POTENTIAL NONCATALEPTIC NEUROLEPTIC AGENTS: SYNTHESIS AND PHARMACOLOGY OF 7-CHLORO-4-[4-(2-HYDROXYETHYL)-PIPERAZINO]-4,5-DIHYDROTHIENO[2,3-*b*]-1-BENZOTHIEPIN*

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Heating of 2,5-dichloroacetophenone with 2-thiophenethiol, potassium carbonate and copper gave 5-chloro-2-(2-thienylthio)acetophenone (*V*) which was subjected to the Willgerodt reaction with sulfur and morpholine. The product was a mixture of the thiomorpholide *VI* and oxothiomorpholide *VII*. After a partial separation the predominating product *VI* was hydrolyzed without characterization with ethanolic potassium hydroxide to give the acid *VIII*. Cyclization by treatment with phosphorus pentoxide in boiling toluene gave 7-chlorothieno[2,3-*b*]-1-benzothiepin-4(5*H*)-one (*X*) which was reduced with sodium borohydride to the alcohol *XII*. A reaction with hydrogen chloride in benzene led to the chloro derivative *XIII* whose substitution reaction with 1-(2-hydroxyethyl)piperazine afforded the title compound *IV*. The product has strong central depressant and discoordinating ativity, a low cataleptic efficicy but in a relatively high dose it does not influence the dopamine metabolism in the rat brain.

The searching after noncataleptic neuroleptics, which would possess in full extent the desired antipsychotic activity but would be free of the extrapyramidal side effects, is being continued. After the very promising clozapine (*I*) (ref.[1]) two further structurally related compounds were eliminated due to some unexpected side effects: docloxythepin (*II*) (ref.[2]) and thilozepine (*III*) (ref.[3,4]). On the basis of apparent structural relations to the molecules of compounds *I*–*III* we have designated the 4,5-dihydrothieno[2,3-*b*]-1-benzothiepin derivative *IV* as a further potential noncataleptic neuroleptic agent. In the series of compounds derived from the same skeleton we have attempted until now at finding incisive neuroleptics having high cataleptic and antiapomorphine activities[5–8]. By placing the atom of chlorine into a position, which is typical for noncataleptic agents, we believed in arranging good conditions for attaining the desired pharmacological profile.

In the preparation of compound *IV* we used an analogy of the modified docloxythepin (*II*) synthesis[9] in which 2,5-dichloroacetophenone[9] is the starting compound and the Willgerodt reaction in the Kindler's modification[10–12] is the crucial step. Heating 2,5-dichloroacetophenone[9], 2-thiophenethiol[13] and potassium carbonate

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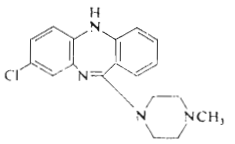
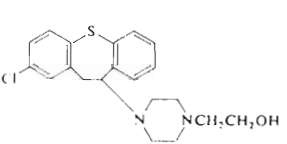
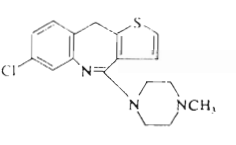
with a catalytic amount of copper to 130 – 140°C led to a mixture from which 5-chloro--2-(2-thienylthio)acetophenone (*V*) could be isolated in moderate yield by chromatography on alumina. Its reaction with sulfur and an excess of boiling morpholine gave again a mixture from which chromatography on silica gel separated a small



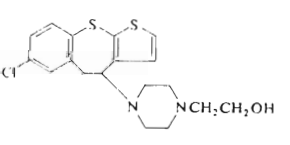
I



II



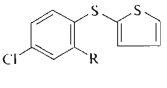
III



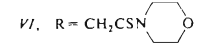
IV

amount of the starting compound *V* and from the more polar fractions there crystallized some 40% of a substance which was identified by analyses and spectra as the oxothiomorpholide *VII*. It was then established that during chromatography on silica gel this by-product is eluted before the desired thiomorpholide *VI*. In the next experiment, therefore, the mixture was separated in this manner and the noncrystallizing thiomorpholide *VI* was subjected without characterization to hydrolysis with a boiling potassium hydroxide solution in ethanol. [5-Chloro-2-(2-thienylthio)-phenyl]acetic acid (*VIII*) was obtained in a moderate yield and from the mother liquor after its crystallization there was isolated in a small amount a further acid which was identified as 5-chloro-2-(2-thienylthio)benzoic acid (*IX*) (ref.[14]). The source of its formation was the hydrolysis of a small amount of the oxothiomorpholide *VII* which was present in the crude starting thiomorpholide *VI*. The crude acid *VIII* was cyclized by treatment with phosphorus pentoxide in boiling toluene, 7-chloro thieno[2,3-*b*]-1-benzothiepin-4(5*H*)-one (*X*) was obtained and its identity was corroborated by spectra. Chromatography of the mother liquors after the crystallization of the ketone *X* gave the lower homologue, *i.e.* 6-chlorothieno[2,3-*b*]-1-benzothiopyran-4-one (*XI*) (ref.[14–17]); it was formed by cyclization of a small amount of the acid *IX* which was present in the crude acid *VIII*. Reduction of the ketone *X* with sodium borohydride in a mixture of ethanol and tetrahydrofuran afforded the

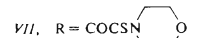
alcohol *XII* which was transformed by treatment with hydrogen chloride in benzene to the chloro derivative *XIII*. Its substitution reaction with 1-(2-hydroxyethyl)piperazine was carried out in boiling chloroform and the title compound *IV* was obtained in a yield of 85%. The base crystallized as a 1 : 6 solvate with benzene and afforded. a bis(hydrogen maleate) which was used in the pharmacological tests. Simultaneously with the substitution reaction there proceeded in a smaller extent the elimination whose product was isolated and identified as 7-chlorothieno[2,3-*b*]-1-benzothiepin (*XIV*).



V, R = $COCH_3$



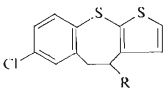
VI, R = CH_2CSN O



VII, R = COCSN O

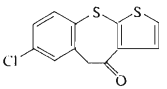
VIII, R = CH_2COOH

IX, R = COOH

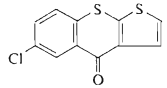


XII, R = OH

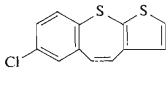
XIII, R = Cl



X



XI



XIV

Compound *IV* was pharmacologically evaluated in the form of the bis(hydrogen maleate) but the following data were calculated for the base. The compound was administered orally. In mice, the compound is little toxic; its LD_{50} is approximately 500 mg/kg. It has a rather intensive discoordinating effect in the rotarod test; ED_{50} = = 3·7 mg/kg. Its central depressant activity, likewise, is very high: a dose of 10 mg/kg reduced the spontaneous locomotor activity of mice (photo-cell method of Dews) to 3·6% of the control value (evaluated 1 h after the administration). In a dose of 50 mg/kg it revealed a very mild cataleptic activity in rats (20% of the animals in catalepsy) and the same dose was inactive towards the apomorphine stereotypies in rats. All the properties mentioned indicated an interesting profile of a noncataleptic neuroleptic agent. A negative result, however, was obtained in the important biochemical test in which the influence of the compound on dopamine metabolism

in the rat brain striatum was evaluated. While docloxythepin (*II*) in an oral dose of 80 mg/kg increased with statistical significancy the homovanillic acid level in the striatum to 142% of the control value[18,19], compound *IV* in the same dose is without effect. It is thus necessary to conclude that compound *IV* possesses rather the character of a tranquillizer than that of a neuroleptic agent.

Compound *IV* showed also some antimicrobial effects in the tests *in vitro*. The tested microorganisms and the minimum inhibitory concentrations of compound *IV* in μg/ml (unless they exceed 100 μg/ml) are given: *Streptococcus* β-*haemolyticus* 25, *Streptococcus faecalis* 25, *Staphylococcus pyogenes aureus* < 12·5; *Proteus vulgaris* 50, *Saccharomyces pasterianus* 50, *Trichopyhton mentagrophytes* 25.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with MCH-1320 and Varian MAT 44S spectrometers. The homogeneity of the compounds and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

5-Chloro-2-(2-thienylthio)acetophenone (*V*)

A stirred mixture of 18·3 g 2,5-dichloroacetophenone[9], 12·5 g 2-thiophenethiol[13] and 0·4 g Cu was slowly treated with 24 g K_2CO_3 and then heated without stirring for 1 h to 130—140°C (bath temperature) under nitrogen. After cooling the mixture was diluted with 300 ml benzene, filtered through a 1 cm layer of silica gel, the filtrate was evaporated and the residue chromatographed through a column of 600 g neutral Al_2O_3 (activity II). A mixture of 80% benzene and 20% chloroform eluted 3·2 g impure 2,5-dichloroacetophenone and a 1 : 1 mixture of the same solvents eluted then 8·7 g (41%) crude product, m.p. 70—74°C. Analytical sample, m.p. 74—76°C (benzene–hexane). UV spectrum: λ_{max} 233 nm (log ε 4·48), 260 nm (4·07), 339 nm (3·63). IR spectrum: 699, 819, 876, 890 (Ar—H), 1 490, 1 583, 3 084 (Ar), 1 670 cm^{-1} (ArCOR). ^{1}H NMR spectrum: δ 7·76 (d, J = 3·0 Hz, 1 H, 6-H), 7·00-7·60 (m, 4 H, 4-H and 3 thiophene H), 6·80 (d, J = 9·0 Hz, 1 H, 3-H), 2·60 (s, 3 H, $COCH_3$). For $C_{12}H_9ClOS_2$ (268·8) calculated: 53·62% C, 3·38% H, 13·19% Cl, 23·86% S; found: 53·91% C, 3·36% H, 13·30% Cl, 23·87% S.

5-Chloro-2-(2-thienylthio)phenylglyoxylic Acid Thiomorpholide (*VII*)

A mixture of 4·0 g *V*, 0·65 g S and 2·6 g morpholine was stirred and heated under reflux (nitrogen atmosphere) for 15 min to 140°C (bath temperature). After cooling it was diluted with chloroform, filtered with charcoal, washed with water, 1 : 9 dilute hydrochloric acid and water, dried with K_2CO_3 and evaporated under reduced pressure. The residue was chromatographed on a column of 80 g silica gel (Silpearl). Elution with benzene gave first 1·9 g mixture consisting mostly of the starting *V*. Further elution with benzene gave 3·1 g oil which deposited by standing for 2 days 2·5 g (42%) *VII*, m.p. 119—121°C. Analytical sample, m.p. 120—123°C (ethanol). UV spectrum: λ_{max} 237 nm (log ε 4·50), 271 nm (4·37), 358 nm (3·84). IR spectrum: 714, 752, 763, 822, 849, 869 (3 adjacent thiophene H, 2 adjacent and solitary Ar-H), 1 110, 1 230, 1 250 (ROR), 1 500, 1 537, 1 590, 3 080 (Ar), 1 640 cm^{-1} (ArCOCSNR$_2$). ^{1}H NMR spectrum: δ 7·78 (d,

J = 2·0 Hz, 1 H, 6-H), 7·59 (dd, J = 5·0; 1·5 Hz, 1 H, thiophene 5-H), *c.* 7·00—7·40 (m, 3 H, 4-H and thiophene 3,4-H_2), 6·85 (d, J = 9·0 Hz, 1 H, 3-H), 3·50—4·40 (m, 8 H, 2 NCH_2 and 2 OCH_2 of morpholine). For $C_{16}H_{14}ClNO_2S_3$ (393·9) calculated: 50·06% C, 3·65% H, 9·24% Cl, 3·65% N, 25·06% S; found: 50·02% C, 3·71% H, 9·69% Cl, 3·56% N, 25·64% S.

[5-Chloro-2-(2-thienylthio)phenyl]acetic Acid (*VIII*)

A mixture of 26·1 g *V*, 5·0 g S and 18·6 g morpholine was stirred and heated under reflux under nitrogen for 2 h to 140°C. After cooling to 60°C it was diluted with chloroform and filtered with charcoal. The filtrate was washed with water, 5% hydrochloric acid and water, dried with K_2CO_3 and evaporated under reduced pressure. The residue was chromatographed on a column of 300 g silica gel (Silpearl). Elution with a mixture of 60% benzene and 40% light petroleum removed the starting *V* and most of the oxothiomorpholide *VII*. The following elution with benzene gave 27·7 g not completely homogeneous oily substance considered to be [5-chloro-2-(2-thienylthio)-phenyl]acetic acid thiomorpholide (*VI*). This product was stirred and refluxed for 2·5 h with a solution of 20·8 g KOH in 42 ml ethanol. It was then diluted with 230 ml water and the solution was acidified after cooling with 50 ml hydrochloric acid under stirring. The separated acid was extracted with benzene, the extract was washed with water, dried with Na_2SO_4—$MgSO_4$ and evaporated. The residue was crystallized first from a mixture of dichloromethane and hexane and the product then from ethanol–hexane, m.p. 133—136°C. After processing the mother liquors by chromatography on 120 g silica gel and crystallization of the benzene eluates from ethanol–hexane, the total yield of *VIII* was 9·4 g (34% calculated per starting *V*). Analytical sample, m.p. 134—138°C (ethanol). UV spectrum: λ_{max} 251 nm (log ε 4·20), infl. 285 nm (3·71). IR spectrum: 719, 811, 870, 891 (3 adjacent thiophene H, 2 adjacent and solitary Ar—H), 1 217, 1 238, 1 270, **1 700**, 2 630, 2 720, infl. 3 120 (RCOOH), 1 520, 1 580 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·75 (dd, J = 5·0; 1·5 Hz, 1 H, 5-H of thiophene), 6·90—7·50 (m, 5 H, remaining Ar—H and thiophene H), 3·80 (s, 2 H, $ArCH_2CO$). For $C_{12}H_9ClO_2S_2$ (284·8) calculated: 50·61% C, 3·19% H, 12·45% Cl, 22·52% S; found: 50·74% C, 3·18% H, 12·99% Cl, 22·29% S.

Evaporation of the mother liquor and crystallization of the residue from a mixture of toluene and hexane gave 2·9 g another acid which was identified as 5-chloro-2-(2-thienylthio)benzoic acid (*IX*), m.p. 190—191°C. Mass spectrum, m/z (%): 269·9560 (M^+ corresponding to $C_{11}H_7ClO_2S_2$, calculated 269·9577, 100%), 252, 237, 224 (36), 190 (22), 171 (27), 115 (27), 71 (70). UV spectrum: λ_{max} 257 nm (log ε 4·18), 323 nm (3·59). IR spectrum: 810, 831, 857, 890 (2 adjacent and solitary Ar—H), 923, 1 247, 1 309, **1 690**, 2 535, 2 600, 2 630, 2 665, 2 728, infl. 3 140 (Ar.COOH), 1 548 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·90 (d, J = 2·5 Hz, 1 H, 6-H), 7·85 (dd, J = 5·0; 1·5 Hz, 1 H, 5-H of thiophene), 7·10—7·50 (m, 3 H, 4-H and thiophene 3,4-H_2), 6·75 (d, J = 9·0 Hz, 1 H, 2-H). For $C_{11}H_7ClO_2S_2$ (270·8) calculated: 48·80% C, 2·61% H, 13·09% Cl, 23·68% S; found: 48·69% C, 2·56% H, 13·11% Cl, 23·50% S.

7-Chlorothieno[2,3-*b*]-1-benzothiepin-4(5*H*)-one (*X*)

A mixture of 6·4 g *VIII*, 8·0 g P_2O_5 and 65 ml toluene was stirred and refluxed for 3 h, after cooling it was washed with 5% KOH solution and with water. Acidification of the washings recovered 2·0 g starting acid *VIII* (m.p. 133—136°C). The toluene solution was dried with K_2CO_3 and evaporated. The residue gave by crystallization from a mixture of 20 ml benzene and 10 ml hexane 2·8 g *X*, m.p. 154—157°C. Evaporation of the mother liquor and chromatography on a column of 30 g silica gel (elution with benzene) gave first further 1·0 g *X*, m.p. 153—156°C; the total yield is thus 3·8 g (92% per conversion). Analytical sample, m.p. 156—157°C (benzene–hexane). UV spectrum: λ_{max} 258 nm (log ε 4·33), 313 nm (3·95). IR spectrum: 812, 880, 900 (2 adjacent

and solitary Ar—H), 1 502, 1 557, 1 577, 3 050, 3 085, 3 100 (Ar), 1 666 cm^{-1} (ArCOR). ^1H NMR spectrum: δ 6·80—7·50 (m, 5 H, ArH), 4·10 (s, 2 H, $ArCH_2CO$). For $C_{12}H_7ClOS$ (266·8) calculated: 54·03% C, 2·64% H, 13·29% Cl, 24·04% S; found: 54·21% C, 2·61% H, 13·54% Cl, 23·91% S.

Continued elution in the chromatography of the mother liquors gave 0·3 g 6-chlorothieno-[2,3-*b*]-1-benzothiopyran-4-one (*XI*), m.p. 180—184°C (benzene). Mass spectrum, *m/z* (%): 251·9495 (M^+ corresponding to $C_{11}H_5ClOS_2$ in agreement with the analysis, calculated 251·9471, 100%), 224 (50), 189 (10), 145 (12). UV spectrum: λ_{max} 263 nm (log ε 4·44), 366 nm (3·86)), inflexes at 288 nm (3·97) and 307 nm (3·67). IR spectrum: 771, 820, 909 (2 adjacent and solitary Ar—H), 1 502, 1 585, 3 069, 3 100 (Ar), 1 613 cm^{-1} (ArCOAr). Lit[14,17], m.p. 180—182, and 174°C, respectively.

7-Chloro-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin-4-ol (*XII*)

A stirred solution of 4·1 g *X* in a mixture of 40 ml ethanol and 20 ml tetrahydrofuran was treated with 0·45 g $NaBH_4$ and refluxed for 10 min. It was evaporated *in vacuo*, the residue was treated with 60 ml water and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated under reduced pressure. The residue was crystallized from ethanol–hexane and the mother liquor was processed in the usual way; 3·5 g (80%), m.p. 133—134°C (ethanol). IR spectrum: 814, 833, 881 (2 adjacent and solitary Ar—H), 1 090 (CHOH in the cycle), 1 555, 1 580 (Ar), 3 100, 3 190, 3 250 cm^{-1} (OH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·90—7·60 (m, 5 H, ArH), 5·60 (bd, J = 5·0 Hz, disappears after ^2H_2O, 1 H, OH), 4·85 (bq, J = 5·0 Hz, 1 H, Ar—CH—O), 3·40 (d, J = 5·0 Hz, 2 H, $ArCH_2$). For $C_{12}H_9ClOS_2$ (268·8) calculated: 53·62% C, 3·38% H, 13·19% Cl, 23·86% S; found: 53·85% C, 3·34% H, 12·98% Cl, 23·68% S:

4,7-Dichloro-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin (*XIII*)

A solution of 3·5 g *XII* in 35 ml benzene was treated with 1·3 g powdered $CaCl_2$ and the suspension was saturated for 2 h with HCl at 10—15°C. After standing overnight the mixture was filtered, the filtrate was evaporated and the residue crystallized from benzene–hexane; 3·5 g (94%), m.p. 145—147·5°C (benzene). For $C_{12}H_8Cl_2S_2$ (287·2) calculated: 50·18% C, 2·81% H, 24·69% Cl, 22·33% S; found: 50·70% C, 2·80% H, 24·43% Cl, 22·13% S.

7-Chloro-4-[4-(2-hydroxyethyl)piperazino]-4,5-dihydrothieno[2,3-*b*]-1-benzothiepin (*IV*)

A mixture of 3·2 g *XIII*, 2·9 g 1-(2-hydroxyethyl)piperazine and 3·0 ml chloroform was stirred and refluxed under nitrogen for 5 h. After standing overnight the mixture was treated with 100 ml water and extracted with dichloromethane. The extract was washed with water and shaken with 50 ml 5% hydrochloric acid. The precipitated hydrochloride was dissolved by the addition of 100 ml water, the aqueous layer was separated, made alkaline with NH_4OH and the base was isolated by extraction with dichloromethane; 3·6 g (85%) crude *IV*. Crystallization from ethanol gave a solvate melting unsharply at 116—126°C. It was crystallized from benzene–hexane but the different substance obtained appears to be a 6 : 1 solvate with benzene, m.p. 130—136°C. Mass spectrum, *m/z* (%): 380·0772 (M^+ corresponding to $C_{18}H_{21}ClN_2OS_2$, calculated 380·0785, 18%), 251 (45), 250 (38), 218 (21), 216 (22), 129 (29), 100 (100), 58 (35), 56 (60). UV spectrum: inflex at 265 nm (log ε 3·90). IR spectrum: 815, 822, 876, 900 (2 adjacent and solitary Ar—H), 1 049 (CH_2OH), 1 555, 1 580 (Ar), 2 820 (CH_2—N), 3 130 cm^{-1} (OH). ^1H NMR spectrum: δ 7·00—7·40 (m, 4 H, 6,8,9-H_3 and 1/6 C_6H_6), 7·05 (d, J = 5·0 Hz, 1 H, 2-H), 6·90 (d, J = = 5·0 Hz, 1 H, 3-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·60 (t, J = 7·0 Hz, 2 H, CH_2O), 3·12 (s, 1 H, OH), *c.* 2·55 (bm, 10 H, 5 NCH_2). For $C_{18}H_{21}ClN_2OS_2 + 1/6\ C_6H_6$ (394·0) calculated: 57·92% C, 5·63% H, 9·00% Cl, 7·11% N, 16·28% S; found: 58·23% C, 5·81% H, 9·10% Cl, 6·99% N, 16·09% S.

Bis(hydrogen maleate), m.p. 129–130°C with decomposition (ethanol–ether). For $C_{26}H_{29}ClN_2O_9S_2$ (613·1) calculated: 50·93% C, 4·77% H, 5·78% Cl, 4·57% N, 10·46% S; found: 51·10% C, 4·79% H, 5·95% Cl, 4·77% N, 10·50% S.

The organic layer, from which the basic product was removed by extraction with dilute hydrochloric acid, was washed with water, dried with Na_2SO_4–$MgSO_4$ and evaporated. The oily residue was chromatographed on a column of 15 g silica gel. Elution with benzene gave 0·40 g (14%) homogeneous 7-chlorothieno[2,3-*b*]-1-benzothiepin (*XIV*), m.p. 50–51°C (cyclohexane–hexane). ^{1}H NMR spectrum: δ 6·70–7·30 (m, ArH and CH=CH). For $C_{12}H_7ClS_2$ (250·8) calculated: 57·47% C, 2·81% H, 14·14% Cl, 25·57% S; found: 57·95% C, 2·95% H, 13·80% Cl, 24·95% S.

The spectra were recorded and interpreted by Drs E. Svátek, J. Holubek, M. Ryska, I. Koruna, J. Schlanger and Mrs A. Hrádková (department of physical chemistry of this institute). The microbiological screening was carried out by Dr V. Holá and coworkers (department of microbiology). The authors are indebted to Mrs J. Komancová and Mrs V. Šmídová for carrying out the analyses (analytical department).

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