NEUROTROPIC AND PSYCHOTROPIC AGENTS. LXV.*

8-CHLORO AND 8-ISOPROPYL-6-PIPERAZINOBENZO[*b*]PYRIDO[3,2-*f*] THIEPIN

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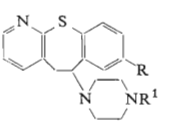
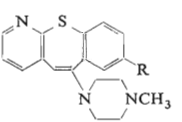
Reaction of 2-chloronicotinic acid with 4-chloro and 4-isopropylthiophenol yielded acids *VIa* and *VIb* which were converted in four steps to acids *Xa* and *Xb*. Cyclization with polyphosphoric acid yielded 8-chloro- and 8-isopropyl-5*H*-benzo[*b*]pyrido[3,2-*f*]thiepin-6-one (*XIIa*, *XIIb*) which were converted by conventional techniques to the piperazine derivatives *Ia*–*Va*, *Ib* and *Vb*. The enamines *Va* and *Vb* show a pronounced neuroleptic activity; in general, compounds of this series are substantially less effective than the analogous dibenzo[*b*,*f*]thiepins.

In a previous communication of this series[1] we described the preparation of 6-piperazinobenzo[*b*]pyrido[3,2-*f*]thiepin derivatives *I*–*V* (R = H) which represent 4-aza analogues of the centrally active and partly neuroleptically effective 10-piperazinodibenzo-[*b*,*f*]thiepin derivatives[2,3]. It was found that the pyridine derivatives[1] are centrally much less active than their benzene analogues. In view of the fact that in the dibenzo[*b*,*f*]thiepin series it was possible to increase the activity by introducing a suitable substituent into position 8 (ref.[4,5]) it was thought useful to verify the effect of a similar change on the activity in the benzo[*b*]pyrido[3,2-*f*]thiepin series. As substituent we used the proven chlorine atom[4] and further the isopropyl group and thus prepared compounds *Ia*–*Va*, *Ib* and *Vb*. During the preparation we used



I, $R^1 = CH_3$
II, $R^1 = (CH_2)_3OH$
III, $R^1 = COOC_2H_5$
IV, $R^1 = H$



V

In formulae: *a*, R = Cl, *b*, R = $CH(CH_3)_2$

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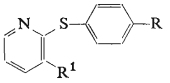
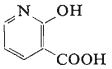
the methodically similar approach as in a previous study of the series of benzo[*b*]pyrido[3,2-*f*]thiepin derivatives[1].

The method of Mann and Reid[6] was employed for the reaction of 2-chloronicotinic acid[7] with 4-chlorothiophenol[8] and 4-isopropylthiophenol[9] to prepare the acids *VIa* and *VIb*. In the case of the isopropyl derivative it was found necessary to modify the method by using dimethylformamide as the reaction medium, since simple heating of the mixture of 2-chloronicotinic acid with 4-isopropylthiophenol led only partly to the conversion to the acid *VIb* when the processing of the reaction mixture was accompanied by hydrolysis of the starting 2-chloronicotinic acid to 2-hydroxynicotinic acid[7] (*XI*) which represented the major product. Reduction of acids *VIa* and *VIb* with sodium bis(2-methoxyethoxy)dihydroaluminate in benzene resulted in high yields of 2-(4-chlorophenylthio)-3-pyridylcarbinol (*VIIa*) and its isopropyl analogue *VIIb*. On heating with excess thionyl chloride the alcohols yielded the corresponding chloro derivatives *VIIIa* and *VIIIb* which reacted with potassium cyanide in aqueous ethanol to the nitriles *IXa* and *IXb*. Alkaline hydrolysis then yielded the 3-pyridylacetic acids *Xa* and *Xb*. On cyclization with polyphosphoric acid at 175



VI, $R^1 = COOH$
VII, $R^1 = CH_2OH$
VIII, $R^1 = CH_2Cl$
IX, $R^1 = CH_2CN$
X, $R^1 = CH_2COOH$

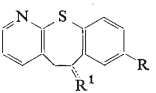


XI

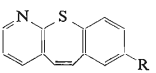
to 190°C the acids *Xa* and *Xb* gave rise to somewhat lower yields (than in the unsubstituted series[1]) of ketones *XIIa* and *XIIb*, *i.e.* 8-chloro- and 8-isopropyl-5*H*-benzo[*b*]pyrido[3,2-*f*]thiepin-6-one. The usual reductions with sodium borohydride in aqueous ethanol led to alcohols *XIIIa* and *XIIIb* which were heated with excess thionyl chloride to convert them to the hydrochlorides of the chloro derivatives *XIVa* and *XIVb*.

Substitution reactions of these products with excess 1-methylpiperazine or with 1-(3-hydroxypropyl)piperazine[10] in boiling chloroform led to the piperazine derivatives *Ia*, *Ib* and *IIa*. Substitution reaction of hydrochloride of *XIVa* with excess 1-(ethoxycarbonyl)piperazine[11] was carried out without solvent, by heating to 125 to 130°C; this resulted in *IIIa*. The substitution reactions are accompanied by elimination reactions which result in 8-chlorobenzo[*b*]pyrido[3,2-*f*]thiepin (*XVa*) and in 8-isopropylbenzo[*b*]pyrido[3,2-*f*]thiepin (*XVb*), the compound *XVb* having been prepared, due to difficulties with isolation from the reaction mixture, by de-

hydrochlorination of the chloro derivative *XIVb* by an ethanolic solution of potassium hydroxide. Alkaline hydrolysis of carbamate *IIIa* yielded the secondary amine *IVa*. Reaction of *XIIa* and *XIIb* with 1-methylpiperazine and titanium tetrachloride in boiling benzene led to enamines *Va* and *Vb*.



XII, $R^1 = O$
XIII, $R^1 = OH$
XIV, $R^1 = Cl$



XV

The piperazine derivatives *Ia Ib*, *Va*, *Vb* were tested pharmacologically with a view to the assumed central depressant and neuroleptic activity (for methods see ref.[12]) in the form of salts, the values shown referring to bases. The results obtained are summarized in Table I which includes also octoclothepin, *i.e.* 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (for parenteral application as methanesulfonate[13], for oral application as maleate[4]). Besides tests of acute toxicity for mice, the central depressant activity was tested in the rotating-rod test (effect on motor coordination) in mice, and the neuroleptic activity by the cataleptic effect on rats. The results are shown in the Table in the form of the usual mean lethal doses LD_{50} and in the form of the mean effective doses ED_{50}, in mg/kg throughout.

The values of Table I indicate that from the point of view of activity of the compounds prepared only enamines *Va* and *Vb* can be compared with octoclothepin[4,13]; the chloro derivative *Va* is a 5 times weaker depressant and a twice weaker cataleptic

TABLE I
Pharmacological Properties of Piperazine Derivatives (in mg/kg)

Compound	Application[a]	Acute toxicity LD_{50}	Rotating rod ED_{50}	Catalepsy ED_{50}
Ia	*i.v.*	19·5	1·4	>10[b] (i.p.)
Ib	*p.o.*	240	19·0	44
Va	*i.v.*	[c]	0·35	5·8 (i.p.)
Vb	*p.o.*	175	2·7	24
Octoclothepin	*i.v.*	46·3	0·06	2·4 (i.p.)
	p.o.	78	2·2	4·3

[a] *i.v.* = intravenously, *i.p.* = intraperitoneally, *p.o.* = *per os*. [b] The dose shown caused catalepsy of 30% animals. [c] Toxicity could not be determined because of instability of the enamine.

than octoclothepin while the isopropyl derivative *Vb* is practically equivalent to octoclothepin in its depressant activity but is a five times weaker cataleptic. The dihydro derivatives *Ia* and *Ib* exhibit depressant and cataleptic activity in only relatively high doses. The work has thus fully confirmed the conclusion of the previous study in the series of 6-piperazinobenzo[*b*]pyrido[3,2-*f*]thiepins[1]. Replacement of =CH— in position 4 of the neuroleptically effective 10-piperazinodibenzo[*b*,*f*]thiepins with a nitrogen atom has an unfavourable effect both on the depressant and on the cataleptic activity.

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block; the samples were dried in the usual way. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in nujol, unless stated otherwise) in a Unicam SP 200 G spectrophotometer and the NMR spectra (in deuteriochloroform, unless stated otherwise) in a ZKR 60 (Zeiss, Jena) spectrometer.

2-(4-Chlorophenylthio)nicotinic Acid (*VIa*)

2-Chloronicotinic acid[7] (m.p. 185°C; analytically pure, it has a m.p. 192—193°C) (10·0 g) was added to 18·4 g 4-chlorothiophenol[8] at 80°C and the mixture was heated for 2 h to 140°C when vigorous reaction has taken place. After cooling, the mixture was dissolved in excess saturated solution of $NaHCO_3$, the solution was filtered with charcoal, the filtrate was washed with ether and made acid with dilute hydrochloric acid; 14·5 g (86%), m.p. 223—225°C (ethanol). IR spectrum: 720, 750, 765 (3 vicinal pyridine C—H), 815, 830 (2 vicinal benzene C—H), 1290 (carboxyl CO), 1560, 1575 (COO^-), 1690 cm^{-1} (Ar—COOH). For $C_{12}H_8ClNO_2S$ (265·7) calculated: 54·24% C, 3·03% H, 13·34% Cl, 5·27% N, 12·07% S; found: 54·27% C, 3·11% H, 13·73% Cl, 5·04% N, 12·20% S.

2-(4-Isopropylphenylthio)nicotinic Acid (*VIb*)

2-Chloronicotinic acid[7] (110 g) was added to a solution of 130 g 4-isopropylthiophenol[9] in 700 ml dimethylformamide and the mixture was refluxed under stirring for 2·5 h in a 140°C bath. After cooling, it was diluted with 3 liters water and, after standing overnight, the precipitated product was filtered, washed with water and dried in air; 170 g (89%), m.p. 180—186°C. Recrystallization from ethanol yielded a product melting at 189—193°C. IR spectrum: 766 (3 vicinal pyridine C—H), 830 (2 vicinal benzene C—H), 930 and 1295 (COOH), 1560 and 1580 (Ar), *1690* (Ar—COOH), 2555 and 2650 cm^{-1} (COO^- of an internal salt). NMR spectrum (CD_3SOCD_3): δ 10·34 (bs, 1 H, disappears on deuterization, COOH), 8·25 (m, 2 H, protons in position 4 and 6 of pyridine), 7·45 (d, J = 9·0 Hz, 2 H, protons in positions 3 and 5 of benzene), 7·24 (d, J = = 9·0 Hz, 2 H, protons in positions 2 and 6 of benzene), 7·15 (dd, 1 H, proton in position 5 of pyridine), 2·87 (m, 1 H, CH of isopropyl), 1·20 (d, J = 6·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{15}H_{15}NO_2S$ (273·3) calculated: 65·90% C, 5·53% H, 5·12% N, 11·73% S; found: 66·24% C, 5·68% H, 5·14% N, 11·77% S.

In an attempt at preparing this compound by a procedure analogous to that of preparing *VIa*, the reaction mixture obtained was only partly soluble in a solution of $NaHCO_3$ and hence a dilute solution of sodium hydroxide was used for the dissolving. The crude product obtained by acidification was purified for analysis by repeated crystallization from ethanol; m.p. 255 to

258°C. This m.p. and its analysis are in agreement with the properties of 2-*hydroxynicotinic acid*[7] (*XI*). For $C_6H_5NO_3$ (139·1) calculated: 51·80% C, 3·62% H, 10·07% N; found: 51·86% C, 3·62%H, 10·15% N.

2-(4-Chlorophenylthio)-3-pyridylcarbinol (*VIIa*)

A suspension of 10·0 g acid *VIa* in 70 ml benzene was stirred and treated dropwise with 25 ml of a 65% benzene solution of sodium bis(2-methoxyethoxy) dihydroaluminate at room temperature. After 30 min of standing it was decomposed with 50 ml 10% NaOH, the benzene phase was dried with $MgSO_4$ and evaporated. The residue (9·3 g, 98%) crystallized; m.p. 95—96°C (benzene–light petroleum). IR spectrum: 742 and 748 (3 vicinal pyridine C—H), 800, 822 and 832 (2 vicinal benzene C—H), 1 010 and 1 021 (CH_2OH), 1 562 and 1 580 (Ar), 3 350 cm^{-1} (OH). For $C_{12}H_{10}ClNOS$ (251·7) calculated: 57·26% C, 4·00% H, 14·08% Cl, 5·56% N, 12·74% S; found: 57·23% C, 4·02% H, 14·28% Cl, 5·26% N, 12·67% S.

2-(4-Isopropylphenylthio)-3-pyridylcarbinol (*VIIb*)

This was prepared by a reduction of acid *VIb* in analogy to the preceding case in a 85% yield; m.p. 89—92°C (benzene–light petroleum). IR spectrum: 790 (3 vicinal pyridine C—H), 832 (2 vicinal benzene C—H), 1 050 (CH_2OH), 1 570, 1 580 (Ar), 3 330 cm^{-1} (OH). NMR spectrum: δ 8·25 (dd, J = 5·0; 2·0 Hz, 1 H, aromatic proton in position 6 of pyridine), 7·70 (dd, J = 7·0; 2·0 Hz, 1 H, aromatic proton in position 4 of pyridine), 7·45 (d, J = 9·0 Hz, 2 H, aromatic protons in positions 3 and 5 of benzene), 7·24 (d, J = 9·0 Hz, 2 H, aromatic protons in positions 2 and 6 of benzene), 7·08 (dd, 1 H, aromatic proton in position 5 of pyridine), 4·65 (d, after deuterization s, 2 H, CH_2O), 3·15 (m, disappears after deuterization, 1 H, OH), 2·85 (m, J = 6·0 Hz, 1 H, CH of isopropyl), 1·21 (d, J = 6·0 Hz, 6 H, 2 CH_3 of isopropyl). For $C_{15}H_{17}NOS$ (259·4) calculated: 69·46% C, 6·61% H, 5·40% N, 12·36% S; found: 69·54% C, 6·76% H, 5·04% N, 12·56% S.

2-(4-Chlorophenylthio)-3-chloromethylpyridine (*VIIIa*)

A mixture of 300 ml thionyl chloride and 158 g alcohol *VIIa* was refluxed for 6 h. The thionyl chloride was then evaporated for the most part under reduced pressure and the residue was combined with 100 ml benzene. A *hydrochloride* of the product crystallized (142 g), the sample of which was recrystallized for analysis from a mixture of ethanol and ether; m.p. 132—133°C. For $C_{12}H_{10}Cl_3NS$ (306·6) calculated: 47·00% C, 3·28% H, 34·69% Cl, 4·57% N, 10·46% S; found: 47·29% C, 3·29% H, 34·45% Cl, 4·78% N, 10·52% S.

Decomposition of the hydrochloride, overlayered with benzene, with 10% NaOH, and treatment of the benzene layer led to 124 g (73%) base, melting at 76—77°C (light petroleum). NMR spectrum: δ 8·46 (dd, J = 5·0; 2·0 Hz, 1 H, aromatic proton in position 6 of pyridine), 7·80 (dd, J = 8·0; 2·0 Hz, 1 H, aromatic proton in position 4 of pyridine), 7·60 and 7·40 (2 d, J = 9·0 Hz, 4 H, aromatic protons of benzene), 7·25 and 7·13 (dd, J = 8·0; 5·0 Hz, 1 H, aromatic proton in position 5 of pyridine), 4·75 (s, 2 H, CH_2Cl). For $C_{12}H_9Cl_2NS$ (270·2) calculated: 53·35% C, 3·35% H, 26·25% Cl, 5·18% N, 11·87% S; found: 53·34% C, 3·34% H, 26·21% Cl, 5·18% N, 12·06% S.

2-(4-Isopropylphenylthio)-3-chloromethylpyridine (*VIIIb*)

Similarly to the preceding case, 5·2 g alcohol *VIIb* yielded the oily hydrochloride, from which the base has been liberated (5·4 g, 97%), also noncrystalline. It was used for further work in the crude

state. To characterize it, a picrate was prepared, m.p. 124–127°C (ethanol). For $C_{21}H_{19}ClN_4O_7S$ (506·9) calculated: 49·76% C, 3·78% H, 6·99% Cl, 11·05% N, 6·33% S; found: 50·40% C, 3·81% H, 7·06% Cl, 11·28% N, 6·69% S.

2-(4-Chlorophenylthio)-3-pyridylacetonitrile (*IXa*)

A mixture of a solution of 60 g KCN in 80 ml water and 120 g chloride *VIIIa* in 500 ml ethanol was refluxed under stirring for 6 h. After partial evaporation at reduced pressure the residue was combined with 500 ml water and the mixture was extracted with benzene. The extract was washed with water, dried with $MgSO_4$, filtered with charcoal and evaporated. The residue (128 g, 96%) is a crude product which was purified for analysis by crystallization from methanol; m.p. 111–113°C. UV spectrum: λ_{max} 220 nm (log ε 4·20), 245 nm (4·07), 259 nm infl. (3·97), 285 nm infl. (3·77). IR spectrum (KBr): 2245 and 2265 cm^{-1} (CN). NMR spectrum: δ 8·49 (dd, J = 5·0; 2·0 Hz, 1 H, aromatic proton in position 6 of pyridine), 7·88 (dd, J = 8·0; 2·0 Hz, 1 H, aromatic proton in position 4 of pyridine), 7·49 (s, 4 H, aromatic protons of benzene), 7·30 and 7·16 (dd, J = = 8·0; 5·0 Hz, 1 H, aromat. proton in position 5 of pyridine), 3·85 (s, 2 H, CH_2). For $C_{13}H_9ClN_2S$ (260·7) calculated: 59·88% C, 3·48% H, 13·60% Cl, 10·74% N, 12·30% S; found: 59·77% C, 3·49% H, 13·98% Cl, 10·69% N, 12·61% S.

2-(4-Isopropylphenylthio)-3-pyridylacetonitrile (*IXb*)

This was prepared from crude chloride *VIIIb* as in the preceding case; the product does not crystallize, b.p. 170–172°C/1 Torr. IR spectrum (film): 783 (3 vicinal pyridine C—H), 822 (2 vicinal benzene C—H), 1558, 1575 (Ar), 2245 cm^{-1} (CN). For $C_{16}H_{16}N_2S$ (268·4) calculated: 71·60% C, 6·01% H, 10·44% N, 11·95% S; found: 71·56% C, 6·26% H, 9·80% N, 12·19% S.

2-(4-Chlorophenylthio)-3-pyridylacetic Acid (*Xa*)

A solution of 120 g KOH in 150 ml water was added to a solution of 120 g nitrile *IXa* in 750 ml ethanol and the mixture was refluxed for 8 h. After cooling, it was diluted with 500 ml water, filtered with charcoal and the filtrate was made acid with dilute hydrochloric acid to the formation of stable turbidity. On standing, 112·8 g (88%) precipitated; after recrystallization from ethanol it melts at 168–170°C. UV spectrum: λ_{max} 247 nm (log ε 4·02), 287 nm infl. (3·76). IR spectrum: 763 (C—H of pyridine), 818 (C—H of benzene), 1335 (COOH), 1572 (Ar), 1695 (COOH) and 2500 cm^{-1} (NH^+). For $C_{13}H_{10}ClNO_2S$ (279·7) calculated: 55·82% C, 3·60% H, 12·67% Cl, 5·00% N, 11·46% S; found: 56·01% C, 3·65% H, 12·94% Cl, 4·99% N, 11·50% S.

2-(4-Isopropylphenylthio)-3-pyridylacetic Acid (*Xb*)

This was prepared from nitrile *IXb* similarly to the preceding case in a 84% yield; m.p. 149–150°C (ethanol). IR spectrum: 760 (C—H of pyridine), 810 and 820 (C—H of benzene), 1330 and 1695 (COOH), 1500 and 1571 (Ar), 2500 cm^{-1} (NH^+). For $C_{16}H_{17}NO_2S$ (287·4) calculated: 66·87% C, 5·96% H, 4·87% N, 11·16% S; found: 66·65% C, 6·20% H, 4·81% N, 11·23% S.

8-Chloro-5*H*-benzo[*b*]pyrido[3,2-*f*]thiepin-6-one (*XIIa*)

A mixture of 300 g polyphosphoric acid (commercial product) and 30·0 g acid *Xa* was heated for 24 h at 180–200°C. After cooling, it was decomposed with 1 liter ice-cold water, the mixture was made alkaline with KOH and extracted with benzene. The extract was washed with 5% KOH,

dried with Na_2SO_4 and evaporated. The residue (14·8 g, 53%) crystallized; m.p. 194—196°C (benzene). UV spectrum: λ_{max} 239 nm (log ε 4·28), 256 nm infl. (4·03), 276 nm (3·87), 336 nm (3·62). IR spectrum: 745 and 766 (C—H of the pyridine ring), 808 and 829 (2 vicinal benzene C—H), 893 (isolated C—H of the benzene ring), 1562 and 1577 (Ar), 1675 cm^{-1} (Ar—CO). NMR spectrum: ϑ 8·45 (dd, J = 5·0; 2·0 Hz, 1 H, aromatic 2-H), 8·15 (d, J = 2 Hz, 1 H, aromatic 7-H), 7·77 (dd, J = 7·0; 2·0 Hz, 1 H, aromatic 4 H), 7·61 (d, J = 9·0 Hz, 1 H, aromatic 10-H), 7·38 (dd, J = 9·0; 2·0 Hz, 1 H, aromatic 9-H), 7·32 (t, 1 H, aromatic 3-H), 4·26 (s, 2 H, CH_2). For $C_{13}H_8ClNOS$ (261·7) calculated: 13·55% Cl, 5·34% N, 12·25% S; found: 13·54% Cl, 5·25% N, 12·28% S.

8-Isopropyl-5*H*-benzo[*b*]pyrido[3,2-*f*]thiepin-6-one (*XIIb*)

Similarly to the preceding case, cyclization of 46 g acid *Xb* with 460 g polyphosphoric acid at 175°C (8 h) yielded 28 g (65%) crude product; after recrystallization from cyclohexane, m.p. 71—74°C. UV spectrum: λ_{max} 237 nm (log ε 4·34), 281 nm (3·77), 332 nm (3·62). IR spectrum: 766 (C—H of the pyridine ring), 832 (2 vicinal benzene C—H), 860 (isolated benzene C—H), 1385 (isopropyl), 1566 and 1600 (Ar), 1680 cm^{-1} (Ar—CO). For $C_{16}H_{15}NOS$ (269·4) calculated: 71·34% C, 5·61% H, 5·20% N, 11·90% S; found: 71·43% C, 5·61% H, 5·36% N, 11·89% S.

Picrate, m.p. 151—153°C (ethanol). For $C_{22}H_{18}N_4O_8S$ (498·5) calculated: 53·01% C, 3·64% H, 11·24% N, 6·43% S; found: 52·93% C, 3·46% H, 11·24% N, 6·53% S.

8-Chloro-5,6-dihydrobenzo[*b*]pyrido[3,2-*f*]thiepin-6-ol (*XIIIa*)

A solution of 1·4 g $NaBH_4$ in 15 ml water containing 3 drops of 20% NaOH was added dropwise under stirring to a suspension of 6·0 g ketone *XIIa* in 100 ml ethanol at 60—70°C. The mixture was refluxed for 3 h, partly evaporated at reduced pressure, the residue decomposed with 50 ml water and extracted with chloroform. The extract was washed with water, dried with $MgSO_4$ and evaporated. The residue crystallized; 5·7 g (95%), m.p. 162—163°C (benzene). IR spectrum: 794 (C—H of the pyridine ring), 820 (2 vicinal benzene C—H), 858 (isolated benzene C—H), 1088 (cyclic alcohol), 1565 and 1573 (Ar), 3220 cm^{-1} (OH). NMR spectrum (CD_3SOCD_3): ϑ 8·26 (dd, J = 5·0; 2·0 Hz, 1 H, aromatic 2-H), 7·00—7·70 (m, 5 H, remaining aromatic protons), 5·88 (d, disappears on deuterization, 1 H, OH), 5·44 (m, after deuterization dd, J = 9·0; 4·0 Hz, 1 H, CH—O), 3·38 (dd, J = 14·0; 4·0 Hz, 1 H) and 3·04 (dd, J = 14·0; 9·0 Hz, 1 H) together CH_2. For $C_{13}H_{10}ClNOS$ (263·7) calculated: 59·20% C, 3·82% H, 13·44% Cl, 5·31% N, 12·16% S; found: 59·56% C, 3·96% H, 13·24% Cl, 5·21% N, 12·23% S.

Hydrochloride, m.p. 187—190°C (ethanol). For $C_{13}H_{11}Cl_2NOS$ (300·2) calculated: 52·01% C, 3·69% H, 23·22% Cl, 4·66% N, 10·68% S; found: 52·04% C, 3·86% H, 23·59% Cl, 4·73% N, 10·60% S.

8-Isopropyl-5,6-dihydrobenzo[*b*]pyrido[3,2-*f*]thiepin-6-ol (*XIIIb*)

Like in the preceding case, reduction of ketone *XIIb* yielded 88% of the desired product; m.p. 110—112°C (benzene). IR spectrum (KBr): 782 (C—H of the pyridine ring), 828 (C—H of the benzene ring), 1090 (cyclic alcohol), 1420 (isopropyl), 1482 and 1570 (Ar), 3420 cm^{-1} (OH). For $C_{16}H_{17}NOS$ (271·4) calculated: 70·81% C, 6·31% H, 5·16% N, 11·83% S; found: 71·06% C, 6·49% H, 4·99% N, 11·67% S.

Hydrochloride, m.p. 190—193°C (ethanol). For $C_{16}H_{18}ClNOS$ (307·8) calculated: 62·42% C, 5·89% H, 11·52% Cl, 4·55% N, 10·42% S; found: 62·61% C, 6·11% H, 11·80% Cl, 4·43% N, 10·33% S.

6,8-Dichloro-5,6-dihydrobenzo[*b*]pyrido[3,2-*f*]thiepin (*XIVa*)

Alcohol *XIa* (5·0 g) was gradually added to 10 ml thionyl chloride and the mixture was refluxed for 1 h. After cooling, the precipitated hydrochloride of the product was filtered and washed with benzene; 5·5 g (94%), m.p. 196–197°C under decomposition (methanol). For $C_{13}H_{10}.Cl_3NS$ (318·6) calculated: 49·00% C, 3·16% H, 33·38% Cl, 4·39% N, 10·06% S; found: 49·43% C, 3·24% H, 33·09% Cl, 4·34% N, 10·19% S.

6-Chloro-8-isopropyl-5,6-dihydrobenzo[*b*]pyrido[3,2-*f*]thiepin (*XIVb*)

Similarly to the preceding case, alcohol *XIIIb* yielded 83% of a hydrochloride, m.p. 140–142°C (ethanol–ether). For $C_{16}H_{17}Cl_2NS$ (326·3) calculated: 4·29% N, 9·83% S; found: 4·24% N, 10·12% S.

6-(4-Methylpiperazino)-8-chloro-5,6-dihydrobenzo[*b*]pyrido[3,2-*f*]thiepin (*Ia*)

Hydrochloride of chloride *XIVa* (5·0 g) was added to a solution of 6·5 g 1-methylpiperazine in 7 ml chloroform and the mixture was refluxed for 10 h. After cooling, the solution was diluted with 50 ml benzene, washed with dilute aqueous ammonia and water, dried with Na_2SO_4, filtered with charcoal and evaporated. From the remaining mixture of bases (4·5 g), neutralization with maleic acid in ethanol yielded the *dimaleate*, m.p. 120–122°C (ethanol). For $C_{26}H_{28}.ClN_3O_8S$ (578·0) calculated: 54·03% C, 4·88% H, 6·13% Cl, 7·27% N; found: 54·21% C, 4·97% H, 6·51% Cl, 7·20% N.

6-(4-Methylpiperazino)-8-isopropyl-5,6-dihydrobenzo[*b*]pyrido[3,2-*f*]thiepin (*Ib*)

Like in the preceding case, 7·6 g hydrochloride of the chloride *XIVb* reacted to 7·7 g of a mixture of bases from which 6·6 g *dimaleate* was prepared,, m.p. 84–87°C (ethanol–ether). For $C_{29}H_{35}.N_3O_8S$ (585·7) calculated: 59·47% C, 6·02% H, 7·17% N, 5·47% S; found: 59·01% C, 6·26% H, 6·93% N, 5·70% S.

6-[4-(3-Hydroxypropyl)piperazino]-8-chloro-5,6-dihydrobenzo[*b*]pyrido[3,2-*f*]thiepin (*IIa*)

Like in the preceding cases, reaction of 2·5 g hydrochloride of chloride *XIVa* with 5·5 g 1-(3-hydroxypropyl)piperazine[10] in 5 ml chloroform yielded 3·1 g mixture of bases, from which the desired product crystallized after dissolving in a small amount of benzene; 1·6 g (52%), m.p. 156–157°C (benzene). IR spectrum (KBr): 752 and 790 (C—H of the pyridine ring), 828 (C—H of the benzene ring), 1065, 1138 and 3200 (OH), 1495, 1555 and 1570 (Ar), 2760 and 2800 cm^{-1} (N—CH_3). NMR spectrum: δ 8·45 (dd, J = 5·0; 2·0 Hz, 1 H, aromatic 2-H), 7·65 (d, J = 2·5 Hz, 1 H, aromatic 7-H), 7·54 (d, J = 5·0 Hz, 1 H, aromatic 4-H), 7·18 (dd, 1 H, aromatic 3-H), 7·20–7·60 (2 H, aromatic 9- and 10-H), 4·95 (bs, disappears on deuterization, 1 H, OH), 3·75 (t, J = 5·0 Hz; 2 H, CH_2O), 3·00–4·00 (m, 3 H, Ar—CH_2CH—Ar), 2·50 (s, 10 H, NCH_2 groups), 1·70 (m, 2 H, CH_2 in the center of the propanol chain). For $C_{20}H_{24}ClN_3OS$ (389·9) calculated: 61·60% C, 6·20% H, 10·78% N, 8·22% S; found: 62·05% C, 6·52% H, 10·78% N, 8·36% S.

6-(4-Ethoxycarbonylpiperazino)-8-chloro-5,6-dihydrobenzo[*b*]pyrido[3,2-*f*]thiepin (*IIIa*)

A mixture of 3·0 g hydrochloride of chloride *XIVa* and 5·0 g 1-(ethoxycarbonyl)piperazine[11] was heated under stirring for 4 h to 100°C and for 2 h to 125–130°C, decomposed with 5 ml water and extracted with benzene. Processing of the extract yielded 3·8 g mixture of bases. This

mixture was chromatographed on a column of 100 g alumina (activity II), eluting with benzene. The front fractions contained 0·5 g elimination product, 8-*chlorobenzo*[*b*]*pyrido*[3,2-*f*]*thiepin* (XVa), m.p. 97—99°C). UV spectrum: λ_{max} 212 nm (log ε 4·21), 263 nm (4·04), 279 nm (3·43). IR spectrum (KBr): 733 (C—H of the pyridine ring), 802 (*cis*-CH=CH), 837 and 873 (C—H of the benzene ring), 1 543 and 1 567 cm^{-1} (Ar). NMR spectrum: ϑ 8·55 (dd, J = 5·0; 2·0 Hz, 1 H, aromatic 2-H), 7·20—7·80 (m, 5 H, remaining aromatic protons), 7·00 (ABq, 2 H, CH=CH). For $C_{13}H_8ClNS$ (245·7) calculated: 63·54% C, 3·28% H, 14·43% Cl, 5·70% N; found: 64·05% C, 3·53% H, 14·08% Cl, 5·45% N. From the following chromatographic fractions, the base *IIIa* was obtained in a 1·5 g yield; m.p. 137—139°C (benzene–light petroleum). IR spectrum (KBr): 747 and 793 (C—H of the pyridine ring), 820 and 847 (C—H of the benzene ring), 1 557 (Ar), 1 693 cm^{-1} (NCOOR). NMR spectrum: ϑ 8·35 (dd, J = 5·0; 2·5 Hz, 1 H, aromatic 2-H), 7·00 to 7·65 (m, 5 H, remaining aromatic protons), 4·10 (q, J = 7·0 Hz, 2 H, OCH_2), 3·20—3·80 (m, 7 H, Ar—CH_2CH—Ar and $CON(CH_2)_2$), 2·50 (t, 4 H, remaining CH_2NCH_2), 1·23 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{20}H_{22}ClN_3O_2S$ (403·9) calculated: 59·47% C, 5·49% H, 8·78% Cl, 10·40% N, 7·94% S; found: 59·72% C, 5·50% H, 8·74% Cl, 10·22% N, 8·47% S.

8-Isopropylbenzo[*b*]pyrido[3,2-*f*]thiepin (*XVb*)

KOH (0·65 g) was added to a solution of 1·0 g hydrochloride of chloride *XIVb* in 5 ml ethanol and the mixture was refluxed for 2 h. After evaporation of ethanol it was decomposed with 5 ml water and extracted with benzene. After drying with $MgSO_4$ the extract was evaporated; 0·70 g (90%) oil. It was converted in the usual way to *picrate*, m.p. 150—154°C (ethanol). For $C_{22}H_{18}$. N_4O_7S (482·5) calculated: 54·76% C, 3·76% H, 11·61% N, 6·65% S; found: 54·89% C, 3·80% H, 11·64% N, 6·80% S.

6-Piperazino-8-chloro-5,6-dihydrobenzo[*b*]pyrido[3,2-*f*]thiepin (*IVa*)

A mixture of 1·0 g carbamate *IIIa*, 1·0 g KOH and 1·5 ml ethanol was refluxed for 3·5 h at 80 to 90°C, diluted with 10 ml water and extracted with benzene. The extract was dried with K_2CO_3, and evaporated. A total of 0·70 g (86%) crude oily base was obtained; it was neutralized with maleic acid in ethanol to yield 0·8 g maleate, m.p. 148—150°C (acetone). For $C_{21}H_{22}ClN_3O_4S$ (447·9) calculated: 56·31% C, 4·95% H, 7·91% Cl, 9·38% N, 7·16% S; found: 55·94% C, 5·12% H, 8·17% Cl, 9.20% N, 7·42% S.

6-(4-Methylpiperazino)-8-chlorobenzo[*b*]pyrido[3,2-*f*]thiepin (*Va*)

$TiCl_4$ (2·3 g) in 10 ml benzene was added dropwise to a mixture of 6·0 g ketone *XIIa*, 10·5 g 1-methylpiperazine and 60 ml benzene. The mixture was refluxed under stirring for 20 h, cooled, diluted with benzene and decomposed with 20 ml water. The benzene phase was separated, washed with water, dried with Na_2SO_4, filtered with charcoal and evaporated. The residue was dissolved in 25 ml warm ethanol; on standing and cooling, a small amount of the starting ketone precipitated and was filtered. The filtrate was combined with a solution of 4·5 g maleic acid in ethanol. On cooling, a *dimaleate* precipitated: 5·8 g, m.p. 154—156°C (ethanol). UV spectrum: λ_{max} 236 nm (log ε 4·21), 267 nm (4·16), 308 nm (4·02). NMR spectrum (CD_3SOCD_3): ϑ 10·80 (bs, 4 H, disappears on deuterization, 4 COOH), 8·42 (d, 1 H, aromat. 2-H), 7·20—8·00 (m, 5 H, remaining aromat. protons), 6·49 (s, 1 H, CH=C in the ring), 6·16 (s, 4 H, 2 CH=CH of maleic acid), 3·30 (m, 8 H, CH_2 groups of piperazine), 2·90 (s, 3 H, NCH_3). For $C_{26}H_{26}ClN_3O_8S$ (576·0) calculated: 54·22% C, 4·55% H, 6·15% Cl, 7·30% N, 5·56% S; found: 54·02% C, 4·57% H, 5·92% Cl, 7·21% N, 5·72% S.

6-(4-Methylpiperazino)-8-isopropylbenzo[*b*]pyrido[3,2-*f*]thiepin (*Vb*)

Like in the preceding case, 8·1 g ketone *XIIb* reacted with 15 g 1-methylpiperazine and 2·9 g $TiCl_4$ in 100 ml benzene and the crude base (10·0 g, 94%) was converted to the *maleate*, which crystallizes from ethanol as a hemihydrate (5·0 g), m.p. 182—184°C. For $C_{25}H_{30}N_3O_{4,5}S$ (476·6) calculated: 63·00% C, 6·34% H, 8·82% N, 6·73% S; found: 63·19% C, 6·30% H, 8·90% N, 6·64% S.

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