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NEUROTROPIC AND PSYCHOTROPIC SUBSTANCES. XLIX.*

3,8-DIAZABICYCLO[3.2.1]OCTYL DERIVATIVES OF DIBENZO[*b*,*f*]THIEPIN

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3,8-Diazabicyclo[3.2.1]octane as a bridged analogue of piperazine may be considered as a component of molecules of potential psychotropic substances in which it would replace the previously proven piperazine fragment. Recently, the synthesis and pharmacology of 3,8-diazabicyclo[3.2.1]-octyl derivatives derived from phenothiazine and 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene were reported[1]. The results obtained pointed to a considerable degree of psychotropic activity of the products.

In connection with our finding of a pronounced neuroleptic activity of some derivatives of 10-piperazinodibenzo[*b*,*f*]thiepin, particularly of 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin ("octoclothepin")[2] and of its 8-methylthio-analogue ("methiothepin")[3]

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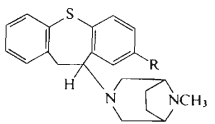
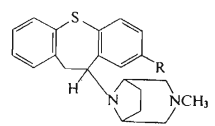
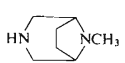
we thought it useful to take up also the 3,8-diazabicyclo[3.2.1]octane analogues of the named compounds. For this reason we prepared now compounds *I*—*IV*. Compounds *I* and *II* were obtained by a substitution reaction of 8,10-dichloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[2] or of 8-methylthio-10-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepin[3], with 8-methyl-3,8-diazabicyclo-[3.2.1]-octane (*V*) (ref.[4]). Compounds *III* and *IV* were obtained analogously by using isomeric 3-methyl-3,8-diazabicyclo[3.2.1]octane (*VI*) (ref.[5]). In view of the high activity of the piperazine enamines of this series[6,7] we prepared now also the enamine *VII*. For this we used the reaction of 8-chloro-11*H*-dibenzo[*b*,*f*]thiepin-10-one[2] with the amine *V* in boiling benzene in the presence of titanium



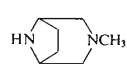
I, R = Cl
II, R = SCH_3



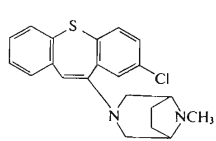
III, R = Cl
IV, R = SCH_3



V



VI



VII

tetrachloride (for methods see ref.[8]). A similar attempt at a reaction of the above ketone with the amine *VI* did not result in the desired product: the original ketone was recovered, apparently due to the lower reactivity of the amine *VI* as well as to the instability of the enamine formed in the presence of maleic acid which was used during the isolation procedure.

3,8-Diazabicyclo[3.2.1]octane derivatives *I*–*IV* and *VII* were pharmacologically evaluated in the form of maleates by using three tests which characterize the central depressant and neuroleptic activity of the compounds. The results are shown in Table I. The compounds were applied either *per os* (*p.o.*) or parenterally, *i.e.* intravenously (*i.v.*) in all the tests with the exception of the catalepsy one where the compounds were administered intraperitoneally. Acute toxicity was determined in mice. In the rotating-rod test in mice we evaluated the effect on motor coordination and the table shows the mean effective dose (ED_{50}). The locomotor activity was also evaluated in mice, using Dew's method; the value shown in the table (D_{50}) is the dose that will decrease the locomotor activity by 50%. The cataleptic effect was studied in rats[9], the mean effective dose (ED_{50}) being shown. All the values shown refer to the bases.

TABLE I

Pharmacological Activity (mg/kg) of the 3,8-Diazabicyclo[3.2.1]octane Derivatives

Compound	Application	Acute toxicity LD_{50}	Rotating rod ED_{50}	Locomotor activity D_{50}	Catalepsy ED_{50}
I	*p.o.*	205	4·8	3·5	12·5
II	*p.o.*	305	7·8	3·6	20·0
III	*i.v.*	82	3·2	16·2	> 10·0
IV	*i.v.*	77	10·0	9·6	> 10·0
VII	*p.o.*	—	10·5	6·3	50·0[a]
Octoclothepin	*p.o.*	78	2·2	1·6	4·3
Octoclothepin	*i.v.*	46	0·06	0·09	2·4
Chlorpromazine	*p.o.*	198	8·2	4·8	16·0
Chlorpromazine	*i.v.*	52	0·58	0·7	8·6

[a] After this dose, catalepsy occurs in 90% treated animals.

Table I includes for the sake of reference also octoclothepin[2] and chlorpromazine. A comparison with the compounds now prepared shows that they are relatively little effective. Of the two types studied, the ones with a tricyclic substituent in position 3 of the diazabicyclooctane system (*I, II*), appear to be more active; for a satisfactory comparison, however, one would have to do away with the fact that they were applied per os (because of low solubility) while the isomers *III* and *IV* were tested after parenteral application. The most effective of the new compounds is the amine *I* which in the rotating-rod and catalepsy tests is 2—3 times weaker than octoclothepin and 1·5—2 times more effective than chlorpromazine. Somewhat surprising is the very low activity of the enamine *VII* in the catalepsy test. On the whole, the replacement of the piperazine fragment in neuroleptics of the 10-piperazinodibenzo[*b,f*]thiepin series with a 3,8-diazabicyclo-[3.2.1]octane residue is to be considered as unfavourable from the point of view of activity.

Compounds *I—IV* and *VII* were further tested by Dr J. Turinová Bacteriological department of this Institute (headed by Dr A. Šimek) for their inhibitory activity against several microbial species *in vitro*. They showed then partly a considerable activity (values of minimal inhibitory concentration in μg/ml are shown), in particular against *Streptococcus β-haemolyticus* (6—12), *Staphylococcus pyogenes aureus* including its penicillin-resistant strain (6—12), *Mycobacterium tuberculosis* $H_{37}Rv$ (12—50). *Trichophyton mentagrophytes* (60—120), *Candida albicans* (125), *Aspergillus niger* (125). This finding corresponds to the previous observation[10] of antimicrobial activity in the series of 10-piperazino-10,11-dihydrodibenzo[*b,f*]thiepin derivatives.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block. The samples were dried for 5 h *in vacuo* (about 0·5 Torr) over phosphorus pentoxide at 70°C. The IR spectra were recorded in a Unicam SP 200G spectrophotometer and the NMR spectra (in deuteriochloroform) were recorded in a ZKR 60 spectrometer (Zeiss, Jena).

3-(8-Chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)-8-methyl-3,8-diazabicyclo[3.2.1]octane (*I*)

A solution of 5·6 g 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[2] and 5·0 g 8-methyl-3,8-diazabicyclo[3.2.1]octane (*V*) (ref.[4]) in 6 ml chloroform was refluxed under stirring on a boiling

water bath for 5 h. After cooling, the mixture was diluted with 50 ml benzene and, under gentle heating, extracted with 50 ml water. The benzene–chloroform layer was separated and shaken with 30 ml 3M-HCl. The acid-aqueous phase together with the precipitated oily hydrochloride was made alkaline with aqueous ammonia and the base was isolated by extraction with benzene: 5·58 g (75%), m.p. 172—174°C (benzene–ethanol). IR spectrum (Nujol): 750 (1,2-disubstituted benzene), 829 and 888 (1,2,4-trisubstituted benzene), 2815 cm^{-1} (CH_3—N). NMR spectrum: δ 7·80—6·85 (multiplet, 7 H of aromatic nuclei), 4·10—3·25 (multiplet, 3 H of $ArCH_2CHAr$), 3·25—2·40 (multiplet, 6 H of NCH_2 and NCH groups in the diazabicyclooctane fragment), 2·23 (singlet, 3 H NCH_3), 2·05—1·50 (multiplet, 4 H of the CH_2CH_2 bridge). For $C_{21}H_{23}ClN_2S$ (370·9) calculated: 67·99% C, 6·25% H, 9·56% Cl, 7·55% N, 8·64% S; found: 68·33% C, 6·21% H, 9·28% Cl, 7·14% N, 8·59% S.

Maleate, m.p. 213—214°C under decomposition (aqueous ethanol). For $C_{25}H_{27}ClN_2O_4S$ (487·0) calculated: 61·65% C, 5·59% H, 7·28% Cl, 5·74% N, 6·58% S; found: 61·64% C, 5·40% H, 6·90% Cl, 5·65% N, 6·80% S.

3-(8-Methylthio-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)-8-methyl-3,8-diazabicyclo[3.2.1]-octane (*II*)

In analogy to the previous case reaction of 2·9 g 8-methylthio-10-chloro-10,11-dihydrodibenzo-[*b,f*]thiepin[3] with 2·5 g amine *V* (ref.[4]) yielded 3·25 g crude base (85%); after recrystallization from ethanol the m.p. was 127—128°C. NMR spectrum: δ 7·75—6·8 (multiplet, 7 H of aromatic rings), 3·80—3·50 (multiplet, 3 H of $ArCH_2CHAr$), 2·43 (singlet, 3 H SCH_3), 2·24 (singlet, 3 H of NCH_3), 3·25—2·00 (multiplet, 6 H of NCH_2 and NCH groups in the six-membered ring), 2·10—1·30 (multiplet, 4 H of the CH_2CH_2 bridge). For $C_{22}H_{26}N_2S_2$ (382·6) calculated: 69·06% C 6·85% H, 7·32% N, 16·76% S; found: 69·06% C, 7·07% H, 6·90% N, 16·53% S.

Maleate, m.p. 198—199°C (aqueous ethanol). For $C_{26}H_{30}N_2O_4S_2$ (498·5) calculated: 62·64% C 6·07% H, 5·62% N, 12·84% S; found: 62·70% C, 6·00% H, 5·24% N, 12·67% S.

3-Methyl-8-(8-chloro-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)-3,8-diazabicylo[3.2.1]-octane (*III*)

A mixture of 5·6 g 8,10-dichloro-10,11-dihydrodibenzo[*b,f*]thiepin[2], 5·0 g 3-methyl-3,8-diazabicyclo[3.2.1]octane (*VI*) (ref.[5]) and 6 ml chloroform was refluxed under stirring for 8 h at 90°C. After cooling, it was processed as before. A total of 4·55 g (61%) oily base was obtained; this was neutralized with 0·90 g maleic acid in 8 ml ethanol directly to the *maleate*; m.p. 175°C (ethanol). For $C_{25}H_{27}ClN_2O_4S$ (487·0) calculated: 61·65% C, 5·59% H, 7·28% Cl, 5·74% N, 6·58% S; found: 61·32% C, 5·48% H, 7·31% Cl, 5·56% N, 6·88% S.

3-Methyl-8-(8-methylthio-10,11-dihydrodibenzo[*b,f*]thiepin-10-yl)-3,8-diazabicyclo[3,2,1]-octane (*IV*)

In analogy with the preceding case, reaction of 2·9 g 8-methylthio-10-chloro-10,11-dihydrodibenzo[*b,f*]thiepin[3] with 2·5 g amine *VI* (ref.[5]) yielded 3·0 g (78%) noncrystalline base which was directly converted to the maleate: m.p. 162—163°C (aqueous ethanol). For $C_{26}H_{30}N_2O_4S_2$ (498·5) calculated: 62·64% C, 6·07% H, 5·62% N, 12·84% S; found: 62·27% C, 6·12% H, 5·32% N, 12·72% S.

3-(8-Chlorodibenzo[*b,f*]thiepin-10-yl)-8-methyl-3,8-diazabicyclo[3.2.1]octane (*VII*)

Titanium tetrachloride (0·38 g) was added under stirring to a solution of 2·10 g 8-methyl-3,8-diazabicyclo[3.2.1]octane (*V*) (ref.[4]) and 0·90 g 8-chloro-11*H*-dibenzo[*b,f*]thiepin-10-one[2] in 10 ml

benzene and the mixture was stirred first for 3 h at room temperature and then refluxed for 25 h. After cooling, the mixture was diluted with 10 ml benzene and shaken with 20 ml water. The precipitate was filtered and washed with benzene. The benzene phase was separated from the filtrate and evaporated to dryness. A total of 1·20 g (96%) crude base was obtained which was found not to be homogeneous but according to chromatography on a thin layer of alumina did not contain the starting ketone. It was purified by recrystallization from ethanol; m.p. 199—200°C. NMR spectrum: δ 7·70—7·05 (multiplet, 7 H of aromatic rings), 6·30 (singlet, 1 H of ArCH=CAr) 3·50—2·50 (multiplet, 6 H of NCH_2 and NCH groups in the six-membered ring), 2·34 (singlet, 3 H of NCH_3), 1·98 (broad singlet, 4 H of the CH_2CH_2 bridge). For $C_{21}H_{21}ClN_2S$ (368·9) calculated: 68·37% C, 5·73% H, 9·61% Cl, 7·59% N, 8·69% S; found: 68·49% C, 5·96% H, 9·49% Cl, 7·32% N, 8·78% S.

Maleate, m.p. 258—260°C (under decomposition, ethanol). For $C_{25}H_{25}ClN_2O_4S$ (485·0) calculated: 61·91% C, 5·19% H, 7·31% Cl, 5·77% N, 6·61% S; found: 61·92% C, 5·29% H, 7·37% Cl, 5·72% N, 6·70% S.

The analytical determinations were done in the analytical department of this Institute (headed by Dr J. Körbl) by K. Havel, J. Komancová and V. Šmídová. The spectra were recorded and interpreted by Dr B. Kakáč, Dr J. Holubek and Dr E. Svátek in the physico-chemical laboratories of this Institute. We are particularly indebted to Prof. P. Sensi, director of Lepetit S.p.A. (Milan, Italy) for a gift of the necessary amounts of 3,8-diazabicyclo[3.2.1]octane derivatives V and VI which facilitated the present work considerably.

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