in the catalepsy test in rats; it does not show antireserpine activity. The compound is thus neither a neuroleptic nor an antidepressive agent. Compound *XII* prepared for comparison[18] is an antihistamine but its active doses are at least one order of magnitude higher than those of *Ia* and *Ib*.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block and are not corrected; the samples were dried at a temperature conformable to the melting point of the substances *in vacuo* (0·5 Torr) over P_2O_5. The UV spectra (in methanol unless stated otherwise) were recorded on a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) on a Unicam SP 200 spectrophotometer and the NMR spectra (in $CDCl_3$ unless stated otherwise) in a Zeiss (Jena) ZKR 60 spectrometer.

2-(2-Thienylthiomethyl)benzoic Acid (*IV*)

A. A usual procedure was employed in the preparation of Grignard's reagent from 4·9 g Mg and 32·6 g 2-bromothiophene[31] in 80 ml ether. This was combined at room temperature and under stirring with 6·4 g powdery sulfur (see ref.[32]). The solution formed was refluxed for 1 h, the ether was then distilled off and the solid was cooled and decomposed by adding 100 ml ethanol. After addition of 25·5 g phthalide[33], remainders of ether were distilled from the mixture and the mixture was refluxed for 2 h. After standing overnight it was diluted with 300 ml water and the solution formed was acidified with 25 ml concentrated hydrochloric acid. The crude product precipitated was purified by dissolving in dilute aqueous ammonia, filtering the solution with charcoal and acidifying with hydrochloric acid; 35·5 g (71%), m.p. 113–117°C. For the product obtained from the isolated 2-thiophenethiol we reported[1] a yield of 71% and a m.p. of 116–117°C.

B. Reaction of 4·8 g Mg with 42·0 g 2-iodothiophene[34] in 180 ml ether resulted in a solution of the Grignard reagent which was processed as before by adding 6·6 g powdered sulfur. After refluxing the reaction mixture for 1 h, most of the ether was distilled off, the residue was combined with 24·1 g phthalide[33] and the mixture was heated under stirring for 1·5 h in a 120°C bath. The hot melt was decomposed with 100 ml water and, after cooling, the mixture was extracted with chloroform. The extract was washed with water, shaken with a solution of 15 g NaOH in 300 ml water and the alkaline solution obtained was acidified after separation with hydrochloric acid; 35·5 g (79%), m.p. 114–117°C.

Thieno[2,3-*b*]benzo[*e*]thiepin-4(9*H*)-one (*V*)

Ethanol (187 ml) was slowly added to a mixture of 375 g P_2O_5 and 3000 ml toluene under stirring and the mixture was heated for 30 min to 100°C. Then 375·3 g acid *IV* was added and the mixture was stirred for 5·5 h at 100°C. After cooling under stirring, it was decomposed by adding 2 liters of water, the toluene layer was washed with 5% NaOH and evaporated. The residue was purified by crystallization from 290 ml ethanol: 260 g (75%), m.p. 57–60°. The compound was obtained before by different procedures in lower yields[1,2]; for an analytical preparation a m.p. of 61–62·5°C was reported.

4-(3-Dimethylaminopropyl)-4,9-dihydrothieno[2,3-*b*]benzo[*e*]thiepin-4-ol (*VI*)

A grain of iodine and a few drops of dibromoethane were added to 11·0 g Mg in 50 ml tetrahydrofuran and, after initiation of reaction, a solution of 55 g 3-dimethylaminopropyl chloride in 90 ml benzene was slowly added dropwise. The mixture was refluxed under stirring for 1 h; after cooling, a solution of 69·7 g ketone *V* in 350 ml benzene was added over a period of 30 min, the mixture was stirred for 30 min and decomposed by adding a solution of 100 g NH_4Cl in 400 ml water. The crude product was isolated in the usual way[1]. Recrystallization from 200 ml boiling acetone yielded 86·2 g (90%) pure product melting at 120–122°C. In the quoted paper[1] we described a less suitable method of this preparation with a yield of 70% and a melting point of the product equal to 118–119°C. NMR spectrum: δ 8·00 (m, 1 H, aromatic 5-H), 7·41 (d,

J = 8·0 Hz, 1 H, aromatic 2-H), c. 7·23 (m, 3 H, aromatic 6,7,8-H_3), 7·00 (d, J = 8·0 Hz, 1 H, aromatic 3-H), 4·70 and 3·88 (2d, J = 14·0 and 14·0 Hz, 2H, $ArCH_2S$), 1·30–3·20 (m, 7 H, 3 CH_2 of the chain and OH), 2·21 (s, 6 H, CH_3—N—CH_3).

trans-4-(3-Dimethylaminopropylidene)-9*H*-thieno[2,3-*b*]benzo[*e*]thiepin (*Ia*)

A solution of 800 g aminoalcohol *VI* in 4 liters of warm acetone was cooled to 20°C, dilute sulfuric acid was slowly added (150 ml H_2SO_4 and 160 ml water) and the mixture was stirred for 1 h at 50°C. Then it was stirred for 2 h at 5°C, the precipitated hydrogen sulfate (872 g) was filtered, dissolved in boiling mixture of 340 ml water and 340 ml ethanol, the solution was diluted with 3400 ml ethanol and the mixture was left for 2 h to crystallize under external cooling and stirring: 819 g (82%), m.p. 189–191°C. According to paper chromatography of the sample the product is practically free of the *cis*-isomer. For $C_{17}H_{21}NO_4S_3$ (399·6) calculated: 51·10% C, 5·30% H, 3·50% N, 24·08% S; found: 51·15% C, 5·38% H, 3·34% N, 23·88% S. Treatment of the aqueous solution of hydrogen sulfate with NH_4OH and extraction with benzene yielded the pure *trans*-base *Ia* which crystallizes after longer standing from a light petroleum solution; m.p. 53–55°C. UV spectrum (heptane): λ_{max} 230 nm (log ε 4·29), 280·5 nm (3·77), 310 nm (3·62). IR spectrum (CS_2): 761 (4 vicinal aromatic C—H), 789 (satellite band of the preceding, due to interaction with the side chain), 826 and 841 (2 vicinal thiophene C—H), 2723, 2766, 2783 and 2813 cm^{-1} (dimethylamino). NMR spectrum: δ c. 7·30 (m, 4 H, protons of benzene ring), 7·04 (s, 2 H, protons of thiophene), 6·07 (m, 1 H, C=CH), 4·10 (bs, 2 H, $ArCH_2S$), 2·34 (m, 4 H, 2 CH_2 of the chain), 2·18 (s, 6 H, CH_3—N—CH_3). For $C_{17}H_{19}NS_2$ (301·5) calculated: 67·72% C, 6·35% H, 4·65% N, 21·28% S; found: 67·41% C, 6·39% H, 4·54% N, 21·17% S. The hydrochloride prepared from the pure base melted at 252–253°C (aqueous ethanol). Our previous value of 243–245°C refers to a product[1] with an admixture of the *cis*-isomer.

Hydrogen maleate, m.p. 150–152°C (ethanol). For $C_{21}H_{23}NO_4S_2$ (417·5) calculated: 60·40% C, 5·55% H, 3·36% N, 15·36% S; found: 60·41% C, 5·68% H, 3·18% N, 14·90% S.

cis-4-(3-Dimethylaminopropylidene)-9*H*-thieno[2,3-*b*]benzo[*e*]thiepin (*Ib*)

Combined mother liquors after the hydrogen sulfate from the previous experiment were evaporated at reduced pressure to a small volume, the residue was diluted with 600 ml acetone and, after several hours of standing at 5°C, the mixture was filtered to remove the small amount of the hydrogen sulfate of the *trans*-base. The filtrate was again evaporated, the residue was dissolved in water, the solution filtered with charcoal and the filtrate made alkaline with NH_4OH. The liberated crude *cis*-base (108 g) was extracted with chloroform, dissolved in 550 ml ethanol and the solution was neutralized with 41·4 g maleic acid. The solution prepared by heating yielded 104·2 g precipitate which was recrystallized from 660 ml ethanol to 93 g pure hydrogen maleate of the *cis*-base *Ib*, m.p. 163–165°C. For $C_{21}H_{33}NO_4S_2$ (417·5) calculated: 60·40% C, 5·55% H, 3·36% N, 15·36% S; found: 60·21% C, 5·73% H, 3·36% N, 15·15% S.

Decomposition of this salt by treatment with NH_4OH and isolation by extraction with benzene led to the oily *cis*-base *Ib* which does not crystallize even on prolonged standing. It was used for the measurement of spectra. UV spectrum (heptane): λ_{max} 230 nm (log ε 4·26), 284 nm (3·77), 307 nm infl. (3·65). IR spectrum (CS_2): 760 (4 vicinal aromatic C—H), 826 and 841 (2 vicinal thiophene C—H), 809, 861 and 879 (satellite bands to the preceding two due to interaction with the side chain), 2723, 2769, 2783 and 2814 cm^{-1} (dimethylamino). NMR spectrum: δ c. 7·30 (m, 4 H, protons of the benzene ring), 7·14 (d, J = 8·0 Hz, 1 H, thiophene 2-H), 6·94 (d, J = 8·0 Hz, 1 H, thiophene 3-H), 5·68 (m, 1 H, C=CH), 4·25 (s, 2 H, $ArCH_2S$), c. 2·45 (m, 4 H, 2 CH_2 of the chain), 2·27 (s, 6 H, CH_3—N—CH_3).

Hydrochloride, m.p. 224—225°C (ethanol). For $C_{17}H_{20}ClNS_2$ (337·9) calculated: 60·42% C, 5·97% H, 10·49% Cl, 4·14% N, 18·98% S; found: 60·52% C, 6·07% H, 10·54% Cl, 3·85% N, 18·88% S.

trans-4-(3-Methylaminopropylidene)-9*H*-thieno[2,3-*b*]benzo[*e*]thiepin (*III*)

A solution of 17·4 g base *Ia* in 60 ml benzene was added dropwise over 30 min at 75°C to a solution of 7·5 g ethyl chloroformate in 25 ml benzene and the mixture was refluxed under stirring for 2 h. After cooling, it was washed with 3% hydrochloric acid and water, dried with Na_2SO_4 and evaporated. The residue (17·3 g, 83%) is the oily carbamate *II* which could not be induced to crystallize. The total amount was dissolved in 16 ml ethanol and, after adding 13·4 g solid KOH, it was heated under stirring for 2 h on a 120°C bath. After cooling, it was decomposed with 50 ml water and extracted with benzene. Processing of the extract yielded 11·9 g (87%) oily base which was converted in an acetone solution with hydrochloric acid to the hydrochloride: after recrystallization from 90% ethanol, m.p. 224—225°C. UV spectrum: λ_{max} 226 nm infl. (log ε 4·24), 237 nm infl. (4·16), 275 nm (3·76), 311 nm (3·67). IR spectrum: 757 (4 vicinal aromatic C—H), 837 and 850 (2 vicinal thiophene C—H), 1585 (Ar), 2440 and 2730 cm^{-1} (NH_2^+). For $C_{16}H_{18}ClNS_2$ (323·9) 59·33% C, 5·60% H, 10·95% Cl, 19·80% S; found: 59·37% C, 5·80% H, 11·04% Cl, 19·67% S.

trans-4-(3-Dimethylaminopropylidene)-9*H*-thieno[2,3-*b*]benzo[*e*]thiepin 10-Oxide (*VIIa*)

Hydrochloride of base *Ia* (23·3 g) was oxidized with 8·8 g 30% H_2O_2 in 100 ml acetic acid similarly to the earlier report[2]. Processing of the mixture yielded 21·9 g (98%) oily base which was neutralized in ethanol with an ether solution of HCl and thus converted to the hydrochloride; after recrystallization from ethanol it melted at 234°C under decomposition. For $C_{17}H_{20}ClNOS$ (353·9) calculated: 57·68% C, 5·70% H, 10·02% Cl, 3·96% N, 18·12% S; found: 57·65% C, 5·86% H, 10·02% Cl, 4·00% N, 17·89% S. Decomposition of the purified hydrochloride by alkali yields a base which is oily and does not crystallize even after prolonged standing. It was used for measurement of spectra. UV spectrum (ethanol): λ_{max} 273 nm (log ε 4·12). IR spectrum (CS_2): 764 (4 vicinal aromatic C—H), 793 (satellite band to the preceding, indicating an interaction with the side chain and hence *trans*-configuration of the product), 852, 879 and 889 (2 vicinal thiophene C—H); continuation of the spectrum in CCl_4: 1060 (SO), 1459, 1489, 1632 (Ar), 2728, 2772 and 2783 cm^{-1} (dimethylamino).

cis-4-(3-Dimethylaminopropylidene)-9*H*-thieno[2,3-*b*]benzo[*e*]thiepin 10-Oxide (*VIIb*)

A solution of 10·6 g base *Ib* in 50 ml acetic acid was combined with 4·4 ml 30% H_2O_2 and the mixture was left to stand for 12 h at room temperature. It was then diluted with 500 ml water, made alkaline with NH_4OH and the base was extracted with chloroform: 9·9 g (89%), m.p. 139—141°C (benzene–light petroleum). UV spectrum (ethanol): λ_{max} 270·5 nm (log ε 4·07). IR spectrum (CS_2): 763 (4 vicinal aromatic C—H), 831, 849, 866 and 884 (2 vicinal thiophene C—H; due to interaction with the side chain the spectrum in this region is richer and the main band is shifted toward 884 cm^{-1}); continuation of spectrum in CCl_4: 1057 (SO), 1460, 1484, 1502, 1632 (Ar), 2728, 2772 and 2783 cm^{-1} (dimethylamino).

Hydrochloride, m.p. 217°C (ethanol–ether). For $C_{17}H_{20}ClNOS_2$ (353·9) calculated: 10·02% Cl, 3·96% N, 18·12% S; found: 10·24% Cl, 3·47% N, 18·19% S.

4-[3-(4-Methylpiperazino)propyl]-6-chloro-4,9-dihydrothieno[2,3-*b*]benzo[*e*]thiepin-4-ol (*VIII*)

Reaction of 2·14 g Mg with 15·6 g 3-(4-methylpiperazino)propyl chloride[15–17] in 35 ml tetrahydrofuran produced a solution of a Grignard reagent[14]. This was cooled and combined under stirring over a period of 10 min with a solution of 15·7 g 6-chlorothieno[2,3-*b*]benzo[*e*]thiepin-4(9*H*)-one[2] in 50 ml tetrahydrofuran. The mixture was stirred for 2 h at room temperature, left to stand overnight and decomposed by a solution of 18 g NH_4Cl in 80 ml water. The crude product obtained by extraction with benzene was purified by crystallization from acetone and recrystallization from benzene: 7·8 g (32%), m.p. 189–191°C. For $C_{20}H_{25}ClN_2OS_2$ (409·0) calculated: 58·73% C, 6·16% H, 8·67% Cl, 6·87% N, 15·68% S; found: 58·96% C, 6·11% H, 8·85% Cl, 6·45% N, 15·71% S.

4-[3-(4-Methylpiperazino)propylidene]-6-chloro-9*H*-thieno[2,3-*b*]benzo[*e*]thiepin (*IX*)

A mixture of 6·7 g aminoalcohol *VIII* and 60 ml dilute hydrochloric acid (1 : 2) was refluxed for 15 min. After cooling it was made alkaline with NH_4OH and the crude oily base (4·5 g, 70%) was extracted with chloroform. Dihydrochloride (sesquihydrate) was obtained by neutralization of the base in acetone solution with hydrochloric acid; it was purified by recrystallization from a mixture of ethanol and ether, m.p. 244–246°C, under decomposition. For $C_{20}H_{28}Cl_3N_2O_{1.5}S_2$ (490·9) calculated: 48·93% C, 5·75% H, 21·66% Cl, 5·71% N, 13·06% S; found: 48·98% C, 5·76% H, 20·98% Cl, 5·54% N, 12·98% S.

Thieno[2,3-*b*]-1-benzothiopyran-4-one (*X*)

Ethanol (23·5 ml) was added dropwise under stirring to a mixture of 43·5 g P_2O_5 and 430 ml toluene and the mixture was refluxed under stirring for 15 min. After this, 41·0 g 2-(2-thienylthio)benzoic acid[19,35] was added and the mixture was refluxed for 3 h. After cooling, it was decomposed with 400 ml water, the toluene solution was separated and washed with 5% NaOH. The solid fraction of the aqueous phase was extracted with chloroform, the extract was washed with 5% NaOH and combined with the toluene phase. After cooling (K_2CO_3), evaporation yielded 32·0 g (84%) product which was recrystallized from a mixture of benzene and light petroleum to melt at 161–162°C. By analogous cyclization with the aid of sulfuric acid[19] the same product was obtained in a 50% yield; ref[19] gives a m.p. of 157–158°C.

4-(3-Dimethylaminopropyl)thieno[2,3-*b*]-1-benzothiopyran-4-ol (*XI*)

Reaction of 1·8 g Mg with 9·2 g 3-dimethylaminopropyl chloride in 25 ml tetrahydrofuran yielded a Grignard reagent which was cooled and combined under stirring with a solution of 11·0 g ketone *X* in 80 ml tetrahydrofuran. The mixture was stirred for 2·5 h at room temperature, left to stand overnight and decomposed with a solution of 16 g NH_4Cl in 70 ml water. Extraction with benzene yielded the base which was recrystallized from acetone; 12·1 g (79%), m.p. 110–112°C. Patents[18] mention the compound, giving a m.p. of 105–107°C. For $C_{16}H_{19}NOS_2$ (305·5) calculated: 62·91% C, 6·27% H, 4·59% N, 21·00% S; found: 62·81% C, 6·29% H, 4·83% N, 20·81% S.

4-(3-Dimethylaminopropylidene)thieno[2,3-*b*]-1-benzothiopyran (*XII*)

A mixture of 11·0 g aminoalcohol *XI* and of dilute sulfuric acid (13 ml H_2SO_4 and 87 ml water) was heated for 1·5 h in a 105°C bath. After cooling, the solution was made alkaline with NH_4OH and the crude base was extracted with benzene; 9·7 g (94%). The base was chromatographed on

a column of 200 g alumina (activity II), elution with benzene producing 5·7 g product. Neutralization with tartaric acid in ethyl acetate and recrystallization from aqueous acetone yielded the hydrogen tartrate(dihydrate) melting at 70—78°C and decomposing above 108°C. For $C_{20}H_{27}NO_8S_2$ (473·6) calculated: 50·72% C, 5·75% H, 2·96% N, 13·54% S; found: 50·90% C, 5·70% H, 2·81% N, 13·44% S. Patents[18] described the preparation of the compound by dehydration of aminoalcohol *XI* with the aid of boiling phosphorus oxychloride and the compound is characterized as a tartrate-hydrate not further identified, with a m.p. of 135°C and softening from 110°C; apparently the salt had a composition different from the present one.

4-Hydroxynaphtho[2,3-*b*]thiophene (*XIV*)

A suspension of 4·8 g 4-acetoxynaphtho[2,3-*b*]thiophene[21] (*XIII*) in 10 ml ethanol was combined with a solution of 3·3 g KOH in 3 ml water. The mixture immediately turned red and under spontaneous heating the solid dissolved. After dissolving, it was at once diluted with 80 ml water, the solution was filtered and the filtrate acidified with dilute hydrochloric acid (1 : 1). The precipitated yellow solid was filtered and recrystallized from benzene; m.p. 129—131°C. UV spectrum: λ_{max} 254·5 nm (log ε 4·69), 338 nm infl. (3·72), 350 nm (3·78), 364 nm (3·78). IR spectrum: 730 (4 vicinal aromatic C—H), 828 and 860 (2 vicinal thiophene C—H), 895 (solitary C—H in position 9), 1199 (phenol OH), 1151, 1350, 1379, 1391, 3330 (OH), 1633 cm^{-1} (ArCOAr); in CCl_4: 1663 (ArCOAr), 3410 and 3605 cm^{-1} (phenol OH). NMR spectrum (CD_3SOCD_3): δ 10·50 (bs, 1 H, OH), *c.* 8·45 (m, 1 H, aromatic proton in position 5), 7·20—8·10 (m, 6 H, remaining aromatic protons). For $C_{12}H_8OS$ (200·3) calculated: 71·97% C, 4·03% H, 16·01% S; found: 72·09% C, 3·94% H, 15·89% S. Only after this work had been concluded was the compound prepared by a different procedure[22], with a reported m.p. of 130—132°C; a spectral analysis determined the approximate representation of tautomers *XIV* and *XV*.

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