CYCLIC ACETALS OF THE 10-PIPERAZINO-10,11-DIHYDRODIBENZO[*b,f*]THIEPIN SERIES*

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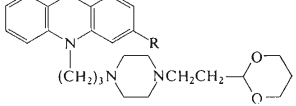
Alkylation of 8-chloro and 8-methylthio-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin with 2-(2-chloroethyl)-1,3-dioxolane and with 2-(2-chloroethyl)-1,3-dioxane yielded compounds *III*– *V* which appear to be effective neuroleptics and have a low toxicity on oral application.

Ratouis and Boissier[1-3] prepared cyclic acetals of the 10-(piperazinoalkyl)phenothiazine series and reported them to possess a high degree of central as well as vegetative neurotropic activity. The practical outcome of this work was the experimental preparation "oxaprazine" (*I*) (refs[1-5]) which is a tranquillizer with antihistamine and anticholinergic activity, and further the therapeutically used "oxaflumazine" (Oxaflumine^R) (*II*) which is an antipsychotically active neuroleptic with a relatively low toxicity[1-3,6-9]. The similarity of the neuroleptics of the 10-(aminoalkyl)phenothiazine and 10-piperazinodibenzo[*b,f*] thiepin series which is displayed in the relationship between structure and activity, led to an orientative study of cyclic acetals derived from 10-piperazino-10,11-dihydrodibenzo[*b,f*] thiepin. To this end, we set out to alkylate 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin[10] and 8-methylthio-10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin[10] with 2-(2-chloroethyl)-1,3-dioxolane[1] and 2-(2-chloroethyl)-1,3-dioxane[1] for the preparation of *III*– *V*.



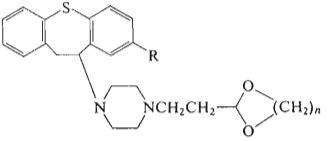
I, R = H
II, R = CF_3

* Part LXXV in the series Neurotropic and Psychotropic Agents; Part LXXIV: This Journal *39*, 3147 (1974).

In the form of maleates, the prepared compounds were subjected to a pharmacological investigation. Compounds *III* and *IV* were administered *per os* because of their low water solubility, *V* was given parenterally. The toxicity of the compounds for mice, expressed by the mean lethal dose LD_{50}, was estimated. Their incoordinating effect in the rotating-rod test was examined in mice and is expressed as the mean effective dose ED_{50} which is taken as indicator of their central depressant action. Finally, the cataleptic effect in the test on rats was carried out (for pharmacological methods see ref.[11]) which serves as indicator of neuroleptic action and is expressed by the mean effective dose ED_{50}. The numerical data on toxicity and activity referred to the corresponding bases are summarized in Table I. For comparison, the table includes the methylpiperazine analogues of *III*—*V*, *i.e.* "clorotepin" (octoclothepin), 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[12–14] and "metitepin" (methiothepin), 8-methylthio-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[15]. The table also includes "chlorpromazine" [2-chloro-10-(3-dimethylaminopropyl)phenothiazine] as standard.

Table I indicates that the acetals *III*—*V* are central depressants as well as cataleptic agents of higher activity than chlorpromazine and are practically as effective as the methylpiperazine derivatives clorotepin and metitepin. Their low toxicity after oral application is remarkable.

Compounds *III* and *IV* were also tested for their antimicrobial activity *in vitro*; they displayed identical inhibitory activity toward the following microorganisms (the minimum inhibitory concentrations in μg/ml are shown): *Mycobacterium tuberculosis* H37Rv (25), *Saccharomyces pasterianus* (125), *Trichophyton mentagrophytes* (62·3), *Aspergillus niger* (125).



III, R = Cl, $n = 2$
IV, R = Cl, $n = 3$
V, R = SCH_3, $n = 2$

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* at about 0·5 Torr over P_2O_5 at 100°C. The NMR spectra (in $CDCl_3$) were recorded in a ZKR 60 (Zeiss Jena) spectrometer. Preparative chromatography of the bases was carried out on neutral alumina of activity II.

1-(8-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-4-[2-(1,3-dioxolan-2-yl)ethyl]piperazine (*III*)

A mixture of 6·65 g 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[10], 8·85 g 2-(2-chloroethyl)-1,3-dioxolane[1] (b.p. 65°C/15 Torr), 6·55 g triethylamine and 45 ml toluene was refluxed under stirring for 35 h. After cooling, it was filtered, the filtrate was evaporated *in vacuo* and the

residue chromatographed on a column of 350 g alumina. After elution of 4·7 g less polar fractions, benzene and then benzene with 5% ethanol were applied to elute a total of 4·09 g (50%) homogeneous base which was converted to a maleate, m.p. 168–169°C (ethanol). NMR spectrum: δ 7·00–7·70 (m, 7 H, aromatic protons), 6·32 (s, 2 H, CH=CH of maleic acid), 4·95 (t, J = 3·0 Hz, 1 H, O—CH—O), 3·50–4·10 (m, 7 H, $ArCH_2CHAr$ and OCH_2CH_2O), c. 3·00 (m, 10 H, 5 NCH_2), 2·20 (m, 2 H, N—C—CH_2—CO_2). For $C_{27}H_{31}ClN_2O_6S$ (547·0) calculated: 59·28% C, 5·71% H, 6·48% Cl, 5·12% N, 5·86% S; found: 59·43% C, 5·84% H, 6·74% Cl, 5·04% N, 6·87% S.

TABLE I

Pharmacological Activity (mg/kg) of Cyclic Acetals *III*–*V*

Compound	Method of administration	Acute toxicity LD_{50}	Rotating rod ED_{50}	Catalepsy ED_{50}
III	*p.o.*	230	2·8	7·0
IV	*p.o.*	270	3·7	11·0
V	*i.v.*	43	0·16	2·0[a]
Clorotepin	*p.o.*	78	2·2	4·3
Clorotepin	*i.v.*	46	0·06	2·4[a]
Metitepin	*p.o.*	94	1·9	10·5
Metitepin	*i.v.*	51	0·09	2·0[a]
Chlorpromazine	*p.o.*	198	8·2	16·0
Chlorpromazine	*i.v.*	52	0·56	8·6[a]

[a] Intraperitoneally.

1-(8-Chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin-10-yl)-4-[2-(1,3-dioxan-2-yl)ethyl]piperazine (*IV*)

Like in the preceding case, 10·0 g 8-chloro-10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin[10], 15·5 g 2-(2-chloroethyl)-1,3-dioxane[1] (b.p. 75–80°C/10 Torr) and 10·0 g triethylamine in 60 ml toluene were heated for 26 h. The crude base obtained was converted to the maleate by treating with 3·0 g maleic acid in a mixture of ethanol and acetone; the maleate crystallized on adding ether; 13·2 g (78%), m.p. 183–184°C (90% ethanol). For $C_{28}H_{33}ClN_2O_6S$ (561·1) calculated: 59·94% C, 5·93% H, 6·32% Cl, 4·99% N, 5·71% S; found: 59·97% C, 6·07% H, 6·71% Cl, 5·26% N, 5·70% S. By treating the crystalline maleate with NH_4OH a base was liberated which was isolated by extraction with benzene but did not crystallize even on prolonged standing; it was used for obtaining the NMR spectrum: δ 7·00–7·80 (m, 7 H, aromatic protons), 4·60 (t, J = 5·0 Hz, 1 H, O—CH—O), 3·00–4·20 (m, 7 H, $ArCH_2CHAr$ and $2OCH_2$), 2·65 (m, 4 H, $CH_2N^1CH_2$), 2·50 (m, 6 H, $(CH_2)_2N^4CH_2$), 1·80 (m, 2 H, N—C—CH_2CO_2), 1·40 (m, 2 H, O—C—CH_2—C—O).

1-(8-Methylthio-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)-4-[2-(1,3-dioxolan-2-yl)ethyl]piperazine (*V*)

Like in the preceding cases, a mixture of 4·4 g 8-methylthio-10-piperazino-10,11-dihydrodibenzo-[*b,f*]thiepin[10], 5·8 g 2-(2-chloroethyl)-1,3-dioxolane[1], 4·3 g triethylamine and 30 ml toluene was refluxed for 30 h. The crude base obtained was chromatographed on a column of alumina (200 g). A mixture of benzene and 5% ethanol eluted 3·61 g (67%) of a practically homogeneous base which was converted to a maleate, m.p. 148—150°C (ethanol). For $C_{28}H_{34}N_2O_6S_2$ (558·6) calculated: 60·20% C, 6·14% H, 5·02% N, 11·46% S; found: 60·61% C, 6·06% H, 4·87% N, 11·64% S.

The spectra were registered and interpreted by Drs B. Kakáč, and J. Holubek at the physico-chemical laboratory of this Institute. The analyses were done by Mr K. Havel, Ms J. Komancová and Ms V. Šmídová at the analytical department. The antimicrobial activity of the compounds was estimated by Dr J. Turinová and Dr A. Čapek at the bacteriological department. Mr J. Pomykáček assisted with the preparative part of the work.

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