NEUROLEPTIC 2-CHLORO-11-(2-PIPERAZINOETHOXY)-10,11-DIHYDRODIBENZO[*b*,*f*]THIEPINS: SYNTHESIS AND PHARMACOLOGY

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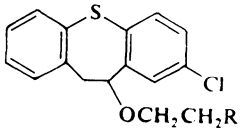
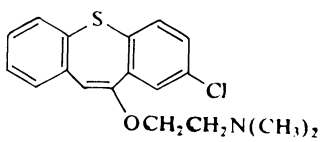
A reaction of 8-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol with 2-bromoethanol and boron trifluoride etherate produced the 2-bromoethyl ether *II* which was subjected to substitution reactions with 1-methylpiperazine, 1-(2-hydroxyethyl)piperazine, 1-(3-hydroxypropyl)piperazine and 1-ethoxycarbonylpiperazine to give the title piperazinoethoxy compounds *IV*–*VII*. Alkaline hydrolysis of the carbamate *VII* afforded the monosubstituted piperazine *VIII*. Compounds *IV*–*VI* are neuroleptics with an interesting activity profile: they are little toxic, have strong central depressant and antiapomorphine activity, mild cataleptic effects, they intensively increase the dopamine metabolism in the rat brain striatum and are almost free of the peripheral adrenolytic efficacy.

The aminoalkyl ethers like compound *I* were the first series of neurotropic and psychotropic substances we found among amines derived from the dibenzo[*b*,*f*]thiepin skeleton[1–4]; central depressant, discoordinating, thiopental potentiating, antihistamine and antiserotonin effects were described. We touched also the analogous enol ethers[5] but a more detailed investigation was given up because of the instability of these compounds in acid solutions and in the form of salts. This view was not completely correct and the company Fujisawa was able to introduce the agent zotepine (*III*) into the therapy of schizophrenia as a mild neuroleptic[6–9]. Our temporary loss of interest in ethers of type *I* and *II* was mainly due to the discovery of more significant depressant and neuroleptic effects in the series of 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin derivatives[10–13] to which our efforts were concentrated.



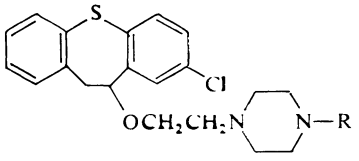
I, R = $N(CH_3)_2$
II, R = Br



III

In the present communication we are coming back to aminoalkyl ethers of type *I* in whose molecules the amino group is a part of a piperazine moiety. We are describing the synthesis and pharmacology of the title compounds *IV*–*VIII*.

The synthesis of ethers *IV*–*VIII* started from 11-(2-bromoethoxy)-2-chloro--10,11-dihydrodibenzo[*b*,*f*]thiepin (*II*) which was obtained by reaction of a mixture of 8-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol[2] and 2-bromoethanol with boron trifluoride etherate in benzene at room temperature. The oily product was obtained in a high yield, its chromatography proved that it is almost homogeneous, it afforded satisfactory analytical results and its ^{1}H NMR spectrum fully confirmed its identity. A reaction of the bromo compound *II* with an excess of 1-methyl-piperazine at 100°C resulted in ether *IV* which was transformed to crystalline salts: the little water-soluble bis(hydrogen maleate) and the excellently soluble dimethanesulfonate. Unsuccessful were our attempts at preparing this ether either by treatment of 8-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol[2] first with sodium amide and then with 1-(2-chloroethyl)-4-methylpiperazine[14] in boiling toluene, or by a reaction of 2,11-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[2] with excessive 1-(2-hydroxyethyl)-4-methylpiperazine[14] in boiling benzene (in this case the starting dichloro compound was recovered unchanged). The ethers *V*–*VII* were obtained by reactions of the bromo compound *II* with 1-(2-hydroxyethyl)piperazine, 1-(3-hydroxypropyl)-piperazine[15] and 1-ethoxycarbonylpiperazine in the presence of potassium carbonate in dimethylformamide at 100°C. The bases were oily and were purified in the form of maleates. In the case of the ether *V*, the highly water-soluble dimethanesulfonate was also prepared. Decomposition of the pure maleate of *VII* with aqueous ammonia afforded the pure oily base whose ^{1}H NMR spectrum corroborated its identity. Hydrolysis of the carbamate *VII* with boiling ethanolic potassium hydroxide gave the monosubstituted piperazine *VIII*, purified in the form of maleate.



IV, R = CH_3 *VI*, R = $CH_2CH_2CH_2OH$
V, R = CH_2CH_2OH *VII*, R = $COOC_2H_5$
VIII, R = H

The ethers *IV*–*VI* were pharmacologically tested in the form of salts described in the Experimental (the doses given were calculated for the bases) upon oral administration. Acute toxicity in mice, LD_{50} (mg/kg): *IV*, 354; *V*, 233; *VI*, 526. Discoordinating effect in the rotarod test in mice, ED_{50} (mg/kg): *IV*, 20·5 (the effect disappears within 24 h); *V*, 25 (after 48 h the effect is over); *VI*, 19 (after 24 h, the effect is over).

Discoordinating effect in rats, ED_{50} (mg/kg): *IV*, 3·4 (the effect disappeared within 24 h); *V*, 1·2 (4·9 after 24 h). Central depressant effect in mice (reduction of spontaneous locomotor activity) estimated by the photo-cell method of Dews in the interval of 1 h after the administration, D_{50} (mg/kg): *IV*, 1·8; *V*, 1·9 (a dose of 5 mg/kg has a significant effect still after 24 h); *VI*, 4·3 (the highest administered dose of 8 mg/kg is without effect after 24 h). Cataleptic effect in rats, ED_{50} (mg/kg): *IV*, 11·9 (67 after 24 h); *V*, 11·9 (within 24 h the effect over); *VI*, 15·5. Antiapomorphine effect (toward stereotypies in rats), D_{50} (mg/kg): *IV*, 32·6 (a dose of 80 mg/kg maintains the effect still after 24 h); *V*, 1·6 (disappears within 24 h); *VI*, 4·1. In a dose of 25 mg/kg compounds *IV*–*VI* do not influence the adrenaline toxicity in mice and their protective doses toward the lethal effect of noradranaline in rats are higher than 50 mg/kg. In a dose of 5 mg/kg compounds *IV*–*VI* increase significantly the dopamine metabolism in the rat brain striatum which is manifested by the increase of the homovanillic acid level in the interval of 3 h after the administration (in per cent of the control value): *IV*, 392 (a dose of 80 mg/kg 1 023% in 3 h, 1 465% in 24 h); *V*, 570; *VI*, 392. Even in a dose of 80 mg/kg compound *IV* does not influence the concentration of 5-hydroxyindole-3-acetic acid in the rat brain striatum.

Compounds *V*–*VIII* were further subjected to a general pharmacological screening. First values of acute toxicity in mice, the way of administration and doses D (doses in mg/kg), used in the screening, are given: *V*, 50, *i.v.*, 10; *VI*, 50 *i.v.*, 10; *VII*, 2 500, *p.o.*, 300; *VIII*, 2 000, *p.o.*, 300. Negative influence on the spontaneous motility in mice: *VII*, ED = 100–300 mg/kg *p.o.* Discoordinating effect in the rotarod test in mice, ED (mg/kg): *VII*, 100–300; *VIII*, 300. Thiopental potentiation (a dose in mg/kg prolonging the thiopental sleeping time in mice to 200% of the control value): *V*, 0·5–1·0 *s.c.*; *VI*, 1–2·5 *i.v.*; *VII*, 100–300 *p.o.*; *VIII*, 100–300 *p.o.* Hypothermic effect (a dose decreasing the rectal temperature of rats by 1·0°C): *V*, 10 *i.v.* (a weak effect); *VII*, 100–300 *p.o.* Antiamphetamine effect (a dose in mg/kg protecting 100% of mice from the lethal effect of a standard dose of amphetamine): *V*, 1–5 *i.v.*; *VI*, 1–5 *i.v.*; *VII*, 50–100 *p.o.*; *VIII*, 50–100 *p.o.* Antihistamine activity (a dose in mg/kg protecting 50% guinea-pigs from the lethal effect of 5 mg/kg histamine administered intrajugularly): *V*, 10 *s.c.*; *VI*, 10 *s.c.* Spasmolytic, parasympatholytic effect (a concentration in μg/ml exhibiting a reduction of the acetylcholine contraction of the isolated rat duodenum by 50%): *V*, 10. Spasmolytic, musculotropic effect (barium chloride contractions): *V*, 10. Corneal anaesthesia (a concentration bringing about in 50% rabbits a complete anaesthesia of the eye cornea): *V*, 0·1 to 0·5%. Antiarrhythmic effect (a dose in mg/kg prolonging with statistical significance the latency of ventricular extrasystoles in rats elicited with aconitine): *VIII*, 300 *p.o.* Effect on the blood pressure in normotensive rats: *V*, a dose of 10 mg/kg *i.v.* brings about deep and brief drops of the blood pressure. Adrenolytic effect (a dose inhibiting the adrenaline pressor reaction by 50%): *V*, 0·1 *i.v.* Anorectic activity (a dose in mg/kg decreasing the food consumption in mice by 50%): *V*, 10–50 *p.o.* (may be the result

of central depression). Antitussic action (a dose in mg/kg reducing to 50% the number of the cough attacks in rats elicited by the aerosol of an aqueous citric acid solution in comparison with the control): *V*, 10 *i.v.* (38%); *VI*, 50 *p.o.* (51%).

In conclusion compounds *IV*–*VI* may be characterized as mild neuroleptic agents with low oral acute toxicity, rather high central depressant and antiapomorphine activity (especially *V*), mild cataleptic activity, very low peripheral adrenolytic effect on oral administration and a rather high dopamine metabolism increasing effect in the striatum of the rat brain (*V* being the most active). Compounds *VII* and *VIII* are less active but produce some peripheral and cardiovascular effects.

Antimicrobial effects *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml unless they exceed 100 μg/ml are give): *Streptococcus* β-*haemolyticus*, *IV* 100, *V* 50, *VI* 50, *VIII* 50; *Streptococcus faecalis*, *V* 100, *VI* 100, *VIII* 50; *Staphylococcus pyogenes aureus*, *IV* 100, *V* 50, *VI* 50, *VIII* 12·5; *Escherichia coli*, *IV* 100, *VIII* 100; *Proteus vulgaris*, *VIII* 100; *Trichophyton mentagrophytes*, *IV* 50, *V* 25, *VI* 50, *VII* 50, *VIII* 50.

EXPERIMENTAL

The melting points of analytical samples were determined partly in a Mettler FP-5 melting point recorder and partly in Kofler's block (are not corrected); the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at 77°C or at room temperature. The ^1H NMR spectra (in C^2HCl_3) were recorded with a Tesla BS 487C (80 MHz) spectrometer. The homogeneity of the compounds and composition of the reaction mixtures and crude products were checked by thin-layer chromatography on silica gel (Silufol).

11-(2-Bromoethoxy)-2-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin (*II*)

A stirred solution of 25·0 g 8-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-ol[2] and 18·0 g 2-bromoethanol in 250 ml benzene was treated dropwise over 30 min with 13·0 ml $BF_3.O(C_2H_5)_2$ and the mixture was stirred for 45 min at room temperature. It was decomposed by the addition of 200 ml water, the organic layer was washed with water, dried with K_2CO_3 and evaporated; 33·7 g (96%) almost homogeneous oil which was used for further work. A sample (3·0 g) was chromatographed on 100 g neutral Al_2O_3 (activity II). Elution with benzene yielded 2·7 g homogeneous oil. ^1H NMR spectrum: δ 7·52 (d, J = 2·0 Hz, 1 H, 1-H), 7·40 (d, J = 8·0 Hz, 1 H, 4-H), 7·30 (m, 1 H, 6-H), 7·10 (q, J = 8·0; 2·0 Hz), 6·90–7·25 (m, together with the preceding signal 4 H, 3,7,8,9-H_4), 5·40 (dd, J = 10·0; 4·0 Hz, 1 H, Ar—CH—O), 3·20–4·00 (m, 6 H, $ArCH_2$ and OCH_2CH_2Br). For $C_{16}H_{14}BrClOS$ (369·7) calculated: 51·98% C, 3·82% H, 21·61% Br, 9·59%Cl, 8·67% S; found: 52·63% C, 3·86% H, 21·06% Br, 9·34% Cl, 8·64% S.

1-[2-(2-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-yloxy)ethyl]-4-methylpiperazine (*IV*)

A mixture of 11·0 g *II* and 11·0 g 1-methylpiperazine was stirred and heated for 3 h to 100°C, dissolved in 10 ml chloroform and the solution was refluxed for 2 h. Chloroform was evaporated and the residue was distributed between benzene and water. The organic layer was washed with water, dried with K_2CO_3 and evaporated; 10·8 g (93%) oil. It was dissolved in 40 ml ethanol and the solution was neutralized with a solution of 6·50 g maleic acid in 60 ml ethanol; 15·3 g bis(hydrogen maleate), m.p. 182–187°C. Analytical sample, m.p. 197–200°C (90% ethanol). For $C_{29}H_{33}ClN_2O_9S$ (621·1) calculated: 56·08% C, 5·36% H, 5·71% Cl, 4·51% N, 5·16% S; found: 56·14% C, 5·48% H, 5·96% Cl, 4·49% N, 5·32% S.

The base, released from the recrystallized maleate by NH_4OH, was isolated by extraction with benzene and was transformed by treatment with methanesulfonic acid in a mixture of ethanol and ether to the dimethanesulfonate, m.p. 164–166°C (ethanol–ether). For $C_{23}H_{33}ClN_2O_7S_3$ (581·2) calculated: 47·53% C, 5·72% H, 6·10% Cl, 4·82% N, 16·55% S; found: 47·57% C, 5·62% H, 6·39% Cl, 4·82% N, 16·36% S.

1-[2-(2-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-yloxy)ethyl]-4-(2-hydroxyethyl)piperazine (*V*)

A mixture of 15·0 g *II*, 6·4 g 1-(2-hydroxyethyl)piperazine, 6·4 g K_2CO_3 and 60 ml dimethylformamide was stirred and heated for 5 h to 100°C, after cooling diluted with 150 ml water and extracted with dichloromethane. The extract was washed with water, dried with K_2CO_3 and evaporated. The oily residue (16·6 g) was neutralized with 8·8 g maleic acid in 100 ml ethanol, the maleate obtained was recrystallized from a mixture of 150 ml ethanol and 15 ml water and the pure maleate was decomposed with NH_4OH and the pure base *V* was isolated by extraction with benzene; 13·1 g (76%) oil.

Bis(hydrogen maleate), m.p. 168–170°C (aqueous ethanol). For $C_{30}H_{35}ClN_2O_{10}S$ (651·1) calculated: 55·34% C, 5·42% H, 5·44% Cl, 4·30% N, 4·92% S; found: 55·52% C, 5·39% H, 4·70% Cl, 4·00% N, 5·06% S.

Dimethanesulfonate, m.p. 182–183°C (ethanol). For $C_{24}H_{35}ClN_2O_8S_3$ (611·2) calculated: 47·16% C, 5·77% H, 5·80% Cl, 4·58% N, 15·74% S; found: 47·38% C, 5·76% H, 6·04% Cl, 5·21% N, 15·70% S.

1-[2-(2-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-yloxy)ethyl]-4-(3-hydroxypropyl)piperazine (*VI*)

A mixture of 7·3 g *II*, 3·6 g 1-(3-hydroxypropyl)piperazine[15], 3·6 g K_2CO_3 and 30 ml dimethylformamide was stirred and heated for 5 h to 100°C. Similar processing like in the preceding case gave 10·5 g (80%) bis(hydrogen maleate) of *VI*, m.p. 168–169°C. Analytical sample, m.p. 170°C (90% ethanol). For $C_{31}H_{37}ClN_2O_{10}S$ (665·2) calculated: 55·97% C, 5·61% H, 5·33% Cl, 4·21% N, 4·82% S; found: 56·15% C, 5·66% H, 5·51% Cl, 3·85% N, 4·95% S.

1-[2-(2-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-yloxy)ethyl]-4-ethoxycarbonylpiperazine (*VII*)

A mixture of 10·0 g *II*, 9·0 g 1-(ethoxycarbonyl)piperazine, 8·0 g K_2CO_3 and 50 ml dimethylformamide was stirred for 3 h at 60°C and processed similarly like in the preceding cases. The crude product was chromatographed on 250 g neutral Al_2O_3 (activity II). Chloroform eluted first 0·9 g less polar component and then 11·9 g (98%) oily base *VII*; neutralization with maleic acid in ethanol gave the hydrogen maleate, m.p. 118–120°C (acetone–ether). For $C_{27}H_{31}Cl.N_2O_7S$ (563·1) calculated: 57·59% C, 5·55% H, 6·30% Cl, 4·98% N, 5·69% S; found: 57·32% C, 5·52% H, 6·52% Cl, 4·75% N, 5·58% S.

A sample of the maleate was decomposed with NH_4OH and the pure oily base was isolated by extraction with dichloromethane. ^1H NMR spectrum: δ 7·58 (d, $J = 2·5$ Hz, 1 H, 1-H), 7·42 (d, $J = 8·0$ Hz, 1 H, 4-H), 7·40 (bd, 1 H, 6-H), *c.* 7·10 (m, 4 H, remaining ArH), 5·36 (dd, 1 H, Ar—CH—O), 4·18 (q, $J = 7·0$ Hz, 2 H, $COOCH_2$), 3·68 (t, $J = 6·5$ Hz, 2 H, 11-OCH_2), *c.* 3·50 (m, 6 H, $ArCH_2$ and $CH_2N^4CH_2$ of piperazine), 2·62 (t, $J = 6·5$ Hz, 2 H, CH_2N in the chain), 2·45 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 1·25 (t, 3 H, CH_3).

1-[2-(2-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-11-yloxy)ethyl]piperazine (*VIII*)

A mixture of 5·3 g *VII*, 5·0 g KOH and 15 ml ethanol was stirred and refluxed for 2·5 h (bath temperature of 120°C). After standing overnight the mixture was diluted with 50 ml water and extracted with benzene. The extract was washed with water, dried with K_2CO_3 and evaporated. The oily residue (3·6 g, 81%) was dissolved in 15 ml ethanol and neutralized with 2·4 g maleic acid in 10 ml ethanol; 4·9 g bis(hydrogen maleate), m.p. 157–158°C (ethanol). For $C_{28}H_{31}ClN_2O_9S$ (607·1) calculated: 55·40% C, 5·15% H, 5·48% Cl, 4·61% N, 5·28% S; found: 54·89% C, 5·23% H, 5·96% Cl, 4·44% N, 5·12% S.

The pure oily base, which was released from the maleate, was used for recording the ^{1}H NMR spectrum: δ 7·58 (d, J = 2·5 Hz, 1 H, 1-H), 7·42 (d, J = 8·0 Hz, 1 H, 4-H), 7·40 (bd, 1 H, 6-H), *c*. 7·10 (m, 4 H, remaining ArH), 5·38 (dd, 1 H, Ar—CH—O), 3·71 (t, J = 6·5 Hz, 2 H, OCH_2), 3·40 (m, 2 H, $ArCH_2$), 2·95 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·62 (t, J = 6·5 Hz, 2 H, CH_2N in the chain), 2·50 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 2·38 (s, 1-H, NH).

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