POTENTIAL ANTIHISTAMINICS: TRICYCLIC CARBOXYLIC ACIDS DERIVED FROM 6,11-DIHYDRODIBENZO[*b*,*e*]THIEPINE AND 4,9-DIHYDROTHIENO[2,3-*c*]-2-BENZOTHIEPINE

Karel ŠINDELÁŘ, Jiří HOLUBEK, Emil SVÁTEK, Jan METYŠ, Hana BLEHOVÁ and Zdeněk POLÍVKA

Research Institute for Pharmacy and Biochemistry, 130 60 Prague 3

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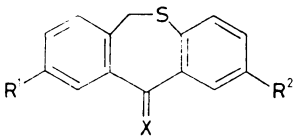
Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

Reaction of nitrile *IVa* with the Grignard's reagent 1-methyl-4-piperidylmagnesium chloride gave carbinol *XIb* as product. Carbinols *XIa* and *XIb* were dehydrated and hydrolysed with dilute hydrochloric acid to give hydrochlorides of the tricyclic amino acids *Vb* and *Vc*. Isomeric compounds with a carboxyl group in position 9 of the tricyclic skeleton were obtained either by hydrolysis of the formerly prepared nitrile *VIIb* (compound *VIIIb*) or on reaction of bromoketone *VIa* with 1-methyl-4-piperidylmagnesium chloride, nucleophilic substitution of the bromine atom by the cyano group at the stage of carbinol *XIIIb*, and subsequent dehydration and hydrolysis of the cyano group, to give amino acid *VIIIc*. In the first case the synthesis of thiophene analogues *XVIIIb* and *XVIIIc* started from ketone *XVa*, which was brominated with bromine in acetic acid into position 2 of the tricyclic skeleton, followed by Grignard's reaction with 3-dimethylaminopropylmagnesium chloride in tetrahydrofuran and hydrolysis to bromo derivative *XVIb*. In the second case derivative *XVIc* was obtained directly by bromination of hydrochloride *XVc*. Basic bromo derivatives *XVIb* and *XVIc* were reacted with butyllithium in tetrahydrofuran at −60°C to afford corresponding organometallic reagents which, when reacted with solid carbon dioxide, afforded the required amino acids *XVIIIb* and *XVIIIc*. Further, some other tricyclic nitriles were synthesized as potential intermediates. The prepared tricyclic amino acids *Vb*, *Vc*, *VIIIb*, *VIIIc*, *XVIIIb* and *XVIIIc* were tested both on animals and in assays of biochemical pharmacology. Some of them displayed considerable antihistaminic activity. The most interesting compound of this series, hydrochloride *Vc* (VÚFB-17689) is a strong antihistaminic with distinctly suppressed sedative effects and it was therefore selected for a more detailed pharmacological testing.

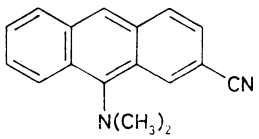
Derivatives of dibenzo[*b*,*e*]thiepine and thieno[2,3-*c*]-2-benzothiepine with an aminoalkylidene substituent (3-dimethylaminopropylidene, 1-methyl-4-piperidylidene) attached to the central carbon atom between the aromatic nuclei are known antihistaminics, of which some have already been introduced into clinical practice. The majority of them, as for example 11-(1-methyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepine (*Ic*, refs[1,2]), methiadene (*IIb*, refs[2–5]), dithiadene (*XVb*, refs[6–8]) and pipethiadene (*XVc*, refs[9,10]), possess outstanding H_1 antihistaminic effects,

which are, however, accompanied by undesirable sedative effects, as in the case of other common antihistamines. These may be caused by their ability to penetrate the hematoencephalic barrier. Recently great attention has been devoted to the development of antihistaminces of a new generation in which the effects on the CNS are considerably suppressed. This has been achieved both by introduction of substances of quite new structural types[11-15] (astemizol, terphenadine, loratadine) and by modifidation of the structure of classical antihistaminics. One of the possiblities is the introduction of a hydrophilic group, for example carboxyl[16,17], which decreases the possibility of penetration of the substance into the brain tissue. The aim of this study was the modification of the structure of classical tricyclic antihistaminics, which proved their value in clinical practice, by introducing a carboxyl group into suitable positions, thus achieving a decrease in their undesirable central effects.

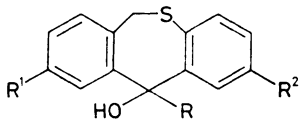
The starting compound for the introduction of the carboxyl group into position 2 of dibenzo[*b*,*e*]thiepine skeleton was the tricyclic bromoketone[4] *IIIa*, which was converted to nitrile[18] *IVa* by nucleophilic substitution of the bromine atom using cuprous cyanide in hexamethylphosphoric triamide at 160°C. The low yield is caused in this case by a side reaction in which 9-dimethylanthracene-2-carbonitrile (*IX*) is formed. This compound, which was isolated by chromatography of the mother liquors after crystallization of the main product on silica gel, is formed by



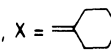
I, $R^1 = R^2 = H$
II, $R^1 = H$; $R^2 = CH_3$
III, $R^1 = H$; $R^2 = Br$
IV, $R^1 = H$; $R^2 = CN$
V, $R^1 = H$; $R^2 = COOH$
VI, $R^1 = Br$; $R^2 = H$
VII, $R^1 = CN$; $R^2 = H$
VIII, $R^1 = COOH$; $R^2 = H$

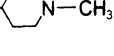


IX



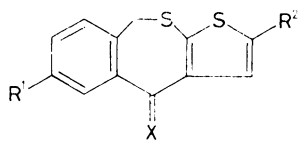
X, $R^1 = R^2 = H$
XI, $R^1 = H$; $R^2 = CN$
XII, $R^1 = H$; $R^2 = CO(CH_2)_3N(CH_3)_2$
XIII, $R^1 = Br$; $R^2 = H$
XIV, $R^1 = CN$; $R^2 = H$

In formulae *I*-*VIII*: *a*, X = O ; *b*, $X = CHCH_2CH_2N(CH_3)_2$; *c*, X = 

In formulae *X*-*XIV*: *a*, $R = (CH_2)_3N(CH_3)_2$; *b*, R = 

extrusion of sulphur from dibenzo[*b*,*e*]thiepine skeleton[19] described earlier and reaction with hexamethylphosphoric triamide. The ketone *IVa* prepared was submitted to Grignard reaction with 1-methyl-1,4-piperidylmagnesium chloride in tetra-

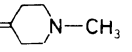
hydrofuran, to give carbinol *XIb*, the dehydration of which and simultaneous hydrolysis of the cyano group with 20% hydrochloric acid gave the required amino acid *Vc* in the form of its hydrochloride hemihydrate. On analogous reaction of ketone *IVa* with 3-dimethylaminopropylmagnesium chloride the required carbinol *XIa* is formed in 48% yield. However, in this case the Grignard's reagent also reacted with the nitrile group and ketone *XIIa* was isolated as a byproduct which was formed by the addition of two molecules of Grignard's reagent and hydrolysis. The compounds were separated by chromatography and subsequent dehydration of the tertiary alcohol *XIa* and simultaneous hydrolysis of the nitrile group with dilute hydrochloric acid afforded crystalline hydrochloride of 11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepine-2-carboxylic acid (*Vb*). An analogous 9-carboxylic acid, *VIIIb*, was obtained on hydrolysis of (*E*)-11-(3-dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepine-9-carbonitrile (*VIIb*) which was prepared in the manner described[18]. The synthesis of 1-methyl-4-piperidylidene analogue *VIIIc* with a carboxyl group in position 9 of the tricyclic skeleton started from bromoketone[18] *VIa*, which, on reaction with 1-methyl-4-piperidylmagnesium chloride afforded carbinol *XVIIIb* in admixture with the debrominated product *Xb* which is formed on reduction with Grignard's reagent under the reaction conditions used. Carbinol *XIIIb* was isolated by chromatography on silica gel and it was converted to corresponding nitrile *XIVb* by reacting it with cuprous cyanide in hexamethylphosphoric triamide (150°C, 15 h). Its hydrolysis and dehydration under the conventional conditions gave the hydrochloride of the final amino acid *VIIIc*.



XV, $R^1 = R^2 = H$ — *XVIII*, $R^1 = H$; $R^2 = COOH$

XVI, $R^1 = H$; $R^2 = Br$ — *XIX*, $R^1 = Br$; $R^2 = H$

XVII, $R^1 = H$; $R^2 = CN$ — *XX*, $R^1 = CN$; $R^2 = H$

In formulae *XV*–*XX*: *a*, X = O; *b*, X = $CHCH_2CH_2N(CH_3)_2$; *c*, X = 

Analogous procedures in the thieno[2,3-*c*]-2-benzothiepine group did not lead to our goal. The brominated derivative[7] *XIXb* was indeed converted with cuprous cyanide to 4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepine-6-carbonitrile (*XXb*) in a low yield, but the attempts at its hydrolysis to the corresponding carboxylic acid under various conditions always led to a varied mixture of compounds. Bromination of 4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-one (*XVa*) with bromine in acetic acid gives 2-bromoketone *XVIa* in high yield. Its

reaction with cuprous cyanide, however, gives primarily polymeric products even under milder conditions, but the required nitrile *XVIIa* was obtained only in a 2% yield. Therefore ketone *XVIa* was submitted to Grignard's reaction with 3-dimethylaminopropylmagnesium chloride and subsequent dehydration of the carbinol (already taking place under the conditions of the isolation of the product) gave 2-bromo derivative *XVIb*. Even in this case reduction with an excess of Grignard's reagent gives the debrominated by-product *XVb*. After chromatographic isolation on an alumina column the bromo derivative was used for the preparation of an organometallic compound with butyllithium (in tetrahydrofuran at −60°C). This compound was reacted with solid carbon dioxide, affording the final amino acid *XVIIIb*, which was converted – for pharmacological purposes – to a crystalline hydrochloride. In the same manner (butyllithium in tetrahydrofuran, −60°C) 1-methyl-4-piperidylidene analogue *XVIIIc* was prepared from the brominated compound *XVIc*. Compound *XVIc* was obtained by direct bromination of pipethiadene (*XVc*) with bromine in acetic acid in high yield.

Tricyclic amino acids *Vb*, *Vc*, *VIIIb*, *VIIIc*, *XVIIIb* and *XVIIIc* were tested pharmacologically in the form of hydrochlorides, described in the Experimental part. The compounds were administered etiher orally (unless stated otherwise) and the doses administered are calculated as bases. In Table I code numbers of individual

TABLE I
Antihistaminic effects of tricyclic amino acids

Compound	Code number VÚFB-	LD_{50} mg/kg p.o. (i.v.)	Inhibition of the binding of [^{3}H]mepyramine IC_{50}, mol l^{-1}	Histamine aerosol PD_{50}, mg/kg, p.o.	Detoxication of histamine PD_{50}, mg/kg, p.o.
Vb	17749	388	$5{\cdot}08 \cdot 10^{-6}$	0·73	<1·0
Vc	17689	697	$1{\cdot}82 \cdot 10^{-7}$	0·14	<0·1[a]
VIIIb	17744	>800	$1{\cdot}90 \cdot 10^{-5}$	inactive[b]	inactive[b]
VIIIc	17789	>1 000 (138)	$2{\cdot}48 \cdot 10^{-6}$	14·3	weak effect[c]
XVIIIb	17740	>1 000	$5{\cdot}01 \cdot 10^{-7}$	5·1	weak effect[c]
XVIIIc	17778	>700 (27·7)	$>1{\cdot}00 \cdot 10^{-6}$	1·0	[d]
Astemizole			$5{\cdot}00 \cdot 10^{-8}$	0·1	0·03–0·10

[a] In oral dose a protective effect was shown in 66% of animals, a 0·01 mg/kg p.o. dose was protectively inactive; [b] tested in a 10 mg/kg p.o. dose (aerosol), or 1 mg/kg p.o. dose (detoxication); [c] a protective effect was found in 1–2 animals (of a group of seven) after administration of a 1 mg/kg p.o. dose; [d] not tested in this assay.

compounds are given, as well as their acute toxicity in mice and the results of the testing of their antihistaminic activity. It consisted of a H_1-receptor-binding study in vitro (inhibition of the binding of 2 nM ^{3}H-mepyramine in rat brain membranes) and classical tests for antihistamine activity in guinea pigs (test with histamine aerosol and detoxication of histamine). The tests were completed by results which characterize the effects of compounds on the CNS in mice (spontaneous locomotor activity – test according to Dews, and incoordination activity – rotation rod).

Compound *Vb*: Does not affect spontaneous locomotor activity in a 100 mg/kg dose. In the rotating rod test crude ataxy is demonstrable in 10–20% of mice at a 200 mg/kg dose, and a 400 mg/kg dose leads to the death of 40% of the animals. Compound *Vc*: A 100 mg/kg dose does not affect spontaneous locomotor activity statistically significantly, while a 200 mg/kg dose leads to a decrease in activity to 54% of the value of the control group of animals. An oral dose of 200 mg/kg elicits disturbance in motoric coordination in 10–20% of animals. Compound *VIIIb*: In a 200 mg/kg dose it does not cause ataxia in mice. In a 800 mg/kg dose it induces a short-term excitation, which, however, does not lead to the animals' deaths. Compound *VIIIc*: In a 500 mg/kg dose it disturbs motoric coordination in mice. An oral administration of high doses (600 – 1 000 mg/kg) elicits an increase in the readiness to convulsions which changes to loss of consciousness. Compound *XVIIIb*: it depresses spontaneous locomotor activity intensively at an oral dose of even 100 mg/kg (decrease to 31% of the value of the control group of mice). In a 100 mg/kg dose it develops a disturbance of motoric coordination in 10% of mice. Compound *XVIIIc*: It depresses spontaneous locomotor activity intensively in a 200 mg/kg dose (a decrease to 52% of the control group value, statistically significant). In a 200 mg/kg dose it does not cause ataxia. A 700 mg/kg dose has *T* depressant effect, it develops dyspnoea and bristling up of fur, and the original state is restored within 60 min.

From the above results it is evident that compound *Vc* (VÚFB-17689) can be indicated as a highly active antihistamine with very low depressant effects and therefore it was selected for more detailed pharmacological testing. Compound *Vb* is also a considerably active antihistamine, but in comparison with the preceding compound it is less advantageous. The other substances of this group tested are less interesting from the pharmacological point of view.

EXPERIMENTAL

The melting points were determined on a Mettler FP-5 instrument. Samples for analysis were dried in a vacuum (about 60 Pa) over P_2O_5, at room temperature. The UV spectra (in methanol, λ_{max} in nm ($\log \varepsilon$)) were recorded on a Unicam SP 8000 spectrometer, the IR spectra predominantly on a Perkin–Elmer 298 spectrometer (Nujol, ν in cm^{-1}) or on a Shimadzu IR-435 instrument using KBr pellets. The NMR spectra were measured in CD_3SOCD_3 (unless stated

otherwise) on a Tesla BS 567A spectrometer (^{1}H at 100 MHz, ^{13}C at 25·14 MHz), chemical shifts are given in ppm (δ-scale), coupling constants (J) in Hz. The mass spectra were measured on a Varian-MAT 44S instrument. The homogeneity of the products was checked by TLC on Silufol (Kavalier, Votice). The extracts were dried over $MgSO_4$ or K_2CO_3 and evaporated under reduced pressure (about 2 kPa) on a rotatory evaporator.

(*E*)-11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]-thiepine-9-carboxylic Acid (*VIIIb*)

A mixture of compound[18] *VIIb* (5·2 g) and 100 ml of 20% HCl was stirred and refluxed for 14 h, then cooled and the product was filtered off under suction and crystallized from ethanol–ether mixture. Yield, 3·5 g (56%) of hydrochloride *VIIIb* (hemihydrate), m.p. 212–217°C. IR spectrum: 754, 787, 840, 880, 890 (4 and 2 vicinal and 1 isolated Ar-H); 1 571, 1 602 (Ar); 1 662 (C=C); 1 698 (COOH); 3 150, 3 340, 3 485 (COOH, H_2O); 2 450, 2 555, 2 660 (NH^+). ^{1}H NMR spectrum: 2·38 bm, 2 H (CCH_2C); 2·68 bs, 6 H ($N(CH_3)_2$); 3·20 bm, 2 H (CH_2N); 3·82 d and 4·86 d, 1 H (AB system, $ArCH_2S$, J = 13); 6·04 t, 1 H (=CH, J = 7); 7·0–8·0 m, 7 H (Ar-H). For $C_{20}H_{22}ClNO_2S.0{\cdot}5\,H_2O$ (384·9) calculated: 62·41% C, 6·02% H, 3·64% N, 8·33% S; found: 61·93% C, 6·02% H, 3·86% N, 8·32% S.

11-Oxo-6,11-dihydrodibenzo[*b*,*e*]thiepine-2-carbonitrile (*IVa*)

A mixture of compound[4] *IIIa* (25·0 g), CuCN (15·0 g) and 60 ml of HMPT was stirred and heated at 160–170°C for 6 h. After cooling the mixture was partitioned (by mixing) between chloroform and aqueous ammonia, filtered, the organic phase of the filtrate was washed with water, dried and evaporated. Crystallization of the residue from a mixture of benzene and ethanol gave 5·7 g (28%) of ketone *IVa*, m.p. 163–166°C (ref.[18] gives m.p. 165–166°C). Working up of the mother liquor by chromatography on silica gel (Fluka 60, elution with benzene) afforded 1·1 g (5·5%) of 9-dimethylaminoanthracene-2-carbonitrile (*IX*), m.p. 115–116·5°C (ethanol). UV spectrum: 259 (4·96), 344 (3·40), 360 (3·48), 380 (3·53), 400 (3·56). IR spectrum 1 554, 1 572, 1 620 (Ar); 2 219 (CN); 2 789 ($N(CH_3)_2$). ^{1}H NMR spectrum ($CDCl_3$): 3·38 s, 6 H ($N(CH_3)_2$); 7·5–8·8 m, 8 H (Ar-H). ^{13}C NMR spectrum ($CDCl_3$): 124·12, 124·52, 125·19, 125·86, 126·68, 129·30, 130·19, 133·03 d (C-1, C-3, C-4, C-5, C-6, C-7, C-8, C-10); 108·23 s (C-2); 128·78, 131·02, 132·44, 134·68 s (C-4a, C-8a, C-9a, C-10a); 147·82 s (C-9); 120·11 s (CN); 45·12 q ($N(CH_3)_2$). Mass spectrum, m/z (%): 246 (M^+, $C_{17}H_{14}N_2$, 100), 245 (42), 231 (15), 230 (11), 229 (13), 204 (22), 203 (22), 202 (10). For $C_{17}H_{14}N_2$ (246·3) calculated: 82·90% C, 5·73% H, 11·37% N; found: 83·09% C, 5·89% H, 11·43% N.

11-Hydroxy-11-(3-dimethylaminopropyl)-6,11-dihydrodibenzo[*b*,*e*]thiepine-2-carbonitrile (*XIa*)

Grignard's reagent was prepared on reaction of 2 g of magnesium with 9·6 g of 3-dimethylaminopropyl chloride in 60 ml THF. After cooling to 10°C a solution of 11 g *IVa* in 100 ml THF was added and the mixture stirred for 6 h at room temperature. After 2 days' standing the reaction mixture was decomposed by dropwise addition of 60 ml of 20% NH_4Cl and diluted with 100 ml of benzene. The organic phase was extracted with 200 ml of 10% HCl, the acid aqueous phase was alkalized with ammonia and the base extracted with chloroform. The residue obtained by working up of the extract was chromatographed on silica gel Fluka 60 with chloroform. Yield 7·1 g (48%) of crude *XIa*, m.p. 161°C (ref.[18] gives 162–163°C).

Further elution with a chloroform–ethanol–ammonia mixture (10 : 2 : 1) gave 1·7 g (9%) of crude base of 2-(4-dimethylaminobutyryl)-11-hydroxy-11-(3-dimethylaminopropyl)-6,11-

-dihydrodibenzo[*b*,*e*]thiepine (*XIIa*). Neutralization with oxalic acid and crystallization of the salt from ethanol afforded 0·55 g of homogeneous bis(hydrogen oxalate) hydrate. For $C_{29}H_{38}.N_2O_{10}S.H_2O$ (624·7) calculated: 55·76% C, 6·45% H, 4·48% N, 5·13% S; found: 55·78% C, 6·38% H, 4·54% N, 5·31% S.

Decomposition of the oxalate with ammonia and extraction with ether gave a homogeneous oily base *XIIa*. Mass spectrum, *m*/*z* (%): 426 (0·3), 408 (0·2), 375 (0·7), 350 (0·8), 276 (1·2),84 (9), 71 (7), 58 (100), 44 (19). ^{1}H NMR spectrum ($CDCl_3$): 2·26 s and 2·13 s, 6 H ($N(CH_3)_2$); 1·80—2·40 m, 10 H (CH_2); 3·01 t, 2 H ($COCH_2$); 3·72 bd and 4·72 bd, 1 + 1 H (AB system, $ArCH_2S$, J = 13); 7·20 m, 4 H (H-4, H-7, H-8, H-9); 7·62 dd, 1 H (H-3, J = 2; 9); 8·00 m, 1 H (H-10); 8·68 d, 1 H (H-1, J = 2). ^{13}C NMR spectrum ($CDCl_3$): 22·18 t (C—CH_2—C); 36·00 t ($COCH_2$); 36·45 t (CH_2S); 39·14 (HO—C); 44·82, 45·34 q ($N(CH_3)_2$); 59·08, 59·83 t (CH_2N); 74·99 s (C-11); 126·09 d (C-3); 127·13 d (C-10); 126·09, 128·04, 128·18 d (C-7, C-8, C-9); 128·85 d (C-4); 129·30 d (C-1); 133·78, 130·79 s (C-2, C-6a); 139·46 s (C-4a); 142·74, 145·21 s (C-10a, C-11a); 199·66 s (CO).

11-Hydroxy-11-(1-methyl-4-piperidyl)-6,11-dihydrodibenzo[*b*,*e*]thiepine-2-carbonitrile (*XIb*)

Grignard's reagent was prepared on reaction of 1·3 g Mg with 6·6 g of 4-chloro-1-methylpiperidine in 30 ml THF. After cooling to 10°C a solution of 6·1 g of *IVa* in 50 ml THF was added and the mixture was stirred at room temperature for 5 h. The next day it was decomposed with 50 ml of 20% NH_4Cl, diluted with 50 ml of benzene, filtered and the organic phase extracted with 100 ml of 10% HCl. The acid aqueous phase was alkalized with ammonia and the base extracted with chloroform. The residue after the working up of the extract was chromatographed on silica gel Fluka 60. Elution with chloroform gave 4·4 g (47%) of homogeneous *XIb* in the form of a 2 : 1 solvate with benzene, m.p. 219—221°C (benzene). UV spectrum: 296 (4·10), 234 infl. (3·94). IR spectrum: 733, 767, 826, 893 (4 and 2 vicinal and 1 isolated Ar-H); 1 490, 1 590, 3 030, 3 056, 3 088 (Ar); 2 225 (CN); 2 675, 2 733, 2 780 (N—CH_3); 3 400 (OH). ^{1}H NMR spectrum ($CDCl_3$): 1·30—3·50 m, 9 H (4 × CH_2, 1 × CH); 2·30 s, 3 H (NCH_3); 3·33 bs, 1 H (OH); 3·84 d and 4·78 d, 1 + 1 H (AB system, CH_2S, J = 13); 7·00—7·40 m, 8 H (H-3, H-4, H-7, H-8, H-9 and benzene); 7·88 m, 1 H (H-10); 8·18 d, 1 H (H-1, J = 2). For $C_{21}H_{22}N_2OS.0{\cdot}5\,C_6H_6$ (389·5) calculated: 74·00% C, 6·47% H, 7·19% N; found: 73·83% C, 6·59% H, 6·77% N.

11-(3-Dimethylaminopropylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepine-2-carboxylic Acid (*Vb*)

A mixture of 6·7 g of compound *XIa* and 100 ml of 20% HCl was refluxed for 14 h, cooled, and the crystallized compound filtered off under suction and recrystallized from ethanol–ether. Yield, 4·6 g (60%) of hydrochloride *Vb* (hemihydrate), m.p. 190—193°C (decomp.). UV spectrum 242 (4·10), 297 infl. (4·08). IR spectrum: 769, 790, 809, 867, 878 (4 and 2 vicinal and 1 isol. Ar-H); 1 670, 1 690, 1 715 (COOH); 3 120, 3 290 (OH); 1 550, 1 589, 3 010, 3 045 (Ar). ^{1}H NMR spectrum: 2·50 m, 2 H (C—CH_2—C); 2·67 s, 6 H ($N(CH_3)_2$); 3·38 m, 2 H (CH_2N); 3·75 d and 4·88 d, 1 + 1 H (AB system, $ArCH_2S$, J = 13); 6·00 t, 1 H (=CH—, J = 7); 7·10 d, 1 H (H-4, J = 9); 7·20—7·50 m, 4 H (H-7, H-8, H-9, H-10); 7·70 dd, 1 H (H-3, J = 2; 9); 7·88 d, 1 H (H-1, J = 2). For $C_{20}H_{22}ClNO_2S.0{\cdot}5\,H_2O$ (384·9) calculated: 62·41% C, 6·02% H, 3·64% N, 8·33% S; found: 62·31% C, 6·36% H, 3·85% N, 8·02% S.

11-(1-Methyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepine-2-carboxylic Acid (*Vc*)

A mixture of 4·75 g of compound *XIb* and 100 ml of 20% HCl was refluxed under stirring for 16 h. After cooling the separated crystals were filtered off under suction and recrystallized from

a mixture of ethanol, water and ether. Yield, 3·4 g (70%) of hydrochloride *Vc* (hemihydrate), m.p. 268—272°C (decomp.). IR spectrum: 760, 770 (Ar-H); 1 249, 1 320, 1 677, 3 330 (COOH); 2 400, 2 500, 2 545, 2 630, 2 650 (NH^+); 1 550, 1 590, 3 010, 3 060 (Ar). ^{1}H NMR spectrum: 2·00—3·00 m, 8 H (CH_2); 2·64 bs, 3 H (NCH_3); 3·78 d and 4·97 d, 1 + 1 H (AB system, CH_2S, J = 13); 7·00—7·80 m, 7 H (Ar-H). For $C_{21}H_{22}ClNO_2S.0{\cdot}5\,H_2O$ (396·9) calculated: 63·54% C, 5·84% H, 8·93% Cl, 3·53% N, 8·08% S; found: 63·55% C, 5·76% H, 9·01% Cl, 3·65% N, 8·13% S.

9-Bromo-11-(1-methyl-4-piperidyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*XIIIb*)

Grignard's reagent was prepared on reaction of 4·9 g Mg with 25 g 1-methyl-4-piperidyl chloride in 110 ml of THF. After cooling to 10°C a solution of 28·1 g of compound[18] *VIa* in 150 ml THF was added and the mixture stirred at room temperature for 5 h. After decomposition by dropwise addition of 220 ml of 20% NH_4Cl solution and dilution with 110 ml of benzene the organic phase was separated and extracted with two 250 ml portions of 10% H_2SO_4. The acid aqueous phase was alkalized with 20% NaOH solution and the base extracted with benzene. The residue, obtained by working up of the extract, was chromatographed on silica gel. Elution with chloroform–ethanol gave 23·8 g (64%) of crude *XIIIb* which was crystallized from ethanol, m.p. 189—191°C. ^{1}H NMR spectrum ($CDCl_3$): 1·20—2·20 m and 2·90 m, $\sum$ 8 H (CH_2); 2·30 s, 3 H (NCH_3); 3·14 s, 1 H (OH); 3·50 m, 1 H (CH—C—O); 3·83 d and 4·58 d, 1 + 1 H (AB system, SCH_2, J = 13); 6·90—7·30 m, 4 H (H-2, H-3, H-4, H-7); 7·35 dd, 1 H (H-8, J = 7; 2); 7·80 m, 1 H (H-1); 8·05 d, 1 H (H-10, J = 2). ^{13}C NMR spectrum ($CDCl_3$): 26·2 t, 25·99 t (C-3′, C-5′); 35·78 t (C-6); 38·92 d (C-4′); 46·61 q (NCH_3); 56·17 t (C-2′, C-6′); 78·65 s (C-11); 122·43 s (C-9); 125·56 d, 127·65 d, 129·97 d (C-2, C-3, C-4); 126·31 d (C-1); 129·45 d (C-10); 129·45 d (C-4a); 131·09 d (C-8); 131·09 s (C-6a); 131·84 d (C-7); 140·88 s (C-11a); 146·48 s (C-10a). For $C_{20}H_{22}BrNSO$ (404·4) calculated: 59·40% C, 5·48% H, 19·76% Br, 3·46% N, 7·93% S; found: 59·49% C, 5·50% H, 19·51% Br, 3·42% N, 8·04% S.

A continuation of the elution with the same mixture and working up afforded 1·1 g of crude 11-(1-methyl-4-piperidyl)-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-ol (*Xb*), m.p. 179—182°C (ethanol) (ref.[1] gives 186—186·5°C). Mass spectrum, *m/z* (%): 325 (M^+, $C_{20}H_{23}NOS$). IR spectrum: 746, 755 (4 vicinal Ar-H); 1 140, 3 300 (OH); 1 559, 1 584, 3 045 (Ar); 2 800 (NCH_3).

11-Hydroxy-11-(1-methyl-4-piperidyl)-6,11-dihydrodibenzo[*b*,*e*]-thiepine-9-carbonitrile (*XIVb*)

A mixture of 11·5 g of compound *XIIIb*, 7·2 g of CuCN and 40 ml of HMPT was heated under stirring at 150°C for 15 h. After cooling the reaction mixture was stirred with benzene and ammonia, filtered and the organic phase of the filtrate washed with water, dried and evaporated. The residue was chromatographed on a column of alumina (activity III) with benzene, to afford 8·0 g of crude base *XIVb* (80%) which would not crystallize. An analytical sample of the amorphous base (hydrate, m.p. 95—105°C) was obtained by alkalization of an aqueous solution of oxalate with ammonia. UV spectrum: 233 infl. (4·25), 255 infl. (3·91). IR spectrum: 746, 838, 843, 888 (4 and 2 vicinal and 1 isolated Ar-H); 1 483, 1 560, 1 572, 1 600, 3 050 (Ar); 2 225 (CN); 2 795 (NCH_3); 3 370 (OH). ^{1}H NMR spectrum ($CDCl_3$): 1·10—3·50 m, 9 H (CH_2 and CH); 2·35 s, 3 H (NCH_3); 3·90 d and 4·62 d, 1 + 1 H (AB system, CH_2S, J = 13); 7·15 m, 3 H (H-2, H-3, H-4); 7·23 d, 1 H (H-7, J = 8); 7·50 dd, 1 H (H-8, J = 1·5; 8); 7·84 m, 1 H (H-1); 8·28 d, 1 H (H-10, J = 1·5). ^{13}C NMR spectrum ($CDCl_3$): 25·84 t, 25·47 t (C-3′, C-5′); 36·15 t (C-6); 36·90 d, 39·14 d (C-4 eq. and ax.); 46·01 q (NCH_3); 55·80 t (C-2′, C-6′); 78·73 s (C-11); 111·89 s (C-9); 118·92 s (CN); 126·68 d (C-1); 126·01 d, 127·88 d, 130·19 d, 130·94 d (C-2, C-3, C-4, C-7); 130·94 d (C-10); 130·94 s (C-4a); 131·54 d (C-8); 135·95 s (C-6a); 140·95 s, 145·73 s (C-10a, C-11a).

For $C_{21}H_{22}N_2OS.H_2O$ (368·5) calculated: 68·45% C, 6·56% H, 7·60% N, 8·70% S; found: 68·69% C, 6·50% H, 7·81% N, 8·45% S.

11-(1-Methyl-4-piperidylidene)-6,11-dihydrodibenzo[*b*,*e*]thiepine-9-carboxylic Acid (*VIIIc*)

A solution of 4·2 g of hydrate of *XIVb* in 50 ml of 20% HCl was refluxed for 16 h, the separated amorphous substance was filtered off under suction (4 g, m.p. 214—219°C) and crystallized from an ether–ethanol mixture to afford 2·25 g (44%) of hydrochloride *VIIIc* (solvate with 1 molecule of water and 1 molecule of ethanol), with m.p. 213—218°C. UV spectrum: 259 infl. (4·01), 302 infl. (3·41). IR spectrum: 730, 747, 760, 785, 883 (4 and 2 vicinal and 1 isolated Ar-H); 1 571, 1 587, 1 600 (Ar); 1 709 (COOH); 2 505, 2 540, 2 575, 2 650 (NH^+); 3 245 (OH). ^{1}H NMR spectrum: 2·00—3·00 m, 8 H (CH_2); 2·76 bs, 3 H (NCH_3); 3·85 bd and 4·98 bd, 1 + 1 H (AB system, CH_2S, J = 13); 7·00—8·00 m, 7 H (Ar-H). For $C_{21}H_{22}ClNO_2S.C_2H_5OH.H_2O$ (452·0) calculated: 61·11% C, 6·69% H, 3·10% N, 7·09% S; found: 61·55% C, 6·57% H, 3·32% N, 7·37% S.

4-(3-Dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepine-6-carbonitrile (*XXb*)

A mixture of 8·3 g of base[7] *XIXb*, 4·7 g CuCN and 20 ml of HMPT was heated under stirring at 150°C. After cooling it was partitioned between benzene and ammonia, filtered, the organic phase separated, washed with water and evaporated. The residue was chromatographed on alumina (activity III) with benzene. Crude starting base *XIXb* (0·65 g) was eluted first, which was identified as oxalate, m.p. 201—203°C (ethanol–ether). ^{1}H NMR spectrum: 2·52 m, 2 H (C—CH_2—C); 2·65 bs, 6 H ($N(CH_3)_2$); 3·14 bt, 2 H (NCH_2); 4·00 bd and 4·60 bd, 1 + 1 H (CH_2S); 6·08 t, 1 H (=CH—); 7·09 d, 1 H (H-3, J = 5); 7·20—7·60 m, 4 H (Ar-H). For $C_{18}H_{19}.BrNO_2S_2$ (425·4) calculated: 50·82% C, 4·50% H, 3·29% N; found: 50·69% C, 4·53% H, 3·05% N.

Further elution with benzene afforded 1·0 g (14%) of crude base *XXb* from which hydrogen oxalate hemihydrate (m.p. 222—223°C, from acetone–ether) was prepared by neutralization with oxalic acid. ^{1}H NMR spectrum: 2·40 m, 2 H (C—CH_2—C); 2·66 s, 6 H ($N(CH_3)_2$); 3·14 t, 2 H (NCH_2); 4·18 bs and 4·90 bs, 1 + 1 H (CH_2S); 6·12 t, 1 H (=CH—); 7·11 d, 1 H (H-3, J = 5); 7·42 d, 1 H (H-2, J = 2); 7·68 d, 1 H (H-8, J = 8·5); 7·72 d, 1 H (H-5, J = 2); 7·88 dd, 1 H (H-7, J = 8·5; 2). 7·72 d, 1 H (H-5, J = 2); 7·88 dd, 1 H (H-7, J = 8·5; 2). For $C_{20}H_{20}N_2.O_4S_2.0{\cdot}5\,H_2O$ (425·5) calculated: 56·45% C, 4·97% H, 6·59% N, 15·07% S; found: 56·52% C, 4·87% H, 6·29% N, 14·66% S.

2-Bromo-4,9-dihydrothieno[2,3-*c*]-2-benzothiepin-4-one (*XVIa*)

A solution of 31·8 g of bromine in 100 ml of acetic acid was added to a solution of 46·0 g of compound[7] *XVa* in 400 ml of acetic acid, over 10 min. The mixture was stirred for 15 min at 20°C, poured into 2 l of water, the separated product was filtered off under suction and crystallized from ethanol. Yield, 50·2 g (81%), m.p. 106—109°C. UV spectrum: 263 (4·27), 352 (3·56). IR spectrum: 760 (Ar-H); 852 (H in thiophene); 1 508, 1 571, 1 590, 3 100 (Ar); 1 613 (CO). Mass spectrum, *m*/*z* (%): 310 (M^+, $C_{12}H_7BrOS_2$, 35), 281 (6), 277 (12), 249 (5), 231 (100), 203 (41). For $C_{12}H_7BrOS_2$ (311·2) calculated: 46·31% C, 2·27% H, 25·68% Br, 20·60% S; found: 46·75% C, 2·34% H, 25·42% Br, 20·09% S.

4-Oxo-4,9-dihydrothieno[2,3-*c*]-2-benzothiepine-2-carbonitrile (*XVIIa*)

A mixture of 9·8 g of compound *XVIa*, 6·0 g of CuCN and 20 ml of HMPT was heated at 140°C

for 14 h, then partitioned between benzene and dilute ammonia, the organic phase was decanted from the precipitated polymers and washed with water. After drying and evaporation of the organic phase the residue was chromatographed on silica gel Fluka 60. Elution with benzene gave only 0·15 g (2%) of *XVIIa*, m.p. 140–146°C (ethanol). IR spectrum: 729, 769 (Ar-H); 870 (H in thiophene); 1 515, 1 590, 3 110 (Ar); 1 624 (CO); 2 210 (CN). ^{1}H NMR spectrum ($CDCl_3$): 4·25 s, 2 H (CH_2S); 7·20–7·90 m, 4 H (Ar-H); 8·20 s, 1 H (H-3). For $C_{13}H_7NOS_2$ (257·3) calculated: 60·68% C, 2·74% H, 5·44% N; found: 60·44% C, 2·88% H, 5·27% N.

2-Bromo-4-(3-dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-
-2-benzothiepine (*XVIb*)

Grignard's reagent was prepared on reaction of 4·0 g of Mg with 20·0 g of 3-dimethylaminopropyl chloride in 60 ml of THF. After cooling to 10°C a solution of 24·4 g of ketone *XVIa* in 60 ml of THF was added dropwise and the mixture was stirred at room temperature for 1 h. After decomposition with 150 ml of 20% NH_4Cl solution it was diluted with chloroform and the aqueous phase separated, then extracted twice more with 100 ml chloroform and the combined organic phases were extracted with 350 ml of 5% HCl. The acid extract was alkalized with 20% NaOH solution and the base extracted with chloroform. Affter work-up the residue was chromatographed on alumina (activity III) with benzene, to give first 5·7 g of crude base *XVIb* (18%) which was purified by conversion to hydrogen oxalate and crystallization from 80% ethanol (3·2 g, m.p. 212–213°C). ^{1}H NMR spectrum: 2·43 m, 2 H (C—CH_2—C); 2·65 s, 6 H ($N(CH_3)_2$); 3·12 bt, 2 H (NCH_2); 4·40 broad peak, 2 H (CH_2S); 6·08 t, 1 H (=CH—); 7·24 s, 1 H (H-3); 7·40 m, 4 H (Ar-H). For $C_{19}H_{20}BrNO_4S_2$ (470·4) calculated: 48·51% C, 4·29% H, 16·99% Br, 2·98% N, 13·63% S; found: 48·90% C, 4·53% H, 16·44% Br, 3·00% N, 13·34% S.

Further elution with benzene gave 3·5 g of an intermediary fraction, followed by 1·5 g of pure *XVb* (cf. ref.[7]). Hydrogen oxalate, m.p. 202–204°C (ethanol–ether). ^{1}H NMR spectrum: 2·40 m, 2 H (C—CH_2—C); 2·64 s, 6 H ($N(CH_3)_2$); 3·10, 2 H (NCH_2); 4·05 bs and 4·52 bs, 1 + 1 H (CH_2S); 6·04 t, 1 H (=CH—); 7·10 d, 1 H (H-3, J = 5); 7·35 d, 1 H (H-2, J = 5); 7·20–7·50 m, 4 H (Ar-H). For $C_{19}H_{21}NO_4S_2$ (391·5) calculated: 58·29% C, 5·41% H, 3·58% N, 16·38% S; found: 57·82% C, 5·58% H, 3·55% N, 16·09% S.

4-(3-Dimethylaminopropylidene)-4,9-dihydrothieno[2,3-*c*]-
-2-benzothiepine-2-carboxylic Acid (*XVIIIb*)

A 1·46M solution of butyllithium in hexane was added to a solution of 4·7 g of compound *XVIb* in 30 ml of ether at −70° to −60°C over 2 min. The mixture was stirred for another 2 min at the same temperature and then poured into a mixture of solid carbon dioxide and ether. After evaporation of CO_2 the ethereal phase was extracted with water, the combined aqueous phases were neutralized with acetic acid and the separated substance was crystallized from a mixture of benzene and ethanol. Yield 2·15 g (46%), m.p. 150–170°C (2 : 1 solvate with benzene). For $C_{18}H_{19}NO_2S_2.0{\cdot}5\,C_6H_6$ (384·5) calculated: 65·59% C, 5·77% H, 3·64% N; found: 65·63% C, 5·84% H, 3·29% N. Neutralization of the solution of the base *XVIIIb* in ethanol with an ethereal solution of hydrogen chloride gave hydrochloride hydrate, m.p. 130–150°C. UV spectrum: 252 (4·16), 326 (4·05). IR spectrum: 763, 865 (Ar-H); 1 531 (Ar); 1 685 (COOH); 2 460, 2 620, 2 670 (NH^+); 3 360 (OH). ^{1}H NMR spectrum: 2·20–3·00 m, 4 H (CH_2); 2·70 bs, 6 H ($N(CH_3)_2$); 4·05 bd and 4·80 bd, 1 + 1 H (AB system, CH_2S, J = 13); 6·20 t, 1 H (=CH—); 7·20–7·60 m, 4 H (Ar-H); 7·76 s, 1 H (H-3). For $C_{18}H_{22}ClNO_3S_2$ (400·0) calculated: 54·05% C, 5·54% H, 3·50% N, 16·03% S; found: 53·92% C, 5·47% H, 3·50% N, 15·81% S.

2-Bromo-4-(1-methyl-4-piperidylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepine (*XVIc*)

Bromine (6·8 g) in acetic acid (20 ml) was added dropwise over 10 min to a solution of hydrochloride[9] *XVc* in 120 ml of acetic acid and the mixture was stirred at room temperature for 3 h. It was poured into water, alkalized with a 20% NaOH solution and extracted with benzene. The residue, which was obtained by working up the extract, was chromatographed on alumina (activity III). Elution with benzene gave 10·4 g (62%) of base *XVIc*, m.p. 132·5–133·5°C. UV spectrum: 240 (4·26), 308 (3·90). IR spectrum: 760, 830 (Ar-H); 1510 (Ar), 2770 (NCH_3). ^{1}H NMR spectrum ($CDCl_3$): 2·20 m, 4 H (H-3′, H-5′); 2·58 m, 4 H (H-2′, H-6′); 2·30 s, 3 H (NCH_3); 3·50 d and 4·94 d, 1 + 1 H (AB system, CH_2S, J = 13); 6·71 s, 1 H (H-3); 7·00–7·40 m, 4 H (Ar-H). For $C_{18}H_{18}BrNS_2$ (392·4) calculated: 55·10% C, 4·62% H, 20·37% Br, 3·58% N, 16·34% S; found: 55·56% C, 4·64% H, 20·09% Br, 3·61% N, 16·06% S. (+)-Hydrogen tartrate (hemihydrate), m.p. 126–130°C (ethanol). For $C_{22}H_{23}BrNO_6S_2.0{\cdot}5\,H_2O$ (551·5) calculated: 47·91% C, 4·57% H, 14·49% Br, 2·54% N, 11·63% S; found: 48·58% C, 4·77% H, 14·27% Br, 2·48% N, 11·44% S.

4-(1-Methyl-4-piperidylidene)-4,9-dihydrothieno[2,3-*c*]-2-benzothiepine-2-carboxylic Acid (*XVIIIc*)

A 1·46M solution of butyllithium in hexane was added to a solution of 4·55 g of compound *XVIc* in a mixture of 50 ml of ether and 30 ml of THF at −70 to −60°C over 2 min and the mixture was stirred for another 2 min. It was poured onto a solid CO_2–ether mixture and after evaporation of CO_2 the organic layer was extracted with water. The combined aqueous phases were neutralized with acetic acid and the precipitated substance was crystallized from benzene–ethanol mixture. Yield, 2·2 g (53%), m.p. 249–252°C. UV spectrum: 251 (4·19), 315 (4·02). IR spectrum: 774 (Ar-H), 1483, 1525, 3035, 3055 (Ar); 1608 (COO^-); 2450 (NH^+). ^{1}H NMR spectrum: 2·00–3·20 m, 8 H (CH_2); 2·30 s, 3 H (NCH_3); 3·90 d and 4·82 d, 1 + 1 H (AB system, CH_2S, J = 13·0); 7·00–7·60 m, 5 H (Ar-H). For $C_{19}H_{19}NO_2S_2$ (357·5) calculated: 63·83% C, 5·36% H, 3·92% N, 17·94% S; found: 63·77% C, 5·23% H, 3·84% N, 17·44% S.

Hydrochloride hemihydrate, m.p. 223–226°C (ethanol–ether). Mass spectrum, *m/z* (%): 357 (M^+, $C_{19}H_{19}NO_2S_2$, 0·1), 324 (2), 70 (28), 45 (100). For $C_{19}H_{20}ClNO_2S_2.0{\cdot}5\,H_2O$ (403·0) calculated: 56·63% C, 5·25% H, 8·80% Cl, 3·48% N, 15·91% S; found: 56·76% C, 5·28% H, 9·11% Cl, 3·37% N, 15·70% S.

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