NEUROTROPIC AND PSYCHOTROPIC AGENTS. LXI.* DERIVATIVES OF 6-PIPERAZINOBENZO[*b*]PYRIDO[3,2-*f*]THIEPIN

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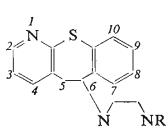
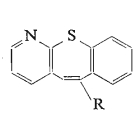
Starting from 2-chloronicotinic acid, a five-step synthesis led to 2-phenylthio-3-pyridylacetic acid (*X*) which was cyclized by polyphosphoric acid to 5*H*-benzo[*b*]pyrido[3,2-*f*]thiepin-6-one (*XII*). The chloride *XIV* prepared in two further steps yielded by substitution reactions the piperazine derivatives *I*–*III*. Reaction of ketone *XII* with 1-methylpiperazine and titanium tetrachloride yielded the enamine *V*. The central depressant and cataleptic activity of bases *I*, *III* and *V* is much weaker than with the benzo-analogues.

The finding of central depressant activity of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin ("perathiepin")[1–3] led to a systematic modification of the molecule of this compound and, at the same time, to the synthesis of analogues where one of the benzene rings of the tricyclic system is replaced by a heterocycle. The first to be studied were the thiophene analogues[4,5] which also displayed significant activity. In the present communication we describe piperazine derivatives *I*–*V*, derived from a novel tricyclic system, benzo[*b*]pyrido[3,2-*f*]thiepin.



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



V, R =
XV, R = H

In the synthesis of amines *I*–*V* we proceeded from 2-phenylthionicotinic acid[6] (*VI*), which is readily available from 2-chloronicotinic acid[7]. Using small modifications, we applied the synthetic pattern used in the series of dibenzo[*b*,*f*]thiepin analogues[1,2,8,9]. Reduction of acid *VI* with sodium bis(2-methoxyethoxy)dihydrido-

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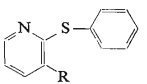
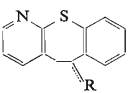
aluminate[10] gave alcohol *VII* which was heated with thionyl chloride[11] to convert it to the chloride *VIII*. Reaction with sodium cyanide in aqueous ethanol produced the nitrile *IX* which underwent alkaline hydrolysis to 2-phenylthio-3-pyridylacetic acid (*X*). Cyclization with polyphosphoric acid at 170–175°C gave a satisfactory yield of 5*H*-benzo[*b*]pyrido[3,2-*f*]thiepin-6-one (*XII*), the structure of which was established both analytically and by means of spectra. In an attempt at converting nitrile *IX* to ketone *XII* with polyphosphoric acid at 120–130°C the sole product obtained was amide *XI*. Reduction of ketone *XII* with sodium borohydride in methanol gave alcohol *XIII* which, on heating with thionyl chloride, yielded the hydrochloride of *XIV*. Heating of this compound with ethanolic solution of potassium hydroxide leads smoothly to elimination of hydrogen chloride and to the formation of benzo[*b*]pyrido[3,2-*f*]thiepin (*XV*). Heating of the hydrochloride of *XIV* with excess 1-methylpiperazine, 1-(ethoxycarbonyl)piperazine[12] or with 1-(3-hydroxypropyl)piperazine[13] resulted in amines *I*–*III*. Alkaline hydrolysis of carbamate *II* yielded the secondary amine *IV*. The enamine *V* was obtained from ketone *XII* and from 1-methylpiperazine by application of the titanium tetrachloride method[14–16].

Table I shows the pharmacological properties of the piperazine derivatives *I*, *III* and *V*, perathiepin[1–3] and chlorpromazine being included as standards. All the compounds were administered intravenously (or intraperitoneally in the catalepsy test) in the form of salts, the values of the table referring to the bases. Besides acute toxicity for mice expressed by the usual mean lethal dose (LD_{50}), the table includes mean effective doses (ED_{50}) in the rotating-rod test in mice which reveals a disturbance of motor coordination and hence in principle a central depressant effect, and also the mean effective doses (ED_{50}) in the catalepsy test in rats. It follows from the table that the pyridine derivatives, *I*, *III* and *V* do not differ fundamentally from the reference standards in toxicity but are at least 10 times less effective as central depressants than perathiepin and 5 times less effective than chlorpromazine. Likewise, in the catalepsy test they are clearly weaker than the references. Replacement of the benzene ring A in the molecule of perathiepin[1–3] thus appears unfavourable for the central activity.

In connection with finding low central depressant activity of the novel substances it may be useful to note the bio-analogy of the pyridine and nitrobenzene deriva-





VI, R = COOH *IX*, R = CH_2CN *XII*, R = =O
VII, R = CH_2OH *X*, R = CH_2COOH *XIII*, R = OH
VIII, R = CH_2Cl *XI*, R = CH_2CONH_2 *XIV*, R = Cl

tives[17,18]. From this point of view it would be probably more correct to compare *I* not with perathiepin[1-3] but rather with its 4-nitro-derivative. The nitroderivative is not known but the 4-chloroderivative[19] has been described and there is some evidence on the equivalence of the chlorine atom and the nitro group from the point of view of activity of the derivative[20]. The 4-chloroderivative of perathiepin was found to have an ED_{50} of 8·1 mg/kg (*i.v.*) in the rotating-rod test. This is rather close to the value for pyridine derivatives *I*, *III* and *V*. It may thus be concluded that replacement of =CH— in position 4 of the perathiepin molecule with an atom of nitrogen has approximately the same unfavourable effect on the activity as the substitution with chlorine, which is typical for the psychotropic substances.

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 NMR spectra (in $CDCl_3$ unless stated otherwise) in the ZKR-60 (Zeiss Jena) spectrometer.

2-Phenylthio-3-pyridylcarbinol (*VII*)

Benzene solution (55%) of sodium bis(2-methoxyethoxy)dihydroaluminate (214 ml) was added dropwise under stirring to a mixture of 65·7 g 2-phenylthionicotinic acid (*VI*) (m.p. 168—170°C) (ref.[6]) and 550 ml benzene. The mixture was stirred for 2 h at room temperature, it was then decomposed by adding dropwise 380 ml 10% NaOH, the benzene phase was dried with $MgSO_4$ and evaporated. A total of 50·4 g (81%) product was obtained and this was processed further. Solution of a sample in benzene and addition of light petroleum yielded a product melting at 100—101°C. UV spectrum: λ_{max} 245 nm (log ε 3·98), 287 nm (2·26). IR spectrum: 688 and 710 (C_6H_5), 797 (2,3-disubstituted pyridine), 1042 (CH_2OH), 1390 and 3330 cm^{-1} (OH). NMR spectrum: δ 8·31 (dd, $J = 4{\cdot}0$; 1·5 Hz, 1 H, aromatic proton in the vicinity of pyridine N), 7·70 (t, $J = 7{\cdot}0$; 1·5 Hz, 1 H, aromatic proton in position 5 of the pyridine ring), 6·95—7·50 (m, 6 H,

TABLE I

Pharmacological Properties of Piperazine Derivatives *I*, *III* and *V*

Compound	Acute toxicity LD_{50} *i.v.* mg/kg	Rotating rod ED_{50} *i.v.* mg/kg	Catalepsy ED_{50} *i.p.* mg/kg
I	42	3·7	>10[a]
III	64	9·0	>10[b]
V	27	2·7	>10[a]
Perathiepin	42	0·2	10
Chlorpromazine	52	0·6	8·6

[a] A dose of 10 mg/kg brought about a cataleptic state only in two rats of the group of ten. [b] A dose of 10 mg/kg caused the cataleptic state in only one rat out of ten.

remaining aromatic protons), 4·65 (s, 2 H, CH_2), 3·27 (bs, 1 H, OH). For $C_{12}H_{11}NOS$ (217·3) calculated: 66·33% C, 5·10% H, 6·45% N, 14·76% S; found: 66·67% C, 5·24% H, 6·46% N, 14·68% S.

2-Phenylthio-3-pyridylmethyl Chloride (*VIII*)

Alcohol *VII* (125 g) was added in parts to 350 ml thionyl chloride and the mixture was refluxed for 2 h. After evaporation of excess thionyl chloride *in vacuo* the residue was dissolved in 100 ml water. Solution of the hydrochloride of the product was hydrolyzed by further dilution with 1000 ml water so that the liberated oily base could be extracted with chloroform; 133·4 g (98%). In this state the product was processed further. For characterization, a picrate was prepared: m.p. 113—114°C (ethanol). For $C_{18}H_{13}ClN_4O_7S$ (464·8) calculated: 46·50% C, 2·81% H, 7·62% Cl, 12·05% N, 6·89% S; found: 46·54% C, 2·83% H, 7·62% Cl, 12·11% N, 7·15% S.

2-Phenylthio-3-pyridylacetonitrile (*IX*)

A solution of 35 g crude chloride *VIII* in 35 ml ethanol was added under stirring to a hot solution of 20·0 g sodium cyanide in a mixture of 35 ml water and 150 ml ethanol and the mixture was refluxed under stirring for 4 h. A part of ethanol was then evaporated at reduced pressure, the residue was diluted with water and extracted with chloroform. The extract after drying with $MgSO_4$ was distilled: 20·0 g (60%), b.p. 189°C/2·5—3 Torr. After redistillation, b.p. 163°C/0·7 Torr; the distillate crystallized, m.p. 52—53°C. IR spectrum: 690 and 710 (C_6H_5), 792 (2,3-disubstituted pyridine), 1575 (Ar), 2260 cm^{-1} (CN). NMR spectrum: δ 8·44 (md, J = 5·0; 2·0 Hz, 1 H, aromatic proton in position 6 of the pyridine ring), 7·81 (md, J = 7·0; 2·0 Hz, 1 H, aromatic proton in position 4 of the pyridine ring), about 7·46 (m, 5 H, phenyl), 7·15 (dd, J = 7·0; 5·0 Hz, 1 H, aromatic proton in position 5 of the pyridine ring), 3·81 (s, 2 H, CH_2). For $C_{13}H_{10}N_2S$ (226·2) calculated: 69·01% C, 4·46% H, 12·38% N, 14·14% S; found: 68·44% C, 4·46% H, 12·18 N, 14·58% S.

2-Phenylthio-3-pyridylacetic Acid (*X*)

A mixture of 20·0 g nitrile *IX* in 135 ml ethanol and 22 g KOH in 22 ml water was refluxed under stirring for 9 h, diluted with 500 ml water, extracted with benzene, the aqueous solution was filtered with charcoal and the filtrate made acid with dilute (1 : 1) hydrochloric acid to pH 5·5. After standing overnight the precipitate was filtered, washed with water and dried: 18·5 g (86%). After recrystallization from benzene the m.p. was 153—154°C. IR spectrum: 690 and 734 (C_6H_5), 1195, 1230, 1276 and 1695 (COOH), 1570 (Ar), 2520 cm^{-1} (COO^-NH^+). NMR spectrum (CD_3SOCD_3): δ 8·37 (md, J = 5·0; 2·0 Hz; 1 H, aromatic proton in position 6 of the pyridine ring), 7·80 (md, J = 7·0; 2·0 Hz, 1 H, aromatic proton in position 4 of the pyridine ring), 7·49 (s, 5 H, phenyl), 7·26 (dd, J = 7·0; 5·0 Hz, 1 H, aromatic proton in position 5 of the pyridine ring), 3·81 (s, 2 H, CH_2). For $C_{13}H_{11}NO_2S$ (245·3) calculated: 5·70% N, 13·08% S; found: 5·96% N, 12·72% S.

2-Phenylthio-3-pyridylacetamide (*XI*)

A mixture of 3·0 g nitrile *IX* and 12 g polyphosphoric acid was heated for 3 h to 120—130°C under occasional stirring. After cooling, it was decomposed with water, the mixture made alkaline with NaOH and the product extracted with benzene. After drying and partial evaporation of the extract, the product crystallized after addition of light petroleum; 2·1 g, after recrystallization from benzene m.p. 128—129°C. IR spectrum (KBr): 691, 707, 747, 756 (C_6H_5), 800 (2,3-disub-

stituted pyridine), 1660 and 1680 ($CONH_2$), 3280, 3355 and 3473 cm^{-1} (NH_2). NMR spectrum (CD_3SOCD_3): δ 8·30 (md, 1 H, aromatic proton in position 6 of the pyridine ring), about 7·60 (2 H, NH_2), about 7·40 (m, 6 H, phenyl protons and aromatic proton in position 4 of pyridine), 7·15 (m, 1 H, aromatic proton in position 5 of pyridine), 3·58 (s, 2 H, CH_2). For $C_{13}H_{12}N_2OS$ (244·3) calculated: 63·91% C, 4·95% H, 11·47% N, 13·12% S; found: 63·46% C, 4·99% H, 11·34% N, 13·24% S.

Hydrochloride, m.p. 173—175°C (ethanol). For $C_{13}H_{13}ClN_2OS$ (280·8) calculated: 55·61% C, 4·67% H, 12·63% Cl, 9·97% N, 11·42% S; found: 55·46% C, 4·84% H, 12·28% Cl, 9·82% N, 11·40% S.

5*H*-Benzo[*b*]pyrido[3,2-*f*]thiepin-6-one (*XII*)

A mixture of 10·0 g acid *X* and 40 g polyphosphoric acid was heated for 6 h to 170—175°C, after partial cooling it was decomposed with ice and water, made alkaline with aqueous ammonia and the precipitated product was extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated. The residue was recrystallized from ethanol: 6·75 g (73%), m.p. 140—141°C. UV spectrum: λ_{max} 237 nm (log ε 4·24), 255 nm infl. (3·97). 279 nm infl. (3·68), 324 nm (3·52). IR spectrum (KBr): 736 and 805 (2,3-disubstituted pyridine), 749, 760, 775 (1,2-C_6H_4), 1560 and 1580 (Ar and hetero-Ar), 1666 cm^{-1} (ArCO). NMR spectrum: δ 8·50 (md, J = 5·0; 2·0 Hz, 1 H, aromatic proton in position 2 of the system), 8·26 (m, 1 H, aromatic proton in position 7 of the system), 7·20—7·95 (m, 5 H, remaining aromatic protons), 4·33 (s, 2 H, $ArCH_2CO$). For $C_{13}H_9NOS$ (227·3) calculated: 68·70% C, 3·99% H, 6·16% N, 14·11% S; found: 68·92% C, 4·02% H, 6·20% N, 14·13% S.

Picrate, m.p. 148—149°C (ethanol). For $C_{19}H_{12}N_4O_8S$ (456·4) calculated: 50·00% C, 2·65% H, 12·88% N, 7·02% S; found: 50·26% C, 2·62% H, 12·53% N, 6·88% S.

5,6-Dihydrobenzo[*b*]pyrido[3,2-*f*]thiepin-6-ol (*XIII*)

Sodium borohydride (1·32 g) was added in parts to a solution of 5·0 g ketone *XII* in 50 ml methanol. The mixture was stirred at room temperature until cessation of gas evolution and then refluxed for 1 h. After evaporation of methanol, the residue was decomposed with 40 ml water and the mixture extracted with chloroform. Processing of the extract yielded 4·9 g (98%) of a product melting at 144—148°C. After recrystallization from ethanol, m.p. 146—147°C. UV spectrum: λ_{max} 250 nm (log ε 3·80), 274 nm (3·88), 290 nm (3·77). IR spectrum: 756, 770 (1,2-C_6H_4), 800 (2,3-disubstituted pyridine), 1054 (CHOH), 1570 (Ar), 3200 cm^{-1} (OH). NMR spectrum: δ 8·24 (md, 1 H, aromatic proton in position 2 of the system), 6·90—7·80 (m, 6 H, remaining aromatic protons), 5·70 (dd, J = 3·0; 9·0 Hz, 1 H, Ar—CH—O), 3·79 (bs, 1 H, OH), 3·00—3·65 (m, 2 H, CH_2). For $C_{13}H_{11}NOS$ (229·3) calculated: 68·10% C, 4·83% H, 6·11% N, 13·98% S; found: 68·34% C, 4·81% H, 6·04% N, 13·66% S.

Hydrochloride, m.p. 185—186°C under decomposition (ethanol–ether). For $C_{13}H_{12}ClNOS$ (265·7) calculated: 5·27% N, 12·07% S; found: 5·15% N, 11·53% S.

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

Alcohol *XIII* (15·0 g) was added in parts to 38 ml thionyl chloride and the mixture was refluxed for 5·5 h. On standing overnight, the hydrochloride precipitated and was filtered (14·0 g, 73%). After recrystallization from a mixture of methanol and ether: m.p. 177°C under decomposition. For $C_{13}H_{11}Cl_2NS$ (284·2) calculated: 54·94% C, 3·90% H, 24·95% Cl, 4·93% N, 11·28% S; found: 54·91% C, 3·92% H, 24·87% Cl, 4·80% N, 11·40% S.

Benzo[*b*]pyrido[3,2-*f*]thiepin (*XV*)

A mixture of 1·0 g hydrochloride of *XIV*, 11 ml ethanol and 0·7 g KOH was refluxed under stirring for 2 h. After cooling, the precipitated KCl was filtered, the filtrate was evaporated to dryness at reduced pressure, the residue was dissolved in benzene, the solution was washed with water, filtered with charcoal, dried with $MgSO_4$ and, after partial evaporation, diluted with light petroleum. A total of 0·50 g needles melting at 102—103°C was obtained (benzene, light petroleum). UV spectrum: λ_{max} 245 nm infl. (log ε 4·12), 262·5 nm (4·24), 297 nm (3·80). IR spectrum: 748 and 815 (2,3-disubstituted pyridine), 764 (1,2-C_6H_4), 780 (CH=CH), 1 545 and 1 570 cm^{-1} (Ar). NMR spectrum: δ 8·50 (dd, J = 5·0; 2·5 Hz, 1 H, aromatic proton in position 2 of the system), 6·70—7·80 (m, 8 H, all the remaining aromatic and olefinic protons). For $C_{13}H_9NS$ (211·3) calculated: 73·90% C, 4·29% H, 6·63% N, 15·18% S; found: 74·02% C, 4·21% H, 6·34% N, 15·29% S.

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

A solution of 5·0 g hydrochloride of *XIV* in 11 g 1-methylpiperazine and 10 ml chloroform was refluxed for 12 h. The mixture was then diluted with benzene, washed with dilute aqueous ammonia and with water, dried with K_2CO_3 and evaporated. The residue (4·95 g, 93%) was converted to crystalline dimaleate and crystallized from a mixture of ethanol and ether. Decomposition of the pure salt with aqueous ammonia and extraction with benzene yielded a base, m.p. 100 to 101°C (cyclohexane). UV spectrum: λ_{max} 248 nm (log ε 3·89), 280 nm (3·90), 288 nm infl. (3·83). IR spectrum: 748 (1,2-C_6H_4), 792 (2,3-disubstituted pyridine), 1 556 and 1 574 (Ar), 2 760 and 2 790 cm^{-1} (N—CH_3). For $C_{18}H_{21}N_3S$ (311·4) calculated: 69·41% C, 6·80% H, 13·49% N, 10·30% S; found: 69·40% C, 6·87% H, 13·68% N, 10·26% S.

Dimaleate, m.p. 110—114°C (ethanol). For $C_{26}H_{29}N_3O_8S$ (543·6) calculated: 57·45% C, 5·38% H, 7·73% N, 5·89% S; found: 57·40% C, 5·37% H, 7·20% N, 5·60% S.

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

A mixture of 1·75 g hydrochloride of *XIV* and 2·8 g 1-ethoxycarbonylpiperazine[12] was heated for 2 h to 100°C. Treatment as above yielded 2·3 g product which was chromatographed on a column of 80 g alumina (activity II). Elution of the column with benzene gave first 0·3 g elimination product *XV*, m.p. 97°C. This was followed by 1·65 g (75%) oily base *II* which was converted to maleate, m.p. 166—167°C (ethanol–ether). For $C_{24}H_{27}N_3O_6S$ (485·5) calculated: 59·37% C, 5·60% H, 8·65% N, 6·60% S; found: 59·66% C, 5·81% H, 8·64% N, 6·76% S.

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

A solution of 7·0 g hydrochloride of *XIV* in 14 g 1-(3-hydroxypropyl)piperazine[13] and 10 ml chloroform was refluxed for 5 h and processed similarly as in preparation of *I*. A total of 7·6 g (87%) oily base was obtained which was converted to the dimaleate. After crystallization from a mixture of ethanol and ether, m.p. 90—94°C. For $C_{28}H_{33}N_3O_9S$ (587·6) calculated: 57·23% C, 5·66% H, 7·15% N, 5·46% S; found: 57·38% C, 5·77% H, 7·23% N, 5·64% S. In one case, a modification with a m.p. of 74—76°C was obtained but its preparation could not be repeated. For $C_{28}H_{33}N_3O_9S$ (587·6) calculated: 57·23% C, 5·66% H, 5·46% S; found: 57·38% C, 5·98% H, 5·27% S.

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

A mixture of 1·1 g oily base *II*, 2 ml ethanol and 1 g KOH was refluxed for 5 h. It was then diluted with 20 ml water and extracted with benzene. Treatment of the extract yielded 0·8 g (96%) oily base which was converted to maleate, m.p. 147—148°C (ethanol–ether). For $C_{21}H_{23}N_3O_4S$ (413·5) calculated: 61·00% C, 5·59% H, 10·17% N, 7·75% S; found: 60·85% C, 5·68% H, 10·23% N, 8·03% S.

6-(4-Methylpiperazino)benzo[*b*]pyrido[3,2-*f*]thiepin (*V*)

A solution of 1·3 ml $TiCl_4$ in 10 ml benzene was added dropwise to a mixture of 3·0 g ketone *XII*, 6·6 g 1-methylpiperazine and 45 ml benzene and the solution was stirred and refluxed for 12 h. After cooling, it was diluted with benzene, washed with aqueous ammonia and water, dried with K_2CO_3, filtered and evaporated. The residue was dissolved in 15 ml ethanol and combined with a solution of 5·8 g maleic acid in 15 ml ethanol. After adding ether, the dimaleate crystallized (6·5 g, 91%), m.p. 143°C (ethanol). For $C_{26}H_{27}N_3O_8S$ (541·6) calculated: 57·66% C, 5·02%H, 7·76% N, 5·92% S; found: 57·34% C, 5·02% H, 7·93% N, 5·80% S.

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