NONCATALEPTIC NEUROLEPTIC AGENTS: SYNTHESIS OF SOME ESTERS OF 2-CHLORO-10-(4-(2-HYDROXYETHYL)PIPERAZINO)-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN

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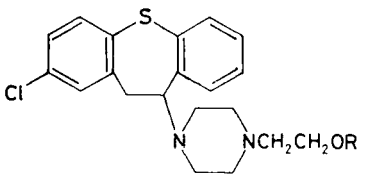
Reactions of 2-chloro-10-(4-(2-hydroxyethyl)piperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*I*) with phenylacetic, methoxyacetic, methylthioacetic, phenoxyacetic and morpholinoacetic acid in dichloromethane and in the presence of N,N'-carbonyldiimidazole gave the title esters *II*—*VI*. Reaction of *I* with succinic anhydride afforded the hemisuccinate *VII*. The esters prepared elicited ataxia in low doses, were low-cataleptic, but only II, *IV*, and *VII* proved some antidopaminergic activity in the test using the affecting dopamine metabolism in rat brain striatum.

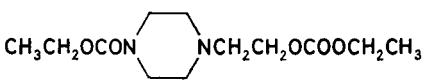
2-Chloro-10-(4-(2-hydroxyethyl)piperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin ("docloxythepin", *I*) (refs[1–3]) showed in animal and biochemical tests[5,6] properties of a potentially useful noncataleptic neuroleptic agent. A pharmacokinetic study[7] of the radioactively labelled compound (10-^{14}C-*I*) in rats, administered orally in the form of the well water-soluble succinate, proved a high-rate elimination of radioactivity in faeces (80% in four days) and indicated thus a low absorption. This indication was partly contradicted by finding high docloxythepin (*I*) levels in bile and an evidently intensive enterohepatic cycle[8]. In the meantime, however, there was attempted to modulate the bioavailability of docloxythepin (*I*) by its substitution with some esters as potential pro-drugs. The choice of these esters was empirical



I, R = H
II, R = $COCH_2C_6H_5$
III, R = $COCH_2OCH_3$
IV, R = $COCH_2SCH_3$
V, R = $COCH_2OC_6H_5$
VI, R = $COCH_2N$O
VII, R = $CO(CH_2)_2COOH$

but at least partly it was tried to maintain the hydrophobic–hydrophilic balance similar like in the docloxythepin (*I*) molecule; some rather hydrophilic acids were therefore used for esterification. The synthesis and pharmacology of esters *II* – *VII* is being described in this communication.

Out of the docloxythepin esters only acetate[2] and decanoate[1] are known. Reactions of phenylacetic, methoxyacetic[9], methylthioacetic[10], phenoxyacetic and morpholinoacetic acid[11] with N,N'-carbonyldiimidazole in dichloromethane and the following treatment with the base *I* at room temperature afforded the esters *II* – *VII* (for the method, *cf.*[12]). With the exception of the ester *III*, the bases were oily. They were transformed to crystalline maleates and characterized by the mass spectra (the base *III* by IR and ^{1}H NMR spectra). Reaction of the base *I* with succinic anhydride in boiling benzene gave the monobasic hemisuccinate *VII*, identified by spectra and transformed to the hydrogen maleate. An attempt to prepare docloxythepin monoethyl carbonate by treatment of the base *I* with an equivalent amount of ethyl chloroformate in benzene at 35°C led to a cleavage of the molecule of *I*. The product, which crystallized from the reaction mixture, was identified as the monohydrochloride of *I*. Processing of the mother liquor with maleic acid gave a crystalline maleate which was identified as 1-(ethoxycarbonyl)-4-(2-ethoxycarbonyloxyethyl)-piperazine (*VIII*) hydrogen maleate (analysis and mass spectrum). Esterification of compound *I* with ethyl chloroformate proceeds under simultaneous cleavage of the $C_{(10)}$—$N_{(1)}$ bond and $N_{(1)}$—acylation. A part of the starting *I* (50% in fact) remains unchanged and binds a part of hydrogen chloride formed to give the monohydrochloride. The neutral product of the cleavage reaction was evidently 2,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[1] (*cf.*[13]) which was not isolated.



VIII

Results of preliminary pharmacological testing of the compounds prepared (compounds *II* – *VII* were tested in the form of maleates, administered orally; the doses given were calculated per bases): Acute toxicity in mice, LD_{50} in mg/kg: *II*, 240; *III*, 220; *V*, 326; *VI*, 170; *VII*, 150. Discoordinating activity in the rotarod test in mice, ED_{50} in mg/kg: *II*, 1·0; *III*, 3·1; *IV*, 3·0; *V*, 1·9; *VI*, 2·0; *VII*, 1·1. Cataleptic effect in rats, percentage of cataleptic animals after the dose of 100 mg/kg: *II*, 10; *III*, 30; *IV*, 30; *V*, 50 (= ED_{50}); *VI*, 30; *VII*, 30 (the cataleptogenic effects of the whole series are negligible). Antiapomorphine effect in rats (antagonization of the stereotypies): compounds *II* – *VII* inactive at the dose of 50 mg/kg. Antidopaminergic effects evaluated by determination of levels of homovanillic (HVA) and 3,4-dihydroxyphenyl acetic acid (DOPAC) (main dopamine metabolites) in rat brain striatum

in comparison with the control: compounds *II* and *VII* in doses of 80 mg/kg brought about rises of HVA levels by 150–200%. The same doses of compounds *III*, *V*, and *VI* were practically without effect. Compound *IV* increased significantly the HVA level at the dose of 40 mg/kg and the DOPAC level at the dose of 20 mg/kg (active in similar doses like docloxythepin[6]). The results were not considered warranting a pharmacokinetic study of any of the esters.

Compounds *II*–*VII* were also tested for antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus*, *III* 50, *V* 50, *VI* 25; *Streptococcus faecalis*, *III* 50, *V* 50, *VI* 100; *Staphylococcus pyogenes aureus*, *III* 25, *V* 25, *VII* 100; *Escherichia coli*, *III* 50, *V* 12·5, *VI* 25; *VII* 100; *Proteus vulgaris*, *V* 100, *VI* 100; *Mycobacterium tuberculosis* H37Rv, *III* 12·5, *VI* 12·5; *Trichophyton mentagrophytes*, *II* 50, *III* 50, *IV* 50, *V* 50.

EXPERIMENTAL

The melting points of analytical samples were determined in a Mettler FP-5 melting point recorder; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. IR spectra (in Nujol) were recorded with a Unicam SP 200G spectrophotometer, ^1H NMR spectra (in C^2HCl_3) with a Tesla BS 487 C (80 MHz) spectrometer, and mass spectra with the MCH-1320 spectrometer. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol).

2-Chloro-10-(4-(2-phenylacetoxyethyl)piperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*II*)

A solution of 3·20 g 90% N,N′-carbonyldiimidazole in 40 ml dichloromethane was stirred under nitrogen and treated with 2·45 g phenylacetic acid. After 10 min stirring 6·0 g *I* (ref.[1]) were added, the mixture was stirred for 2 h at room temperature, allowed to stand for 48 h, and evaporated *in vacuo*. The residue was dissolved in 50 ml benzene, precipitated imidazole was filtered off after 2 h and washed with benzene. The filtrate was evaporated *in vacuo*, the glassy residue was dissolved in 20 ml acetone and the solution was treated with a solution of 1·80 g maleic acid in 10 ml acetone. It was followed by crystallization of 0·80 g substance, m.p. 136–137°C with decomposition (needles from ethanol), which was identified as imidazole hydrogen maleate. For $C_7H_8N_2O_4$ (184·2) calculated: 45·65% C, 4·38% H, 15·22% N; found: 46·07% C, 4·45% H, 15·43% N.

The mother liquor was partly evaporated *in vacuo* and by standing for 3 h the maleate of *II* crystallized; 5·20 g (54%), m.p. 154–155°C (acetone). Mass spectrum (*m/z*): 492 (M^+ corresponding to $C_{28}H_{29}ClN_2O_2S$), 356, 245, 163, 91. For $C_{32}H_{33}ClN_2O_6S$ (609·2) calculated: 63·10% C, 5·46% H, 5·82% Cl, 4·60% N, 5·26% S; found: 62·60% C, 5·65% H, 6·03% Cl, 4·70% N, 5·40% S.

2-Chloro-10-(4-(2-methoxyacetoxyethyl)piperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (*III*)

A stirred solution of 3·25 g 90% N,N′-carbonyldiimidazole in 30 ml dichloromethane was treated under nitrogen with a solution of 1·80 g methoxyacetic acid (b.p. 97–99°C/2 kPa) (ref.[9]) in 4 ml

dichloromethane. It was stirred for 10 min, treated with a solution of 6·0 g *I* (ref.[1]) in 10 ml dichloromethane, stirred for 2 h at room temperature, allowed to stand for 48 h, and evaporated *in vacuo*. The residue was dissolved in 50 ml benzene, the solution deposited crystalline imidazole which was filtered off, the filtrate was evaporated and the residue crystallized by standing; 5·78 g (81%), m.p. 103–104°C (acetone). IR spectrum: 760, 819, 875 (4 and 2 adjacent and solitary Ar—H), 1 137, 1 200 (C—O of ether and ester), 1 560, 1 583, 3 038, 3 060 (Ar), 1 750 cm^{-1} (RCOOR'). ^1H NMR spectrum: δ 6·90–7·70 (m, 7 H, ArH), 4·25 (t, J = 7·0 Hz, 2 H, CH_2OCO), 4·00 (s, 2 H, $COCH_2O$), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·40 (s, 3 H, CH_3O), 2·40–2·80 (m, 10 H, 5 CH_2N). For $C_{23}H_{27}ClN_2O_3S$ (447·0) calculated: 61·80% C, 6·09% H, 7·93% Cl, 6·27% N, 7·17% S; found: 62·27% C, 6·01% H, 7·92% Cl, 6·19% N, 7·48% S.

Maleate, m.p. 153–154°C (acetone). For $C_{27}H_{31}ClN_2O_7S$ (563·1) calculated: 57·59% C, 5·55% H, 6·30% Cl, 4·98% N, 5·69% S; found: 58·00% C, 5·48% H, 6·31% Cl, 5·24% N, 5·90% S.

2-Chloro-10-(4-(2-methylthioacetoxyethyl)piperazino)-
-10,11-dihydrodibenzo[*b*,*f*]thiepin (*IV*)

A similar reaction of 3·25 g 93% N,N'-carbonyldiimidazole with 1·7 g methylthioacetic acid (b.p. 108°C/1·3 kPa) (ref.[10]) in 70 ml dichloromethane, treatment with 6·0 g *I* (ref.[1]) in 15 ml dichloromethane, and similar processing gave 6·1 g oily product containing some imidazole. It was chromatographed on 90 g neutral Al_2O_3 (activity II). Elution with benzene afforded 5·5 g (74%) homogeneous oily *IV*. Neutralization with maleic acid in acetone and addition of ether gave the maleate, m.p. 137–137·5°C (acetone–ether). Mass spectrum, *m/z*: 462 and 464 (M^+, corresponding to $C_{23}H_{27}ClN_2O_2S_2$), 356, 357, 245 (base peak). For $C_{27}H_{31}ClN_2O_6S_2$ (579·1) calculated: 56·00% C, 5·39% H, 6·12% Cl, 4·84% N, 11·07% S; found: 56·00% C, 5·40% H, 6·22% Cl, 4·74% N, 10·88% S.

2-Chloro-10-(4-(2-phenoxyacetoxyethyl)piperazino)-
-10,11-dihydrodibenzo[*b*,*f*]thiepin (*V*)

Similarly like in the case of *II*, 3·2 g N,N'-carbonyldiimidazole were treated first with 2·75 g phenoxyacetic acid and then with 6·0 g *I* (ref.[1]) in 40 ml dichloromethane. Similar processing including removal of imidazole gave 8·0 g crude oily product which was neutralized with 1·90 g maleic acid in 40 ml acetone. A small quantity of imidazole hydrogen maleate was filtered off and the filtrate gave by crystallization 7·30 g (72%) V maleate hemihydrate, m.p. 150–152°C (acetone). For $C_{32}H_{33}ClN_2O_7S + 0{\cdot}5\ H_2O$ (634·1) calculated: 60·60% C, 5·40% H, 5·59% Cl, 4·42% N, 5·06% S; found: 60·91% C, 5·36% H, 6·00% Cl, 4·52% N, 5·16% S.

2-Chloro-10-(4-(2-morpholinoacetoxyethyl)piperazino)-
-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VI*)

N,N'-Carbonyldiimidazole (3·25 g, 93%) was similarly treated with 2·32 g morpholinoacetic acid (m.p. 162–163°C) (ref.[11]) in 70 ml dichloromethane and after 15 min of stirring with a solution of 6·0 g *I* (ref.[1]) in 15 ml dichloromethane. The mixture was stirred for 2 h at room temperature, allowed to stand for 20 h and evaporated. The residue was dissolved in 50 ml benzene and the solution allowed to stand overnight. The crystallized imidazole was filtered off and the filtrate was evaporated *in vacuo*. The residue was dissolved in 70 ml acetone and the solution was neutralized with 3·8 g maleic acid in 12 ml acetone. The resulting solution was partly evaporated and diluted with ether; 8·20 g (69%) *VI* dimaleate hemihydrate, m.p. 132·5–133·5°C (acetone–ether). Mass spectrum, *m/z*: 501 (M^+ corresponding to $C_{26}H_{32}ClN_3O_3S$), 245 (100%), 210, 144, 113

100 (100%), 84, 70, 55. For $C_{34}H_{40}ClN_3O_{11}S + 0{\cdot}5\ H_2O$ (743·2) calculated: 54·94% C, 5·56% H, 4·77% Cl, 5·65% N, 4·32% S; found: 54·92% C, 5·50% H, 5·13% Cl, 5·56% N, 4·64% S.

2-Chloro-10-(4-(2-(3-carboxypropionoxy)ethyl)piperazino)-
-10,11-dihydrodibenzo[*b*,*f*]thiepin (*VII*)

A solution of 6·0 g *I* (ref.[1]) in 75 ml benzene was treated with 1·6 g succinic anhydride and the mixture was stirred and refluxed for 5 h. After evaporation of benzene *in vacuo*, the residue was triturated with a mixture of 20 ml light petroleum and 20 ml acetone and allowed to stand overnight; 6·6 g (87%) *VII*, m.p. 149°C (acetone). IR spectrum: 749, 821, 890 (4 and 2 adjacent and solitary Ar—H), 1 175, 1 360, 1 380 (C—O), 1 563, 1 580, 3 030, 3 050 (Ar), 980, 1 700 (COOH), 1 749 cm^{-1} (RCOOR'). ^1H NMR spectrum: δ 11·68 (bs, 1 H, COOH), 6·90—7·70 (m, 7 H, ArH), 4·25 (bt, 2 H, CH_2OCO), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·70 (bs, 10 H, 5 CH_2N), 2·54 (s, 4 H, $COCH_2CH_2CO$). For $C_{24}H_{27}ClN_2O_4S$ (475·0) calculated: 60·69% C, 5·73% H, 7·46% Cl, 5·90% N, 6·75% S; found: 61·14% C, 6·07% H, 7·27% Cl, 5·92% N, 6·78% S.

Maleate, m.p. 141·5—142°C (acetone–ether). For $C_{28}H_{31}ClN_2O_8S$ (591·1) calculated: 56·90% C, 5·29% H, 6·00% Cl, 4·74% N, 5·42% S; found: 57·20% C, 4·75% H, 6·11% Cl, 4·70% N, 5·61% S.

1-(Ethoxycarbonyl)-4-(2-ethoxycarbonyloxyethyl)piperazine (*VIII*)

A stirred solution of 6·0 g *I* (ref.[1]) in 30 ml benzene was treated dropwise with a solution of 1·80 g ethyl chloroformate in 10 ml benzene at 35°C. The mixture was allowed to stand for 72 h at room temperature and the precipitate was filtered, washed with benzene and crystallized from a mixture of aqueous ethanol and acetone; 3·3 g (50%) *I* monohydrochloride, m.p. 220—223°C. Mass spectrum, *m/z*: 374 (M^+ corresponding to $C_{20}H_{23}ClN_2OS$), 343 (M—CH_2OH), 273, 272, 245, 129, 100 (base peak). For $C_{20}H_{24}Cl_2N_2OS$ (411·4) calculated: 58·39% C, 5·88% H, 17·24% Cl, 6·81% N, 7·79% S; found: 59·02% C, 5·86% H, 16·87% Cl, 6·63% N, 7·70% S.

The mother liquor was evaporated *in vacuo*, the residue was dissolved in 5 ml acetone and the solution was treated with 1·0 g maleic acid in 2 ml acetone. Crystallization by standing gave 3·85 g mixture melting at 122—123°C. Repeated crystallization from acetone gave finally 1·08 g (17%) *VIII* hydrogen maleate, m.p. 140—141°C. Mass spectrum (*m/z*): 274 (M^+ corresponding to $C_{12}H_{22}N_2O_5$), 229, 185, 184, 171 (base peak). For $C_{16}H_{29}N_2O_9$ (390·4) calculated: 49·22% C, 6·71% H, 7·17% N, found: 49·19% C, 6·78% H, 7·25% N.

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