NEUROTROPIC AND PSYCHOTROPIC AGENTS. LXIII.*

7-METHOXY-10-(4-METHYLPIPERAZINO)DIBENZO[*b,f*]THIEPIN AND ITS 10,11-DIHYDRO DERIVATIVE

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Received November 10th, 1972

2-(3-Methoxyphenylthio)benzoic acid (*VII*) was converted in five steps to 7-methoxy-11*H*-dibenzo[*b,f*]thiepin-10-one (*II*). Reaction with 1-methylpiperazine and titanium tetrachloride yielded 7-methoxy-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*V*) which was reduced by diborane to the 10,11-dihydro derivative *I*. This compound has a relatively high antihistamine activity while it is a weak central depressant and cataleptic. The enamine *V* shows only a slight antihistamine activity but it is a powerful central depressant and at higher doses shows cataleptic and antiemetic activities.

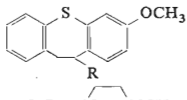
The basic compounds of the group of central depressant and neuroleptic 10-piperazinodibenzo[*b,f*]thiepins, *viz.* 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin ("perathiepin")[1] and 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*] thiepin ("octoclothepin")[2] displayed in *in vivo* tests a pronounced antihistamine activity, perathiepin with unsubstituted rings being more potent than octoclothepin with a chlorine atom in the *m*-position with respect to the carbon carrying the piperazine residue. According to established relationships between structure and activity in the group of antihistamines[3,4] it could be predicted that suitable *para* substitution with respect to the carbon carrying the amino group will have a favourable effect on antihistamine activity. From this point of view, a particularly suitable substituent appeared to be the methoxy group[3]; hence the present communication deals with the synthesis of *I* and *V*.

So far a single 7-substitution derivative of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]-thiepin has been known, *viz.* the 7-chloro derivative[5] (synthesis of the 7-trifluoromethyl analogue[6] stopped at the stage of the tricyclic ketone). The 8-methoxy analogue had also been synthesized before[7]. The initial phases of the present synthesis of *I* were analogous to the procedure described before[5,7] but some newer modifications were employed[8].

The reaction of 2-iodobenzoic acid[9] with 3-methoxythiophenol[10] produced a high yield of 2-(3-methoxyphenylthio)benzoic acid (*VII*). Its reduction with sodium bis(2-methoxyethoxy)dihydroaluminate[8] in benzene yielded the alcohol *VIII* which

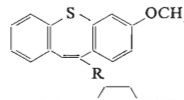
* Part LXII: This Journal *38*, 2137 (1973).

was transformed by a reaction with thionyl chloride in benzene to the chloride *IX*. This unstable product was processed in the crude state by a reaction with potassium cyanide in aqueous ethanol to the nitrile *X* which was hydrolyzed by an ethanolic solution of potassium hydroxide to 2-(3-methoxyphenylthio)phenylacetic acid (*XI*).



I, R = N NCH$_3$

II, R = :O
III, R = OH
IV, R = Cl

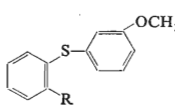


V, R = N NCH$_3$

VI, R = H

Cyclization of acid *XI* to 7-methoxy-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*II*) was carried out in toluene[7] with the aid of polyphosphoric acid. Cyclization makes it possible for the isomeric 9-methoxy ketone to be formed but the ketone *II* obtained in a high yield (85%) is homogeneous already in the crude state and its IR spectrum supports its identity. Reduction of the ketone *II* with sodium borohydride in aqueous ethanol produced a quantitative yield of alcohol *III*. Its reaction with thionyl chloride in benzene or with anhydrous hydrogen chloride in benzene gives rise to the unstable chloro derivative *IV* which eliminates hydrogen chloride spontaneously. This elimination takes place during attempts at purification of the compound by recrystallization from a mixture of benzene and light petroleum and is quantitative during a single recrystallization from ethanol; the elimination product is 3-methoxydibenzo[*b*,*f*]-thiepin (*VI*). A practically complete elimination takes place in an attempt at substitution reaction of the crude chloride *IV* with 1-methylpiperazine. For this reason, ketone *II* was left to react with 1-methylpiperazine and titanium tetrachloride in boiling benzene[11,12] to give rise to the enamine *V* which was reduced to the desired product *I* by diborane, generated in a reaction of sodium borohydride and acetic acid in tetrahydrofuran[13,14].

The pharmacological evaluation of *I* was concentrated to the antihistamine and central activities. The substance was applied per os in the form of dihydrochloride and the values shown refer to the base. Its acute toxicity for mice, LD_{50}, was 200 mg/kg. The antihistamine activity was determined in two *in vivo* tests in guinea pigs: in the aerosol test and in the histamine de-



VII, R = COOH
VIII, R = CH$_2$OH
IX, R = CH$_2$Cl

X, R = CH$_2$CN
XI, R = CH$_2$COOH

toxication test. The mean effective doses in these two tests were $PD_{50} = 1{\cdot}9$ and $2{\cdot}4$ mg/kg, respectively. This is a rather high activity even if almost an order of magnitude lower than the activity of dithiadene[15]. A direct comparison with the activity of perathiepin[1] or octoclothepin[2] is not possible since these substances were administered parenterally. In the test of motor coordination in mice the mean effective dose ED_{50} is 36·0 mg/kg; thus, compound *I* is a substantially weaker depressant than its 8-methoxy isomer[7]. In an attempt at establishing the cataleptic effect in rats it was observed that a *p.o.* dose of 50 mg/kg is still too low to bring about a cataleptic state of one out of ten rats. It can thus be considered as uneffective. In this respect the difference from the cataleptically highly effective 8-methoxy isomer[16] is even more striking.

The enamine *V* was evaluated in a broader selection of tests by pharmacological screening at the unit of this institute at Rosice n/L, using *p.o.* administration in the form of the base. The methods were not fully identical with those used for evaluating *I* and this may account for some of the discrepancies between the results. The very low acute toxicity of *V* for mice is very surprising: $LD_{50} = 625$ mg/kg. In the histamine detoxication test, a dose of 10—25 mg/kg protected guinea pigs from the lethal effect of the dose of 5 mg/kg histamine applied intravenously. In the rotating-rod test in mice (effect on motor coordination) the mean effective dose ED_{50} was 1—2·5 mg/kg. In this test the compound appears to be very effective and comparable to octoclothepin[12]. In the catalepsy test in rats the mean effective dose ED_{50} was 25—50 mg/kg (about 10 times weaker than octoclothepin[12]). The compound shows a hypothermic effect on rats (a dose of 1 to 2·5 mg/kg decreases body temperature by 1°C), an antiemetic effect in guinea-pigs (a dose of 120 mg/kg has the same effect as 100 mg prochlorperazine/kg, *p.o.*[17]), an antiamphetamine effect in mice (a dose of 1·0 mg/kg protects 50% mice from the effect of a lethal dose of amphetamine) and it potentiates the thiopental sleep in mice (a dose of 0·1—0·5 mg/kg prolongs the duration of thiopental sleep to double the control value).

Both *I* and *V* show a certain antimicrobial activity in *in vitro* tests (determined by Dr J. Turinová); this is expressed by the minimum inhibitory concentrations in μg/ml: *Streptococcus β-haemolyticus* (50, 12·5), *Staphylococcus pyogenes aureus* (50, 12·5), *Mycobacterium tuberculosis* H 37 Rv (25, 12·5), *Saccharomyces pasterianus* (>100, 12·5), *Trichophyton mentagrophytes* (>100, 12·5).

EXPERIMENTAL

The melting points of the analytical preparations were determined in Kofler's block; the samples were dried in the usual way. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in KBr, unless stated otherwise) in a Unicam SP 200 G spectrophotometer and the NMR spectra (in deuteriochloroform) in a ZKR-60 (Zeiss, Jena) spectrometer.

2-(3-Methoxyphenylthio)benzoic Acid (*VII*)

A. A mixture of 20·0 g 3-methoxythiophenol[10], 70 ml dimethylformamide and 20 g K_2CO_3 was stirred for 15 min. 2-Iodobenzoic acid[9] (35·4 g) was then added and the mixture was stirred for 8·5 h under a reflux condenser in a 140°C bath. After cooling, it was diluted with 750 ml water, the solution was filtered with charcoal and the filtrate made acid with hydrochloric acid. A total of 32·7 g (88%) product precipitated: m.p. 166—169°C. The analytical sample was obtained by recrystallization from ethanol: m.p. 173—174°C. For $C_{14}H_{12}O_3S$ (260·3) calculated: 64·60% C, 4·64% H, 12·32% S; found: 64·86% C, 4·78% H, 12·42% S.

B. 3-Methoxythiophenol (100 g)[10] was added to a solution of 145 g KOH (85%) in 1 600 ml water and, after 15 min of standing, this was followed by 178 g 2-iodobenzoic acid[9] and by 5 g powdered copper. The mixture was refluxed for 6 h, filtered with charcoal and the cooled filtrate was made acid with hydrochloric acid. The precipitated crude product (170 g) was recrystallized from 600 ml ethanol; 140 g (76%), m.p. 169—173°C.

2-(3-Methoxyphenylthio)benzyl Alcohol (*VIII*)

A suspension of 200 g acid *VII* in 1 500 ml benzene was stirred and treated dropwise with 480 ml of a 65% solution of sodium bis(2-methoxyethoxy)dihydroaluminate in benzene, the mixture was stirred for 3 h at room temperature and then left to stand overnight. With constant stirring, it was decomposed by adding 1 liter of 10% NaOH, the benzene phase was washed with water, dried and distilled: 134·9 g (71%), b.p. 175—178°C/1 Torr. The analytical sample was redistilled, b.p. 163—164°C/0·7 Torr. IR spectrum (film): 690, 760 and 860 (aromatic C—H), 1 040 (CH_2OH), 1 250 ($ArOCH_3$), 1 575 and 1 590 (Ar), 3 400 cm^{-1} (OH). NMR spectrum: δ 6·60—7·70 (m, 8 H, aromatic protons), 4·76 (bs, 2 H, $ArCH_2O$), 3·73 (s, 3 H, OCH_3), 2·30 (bs, 1 H, OH). For $C_{14}H_{14}O_2S$ (246·3) calculated: 68·26% C, 5·73% H, 13·02% S; found: 68·22% C, 5·75% H, 12·95% S.

2-(3-Methoxyphenylthio)phenylacetonitrile (*X*)

Thionyl chloride (70 g) was added dropwise to a boiling solution of 134·9 g alcohol *VIII* in 300 ml benzene and the mixture was refluxed for 2 h. Evaporation of the volatile components from the mixture yielded the crude chloride *IX*, which was dissolved in 250 ml ethanol, then combined with a solution of 75 g KCN in 100 ml water and the mixture was refluxed for 9 h. After cooling, it was diluted with 1 litre water and the product (138 g, almost the theoretical yield) was isolated by chloroform extraction. For analysis, the sample was distilled: b.p. 182°C/2 Torr For $C_{15}H_{13}NOS$ (255·3) calculated: 70·56% C, 5·13% H, 12·56% S; found: 71·05% C, 5·42% H, 12·59% S.

2-(3-Methoxyphenylthio)phenylacetic Acid (*XI*)

A mixture of 25·9 g nitrile *X*, 29 g KOH, 180 ml ethanol and 30 ml water was refluxed for 5 h. After cooling and diluting with 250 ml water, the solution was washed with benzene, made acid with hydrochloric acid and the oily product was isolated by chloroform extraction. The residue was recrystallized from a mixture of benzene and light petroleum; 21·9 g (76%), m.p. 65—66°C. IR spectrum: 683, 769 and 851 (aromatic C—H), 960 (COOH), 1 040 and 1 225 ($ArOCH_3$), 1 590 (Ar), 1 695 and 2 600 cm^{-1} (COOH). NMR spectrum: δ 10·58 (bs, 1 H, COOH), 7·20—7·60 (m, 4 H, aromatic protons in the residue of phenylacetic acid), 6·50—7·20 (m, 4 H, aromatic protons in the anisol residue), 3·86 (s, 2 H, $ArCH_2COO$), 3·69 (s, 3 H, OCH_3). For $C_{15}H_{14}O_3S$ (274·3) calculated: 65·69% C, 5·13% H, 11·69% S; found: 65·85% C, 5·24% H, 11·60% S.

7-Methoxy-11*H*-dibenzo[*b*,*f*]thiepin-10-one (*II*)

A solution of 32 g acid *XI* in 150 ml toluene was added at 110°C to polyphosphoric acid prepared from 70 g phosphorus pentoxide and 59 ml sirupy phosphoric acid (1·5 h at 140°C). The mixture was stirred and refluxed for 3 h, after cooling was decomposed with 1 litre of ice-cold water and extracted with benzene. The extract was washed with 5% NaOH and water, dried and evaporated. The residue (23·9 g, 85%; m.p. 130—132°C) is practically pure ketone *II*. A sample for analysis was recrystallized from benzene: m.p. 131—132°C. UV spectrum: λ_{max} 259 nm ($\log \varepsilon$ 4·33), 280 nm infl. (4·03), 313 nm (3·48). IR spectrum: 748 and 769 (4 vicinal aromatic C—H), 825 (2 vicinal aromatic C—H), 867 (1 isolated aromatic C—H), 1 030 and 1 263 ($ArOCH_3$), 1 587 (Ar), 1 662 cm^{-1} (ArCO). NMR spectrum: δ 8·24 (d, J = 9·0 Hz, 1 H, aromatic proton in position 9), 7·15—7·80 (m, 4 H, aromatic protons in positions 1,2,3,4), 7·10 (d, J = 2·0 Hz, 1 H, aromatic proton in position 6), 6·80 (q, J = 9·0; 2·0 Hz, 1 H, aromatic proton in position 8), 4·33 (s, 2 H, CH_2CO), 3·85 (s, 3 H, OCH_3). For $C_{15}H_{12}O_2S$ (256·3) calculated: 70·29% C, 4·72% H, 12·51% S; found: 70·07% C, 4·84% H, 12·40% S.

7-Methoxy-10-hydroxy-10,11-dihydrodibenzo[*b,f*]thiepin (*III*)

A solution of 3·0 g $NaBH_4$ in 30 ml water containing 0·3 ml 20% NaOH was added dropwise at 60—70°C to a solution of 13·0 g ketone *II* in 250 ml ethanol. The mixture was refluxed for 3 h and ethanol was evaporated. The residue was distributed between water and benzene, the benzene layer was washed with 3% NaOH and water, dried and evaporated. The residue was 13·1 g (theoretical yield) of a product melting at 127—128°C. The analytical sample melted at 129·5 to 130·5°C (benzene). IR spectrum: 759 (4 vicinal aromatic C—H), 845 (2 vicinal aromatic C—H), 889 (1 isolated aromatic C—H), 1050 (CHOH), 1234 and 1262 ($ArOCH_3$), 1495, 1600 (Ar), 2840 ($ArOCH_3$), 3445 cm^{-1} (OH). NMR spectrum: δ 7·1—7·8 (m, 5 H, aromatic protons in positions 1,2,3,4,9), 6·98 (d, $J = 3·0$ Hz, 1 H, aromatic proton in position 6), 6·78 (q, $J = 9·0$; 3·0 Hz, 1 H, aromatic proton in position 8), 5·12 (m, 1 H, ArCH—O), 3·72 (s, 3 H, OCH_3), 3·1—3·9 (m, 2 H, $ArCH_2$), 2·0 (d, 1 H, OH). For $C_{15}H_{14}O_2S$ (258·3) calculated: 69·74% C, 5·46% H, 12·41% S; found: 69·72% C, 5·62% H, 12·55% S.

3-Methoxydibenzo[*b,f*]thiepin (*VI*)

A solution of 10·7 g alcohol *III* in 100 ml warm benzene was cooled and, after adding 10 g anhydrous powdery $CaCl_2$ it was saturated for 4·5 h at room temperature with anhydrous hydrogen chloride. After filtration it was evaporated and the residue recrystallized from 60 ml ethanol. A total of 8·5 g of a homogeneous compound was obtained (thin-layer chromatography), m.p. 84°C. UV spectrum: λ_{max} 230 nm (log ε 4·35), 267 nm (4·36), 297 nm (3·71). IR spectrum: 750 (4 vicinal aromatic C—H), 801, 854 (2 vicinal aromatic C—H), 905 (1 isolated aromatic C—H), 1029, 1240 ($ArOCH_3$), 1591 cm^{-1} (Ar.) NMR spectrum: δ 7·00—7·60 (m, 6 H, aromatic protons in position 1,2,3,4,6,9), 6·95 (s, 2 H, olefinic CH=CH), 6·76 (q, $J = 9·0$; 3·0 Hz, 1 H, aromatic proton in position 8), 3·74 (s, 3 H, OCH_3). For $C_{15}H_{12}OS$ (240·3) calculated: 74·96% C, 5·03% H, 13·34% S; found: 74·74% C, 5·16% H, 12·98% S.

7-Methoxy-10-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*V*)

1-Methylpiperazine (13·5 g) was added to a solution of 7·0 g ketone *II* in 60 ml benzene and a solution of 2·7 g $TiCl_4$ in 8 ml benzene was added dropwise under stirring. The mixture was refluxed with stirring for 6 h, cooled, decomposed with 100 ml water, filtered, the benzene layer separated from the filtrate, washed with water, dried with $MgSO_4$ and evaporated. The remaining base (8·4 g) was crystallized from ethanol; m.p. 140—141°C. UV spectrum: λ_{max} 250 nm (log ε 4·38), 268 nm (4·17), 302 nm (3·94). IR spectrum: 760 (4 vicinal aromatic C—H), 829 and 850 (2 vicinal aromatic C—H), 852 (1 isolated aromatic C—H), 1011 and 1228 ($ArOCH_3$), 1499 and 1600 (Ar), 1620 (C=C), 2770 (N—CH_3), 2820 cm^{-1} ($ArOCH_3$). NMR spectrum: δ 7·40 to 7·70 (m, 2 H, aromatic protons in positions 6 and 8), 6·75—7·40 (m, 5 H, remaining aromatic protons), 6·29 (s, 1 H, ArCH=C), 3·75 (s, 3 H, OCH_3), 3·00 and 2·52 (2 m, 8 H, CH_2 groups of piperazine), 2·33 (s, 3 H, N—CH_3). For $C_{20}H_{22}N_2OS$ (338·5) calculated: 70·97% C, 6·55% H, 8·28% N, 9·47% S; found: 70·57% C, 6·56% H, 8·04% N, 9·48% S.

7-Methoxy-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*I*)

$NaBH_4$ (1·4 g) was added to a solution of 4·8 g enamine *V* in 25 ml tetrahydrofuran; this was followed by 10 ml acetic acid. The mixture was refluxed for 3 h, cooled, diluted with chloroform, washed with 15 ml 2M-NaOH and with water. The organic layer was processed to obtain a residue which crystallized; m.p. 112—113°C (benzene–light petroleum). UV spectrum: λ_{max} 227 nm

(log ε 4·33), 262 nm infl. (3·85), 291 nm infl. (3·51). IR spectrum: 764, 812, 831 and 843 (aromatic C—H), 1241 ($ArOCH_3$), 1498 and 1602 (Ar), 2738, 2783 and 2792 cm^{-1} ($ArOCH_3$ and NCH_3). NMR spectrum: δ 7·60 (d, J = 9·0 Hz, 1 H, aromatic proton in position 9), 7·56 (m, 1 H aromatic proton in position 4), 7·00—7·40 (m, 3 H, aromatic protons in positions 1,2,3), 6·95 (d, J = 2·5 Hz, 1 H, aromatic proton in position 6), 6·72 (q, J = 9·0; 2·5 Hz, 1 H, aromatic proton in position 8), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·72 (s, 3 H, OCH_3), 2·60 and 2·45 (2 m, 8 H, CH_2 groups of piperazine), 2·25 (s, 3 H, NCH_3). For $C_{20}H_{24}N_2OS$ (340·5) calculated: 70·55% C, 7·10% H, 8·23% N, 9·42% S; found: 70·51% C, 7·11% H, 7·55% N, 9·06% S.

Monomaleate, m.p. 170—172°C (ethanol–ether). For $C_{24}H_{28}N_2O_5S$ (456·5) calculated: 63·14% C, 6·18% H, 6·14% N, 7·02% S; found: 63·34% C, 6·30% H, 5·91% N, 7·07% S.

Dihydrochloride, m.p. 213—217°C (crude product, it decomposes on crystallization from ethanol). For $C_{20}H_{26}Cl_2N_2OS$ (413·4) calculated: 58·11% C, 6·34% H, 17·15% Cl, 6·78% N, 7·75% S; found: 58·24% C, 6·55% H, 17·18% Cl, 6·49% N, 7·97% S.

The UV, IR *and* NMR *spectra were kindly recorded and interpreted by Dr B. Kakáč, Dr E. Svátek, Dr J. Holubek and Mrs P. Vejdělková at the physicochemical department of this institute. The analytical estimations were done by Mr K. Havel, Mrs V. Šmídová, Mrs J. Komancová and Mrs J. Hrdá at the analytical department of this institute. The cooperation of Mrs M. Jandová and Mrs L. Müllerová with the pharmacological tests is acknowledged.*

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Translated by A. Kotyk.