# SYNTHESIS OF 7-(4-METHYLPIPERAZINO)-7,8-DIHYDROBENZO[*b*]NAPHTHO[2,1-*f*]THIEPIN AND OF RELATED COMPOUNDS*

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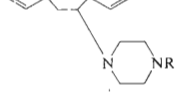
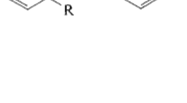
Benzo[*b*]naphtho[2,1-*f*]thiepin-7(8*H*)-one (*VIII*) was synthesized from 2-(1-naphthylthio)benzoic acid in five steps. It was then converted to chloride *X via* alcohol *IX*. Substitution reaction with 1-methylpiperazine yielded the title compound (*I*); the ethoxycarbonylpiperazino analogue *II*, prepared similarly, was hydrolyzed to the secondary amine *III*. The central activity of *I* is negligible, compounds *I* and *III* exhibit a certain antimicrobial activity *in vitro*.

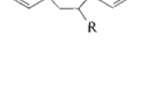
In an attempt to define the structural field of neuroleptic activity in the group of 10-piperazinodibenzo[*b*,*f*]thiepin derivatives[1] we set out to study compounds containing another ring condensed to the tricyclic system of dibenzo[*b*,*f*]thiepin. In the present communication we describe the synthesis of *I*–*III*, which all contain a benzo[*b*]naphtho[2,1-*f*]thiepin system. The only previously known compound of this type was 10-nitrobenzo[*b*]naphtho[2,1-*f*]thiepin-7-carboxylic acid[2] which was obtained through the reaction of 2-(1-naphthylthio)-5-nitrophenylpyruvic acid with polyphosphoric acid. In the synthesis of *I*–*III* an analogy of the procedure employed for the basic tricyclic compounds was used[3–6].




*I*, R = $CH_3$
*II*, R = $COOC_2H_5$
*III*, R = H




*IV*, R = $CH_2OH$
*V*, R = $CH_2Cl$
*VI*, R = $CH_2CN$
*VII*, R = $CH_2COOH$




*VIII*, R = =O
*IX*, R = OH
*X*, R = Cl

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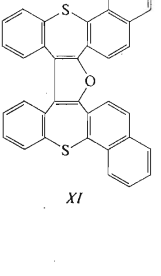
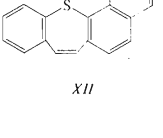
The starting compound was 2-(1-naphthylthio)benzoic acid, the preparation of which was described earlier[7]. Its reduction with sodium bis(2-methoxyethoxy)-dihydroaluminate[6,8] yielded alcohol *IV* which was treated with thionyl chloride to yield *V*. Reaction with sodium cyanide in dimethylformamide converted the chloride to nitrile *VI* which was hydrolyzed under alkaline conditions to 2-(1-naphthylthio)phenylacetic acid (*VII*). Reaction of this acid with polyphosphoric acid at 110°C results in a high yield of benzo[*b*]naphtho[2,1-*f*]thiepin-7(8*H*)-one (*VIII*). When the reaction temperature is raised to 130°C a mixture was formed from which a small amount of ketone *VIII* was obtained by repeated crystallization and chromatography of mother liquors. The least polar component eluted in this chromatography was a yellow compound not melting below 350°C which appears to be furo[2,3-*i*;5,4-*i'*]bis(benzo[*b*]naphtho[2,1-*f*]thiepin) (*XI*) on the basis of analysis, spectra and analogy[6].

Reduction of ketone *VIII* with sodium borohydride yielded alcohol *IX* which was transformed by anhydrous hydrogen chloride in benzene to chloride *X*. Substitution reaction with 1-methylpiperazine in boiling chloroform resulted in 62% amine *I*. The simultaneously obtained neutral fraction which should contain benzo[*b*]naphtho[2,1-*f*]thiepin (*XII*) formed by elimination, was too inhomogeneous so that compound *XII* could not be isolated from it even by chromatography. Compound *XII* was finally prepared by dehydrochlorination of the chloro derivative *X* by heating with 2,4,6-collidine. Substitution reaction of chloride *X* with 1-ethoxycarbonylpiperazine[9] yielded carbamate *II* which underwent alkaline hydrolysis to the secondary amine *III*.

Amine *I* was evaluated pharmacologically in the form of maleate with emphasis on the expected neuroleptic activity. The values shown refer to the base. It is very little toxic, its mean lethal dose $LD_{50}$ for mice on oral application being greater than 500 mg/kg (this dose is lethal for two out of ten animals). In the rotating-rod test in mice one can observe an incoordinating effect on the basis of central depression at high doses; the mean effective dose on oral application is 165 mg/kg. Likewise, in the catalepsy test on rats the compound shows very little effect, its




*XI*




*XII*

mean effective dose on oral application being higher than 50 mg/kg (this dose brought about a cataleptic state in one out of ten rats). Condensation of a further benzene ring to positions 6, 7 of the "perathiepin" molecule[4] and absence of the typical substituent in position 8 led thus to a practically complete loss of central activity.

Amines *I* and *III* were evaluated by *in vitro* tests for antimicrobial activity. A substantial activity toward cocci and mycobacteria was found, a somewhat weaker one toward yeasts and fungi. The microorganisms and the minimal inhibitory concentrations in μg/ml are shown: *Streptococcus* β-*haemolyticus*, I, 12·5; III, 12·5; *Staphylococcus pyogenes aureus* (including a penicillin-resistant strain), *I*, 12·5; *III*, 12·5; *Mycobacterium tuberculosis* H37Rv, *I*, 12·5; *III*, 12·5; *Saccharomyces pasterianus*, *I*, 62·5; *III*, 125; *Trichophyton mentagrophytes*, *I*, 62·5; *Candida albicans*, *I*, 125; *Aspergillus niger*, *I*, 125.

## EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 0·5 Torr over $P_2O_5$. The UV spectra (in methanol) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200G spectrophotometer or in a Hilger-Watts Infrascan, the NMR spectra (in $CDCl_3$) in a ZKR 60 (Zeiss Jena) spectrometer. The homogeneity of the compounds was tested by chromatography on a thin layer of silica gel. Preparative chromatography was done on alumina of activity II.

### 2-(1-Naphthylthio)benzyl Alcohol (*IV*)

A suspension of 89·4 g 2-(1-naphthylthio)benzoic acid[7] in 75 ml benzene was combined dropwise under stirring over a period of 75 min with 170 ml 70% benzene solution of sodium bis(2-methoxyethoxy)dihydroaluminate. The mixture was stirred for 4 h at room temperature and decomposed by slowly adding 500 ml 2M-NaOH. The benzene layer was separated, washed with water, dried with $MgSO_4$ and evaporated. A total of 68·7 g (81%) product melting at 81—85°C was obtained. After recrystallization from a mixture of benzene and light petroleum it melted at 85—87°C. IR spectrum: 760 and 789 (4 and 3 adjacent Ar—H), 1032 ($CH_2OH$), 1500, 1562, 1587 (Ar), 3255 and 3340 $cm^{-1}$ (OH). For $C_{17}H_{14}OS$ (266·4) calculated: 76·66% C, 5·30% H, 12·04% S; found: 76·86% C, 5·25% H, 12·05% S.

### 2-(1-Naphthylthio)benzyl Chloride (*V*)

$SOCl_2$ (25 ml) was added dropwise to a boiling solution of 53·2 g alcohol *IV* in 500 ml benzene and the mixture was refluxed for 2 h. After cooling, the volatile fractions were evaporated at reduced pressure. A total of 51·3 g (90%) residue was obtained and this was used for further work. The sample for analysis was distilled, b.p. 204—207°C/1·5 Torr; the solidified distillate was recrystallized from a mixture of benzene and light petroleum, m.p. 53°C. For $C_{17}H_{13}ClS$ (284·8) calculated: 71·69% C, 4·60% H, 12·45% Cl, 11·26% S; found: 71·60% C, 4·60% H, 12·32% Cl, 11·51% S.

### 2-(1-Naphthylthio)phenylacetonitrile (*VI*)

NaCN (12·5 g) was added to a solution of 58·2 g crude chloride *V* in 250 ml dimethylformamide, the mixture was stirred for 30 min at room temperature and then for 4 h at 100°C. After standing overnight the dimethylformamide was evaporated *in vacuo* and the residue was distributed

between 800 ml benzene and 300 ml water. The benzene layer was dried with $CaCl_2$ and evaporated after filtration. A total of 50·6 g (90%) residue was obtained and this was used for further work. If the reaction is carried out in aqueous ethanol, even after 10 h of boiling some of the starting chloride *V* is intact. For analysis, the sample was purified by distillation; b.p. 220°C/1·5 Torr. NMR spectrum: $\delta$ 8·30 (m, 1 H, 8-H of naphthyl), 7·00—8·10 (m, 10 H, remaining aromatic protons), 3·86 (s, 2 H, $ArCH_2CN$). For $C_{18}H_{13}NS$ (275·4) calculated: 78·51% C, 4·76% H, 5·09% N, 11·64% S; found: 78·59% C, 4·90% H, 4·83% N, 11·35% S.

2-(1-Naphthylthio)phenylacetic Acid (*VII*)

A solution of 46 g KOH in 100 ml water was added to a solution of 50·6 g crude nitrile *VI* in 180 ml ethanol and the mixture was refluxed for 5 h. The ethanol was then distilled off, the residue was dissolved in 1 500 ml warm water, the turbid solution was neutralized and acidified with dilute hydrochloric acid. The precipitated product was immediately extracted with warm chloroform. Processing of the extract and recrystallization of the crude product from a small volume of chloroform yielded 42·8 g (79%), m.p. 125—128°C. IR spectrum: 745, 755, 770 and 792 (4 and 3 adjacent Ar—H), 940 (COOH), 1 232 (C—O), 1 500, 1 590 (Ar), 1 710, 2 540 and 2 730 $cm^{-1}$ (COOH). For $C_{18}H_{14}O_2S$ (294·4) calculated: 73·44% C, 4·79% H, 10·89% S; found: 73·53% C, 4·90% H, 11·05% S.

Benzo[*b*]naphtho[2,1-*f*]*thiepin*-7(8*H*)-one (*VIII*)

A mixture of 72 ml 85% $H_3PO_4$ and 108 g $P_2O_5$ was stirred and heated for 5·5 h to 110°C, on the following day it was combined with 33·3 g acid *VII* and the mixture was stirred for 3 h at 110°C. After cooling, it was decomposed by pouring over ice and the separated product was isolated by extraction with a larger volume (800 ml) warm benzene. The extract was washed with a 15% solution of NaOH and water, dried with $K_2CO_3$ and filtered with charcoal. Evaporation at reduced pressure yielded 25·0 g (80%) crude product melting at 142—163°C. Constant m.p. (168°C) was reached after several recrystallizations of the sample from benzene. UV spectrum: $\lambda_{max}$ 217 nm (log $\varepsilon$ 4·47), 247 nm (4·51), 262 nm (4·49), 298 nm (3·87), 311 nm (3·78). IR spectrum: 740, 755, 765 and 818 (4 and 2 adjacent Ar—H), 1 310 (ArCO), 1 548, 1 594, 1 615 (Ar), 1 658 (ArCO), 3 060 $cm^{-1}$ (aromatic C—H). NMR spectrum: $\delta$ 8·80 (m, 1 H, 1-H), 8·15 (d, $J$ = 9·0 Hz, 1 H, 6-H), 6·90—7·80 (m, 8 H, remaining aromatic protons), 4·38 (s, 2 H, Ar. $.CH_2CO$). For $C_{18}H_{12}OS$ (276·3) calculated: 78·23% C, 4·28% H, 11·61% S; found: 78·26% C, 4·32% H, 11·45% S.

When the reaction was conducted at 130°C a neutral oily fraction was obtained in a yield of about 50%. Crystallization from benzene and chromatography of the mother liquor on a column of alumina isolated crude ketone *VIII* (m.p. 142—164°C) in a yield of 20%. In this chromatography, the least polar fraction eluted with benzene was a compound which, after recrystallization from benzene, does not melt below 350°C and which is believed (for analogy see ref.[6]) to be furo[2,3-*i*; 5,4-*i'*]bis(benzo[*b*]naphtho[2,1-*f*]thiepin) (*XI*). UV spectrum: $\lambda_{max}$ 230, 268, 350 nm. IR spectrum: 730, 746, 750, 757 (4 adjacent Ar—H), 805, 813 (2 adjacent Ar—H), 1 052, 1 113 (C═C—O—C═C), 1 480, 1 547, 1 590 (Ar), 3 030 $cm^{-1}$ (aromatic C—H). For $C_{36}H_{20}OS_2$ (532·6) calculated: 81·17% C, 3·79% H, 12·04% S; found: 81·53% C, 3·99% H, 11·73% S.

7-Hydroxy-7,8-dihydrodibenzo[*b*]naphtho[2,1-*f*]thiepin (*IX*)

A solution of 6·0 g $NaBH_4$ in 50 ml water with two drops of 15% NaOH was added dropwise and under stirring to a warm suspension of 29·0 g crude ketone *VIII* in 950 ml ethanol. The mix-

ture was refluxed under stirring for 4·5 h and ethanol was then evaporated at reduced pressure. The residue was diluted with water and the product was extracted with 1 litre boiling benzene. The extract was washed with 3% NaOH and with water, dried with $K_2CO_3$ and evaporated. A total of 28·6 g (98%) crude product melting at 135—147°C was obtained. The sample was purified by recrystallization from benzene or aqueous ethanol, m.p. 146—149°C. IR spectrum: 749, 762, 805, 818 (4 and 2 adjacent Ar—H), 1030, 1052 (CHOH in a ring), 1500, 1552 (Ar), 3055 (aromatic C—H), 3180 $cm^{-1}$ (OH with a hydrogen bond). NMR spectrum: $\delta$ 7·00—8·00 (m, 10 H, aromatic protons), 5·85 (m, 1 H, Ar—CH—O), 3·75 and 3·30 (2 dd, $J$ = 14·0; 6·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$), 2·35 (bs, 1 H, OH). For $C_{18}H_{14}OS$ (278·4) calculated: 77·76% C, 5·07% H, 11·52% S; found: 77·33% C, 5·18% H, 11·50% S.

7-Chloro-7,8-dihydrobenzo[*b*]naphtho[2,1-*f*]thiepin (*X*)

A solution of 28·3 g crude alcohol *IX* in 1 litre benzene was saturated for 3 h in the presence of 10 g $CaCl_2$ with anhydrous hydrogen chloride at room temperature. The mixture was left to stand for 20 h, was filtered and the filtrate was evaporated at reduced pressure. A total of 28·4 g (94%) crude product melting at 112—122°C was obtained, a sample of which crystallized from cyclohexane; m.p. 124—127°C. NMR spectrum: $\delta$ 8·90 (m, 1 H, 1-H), 7·00—8·00 (m, 9 H, remaining aromatic protons), 6·18 (dd, $J$ = 9·0; 5·5 Hz, 1 H, Ar—CH—Cl), c. 3·90 (m, 2 H, $ArCH_2$). For $C_{18}H_{13}ClS$ (296·8) calculated: 72·84% C, 4·41% H, 11·95% Cl; found: 72·60% C, 4·44% H, 12·06% Cl.

7-(4-Methylpiperazino)-7,8-dihydrobenzo[*b*]naphtho[2,1-*f*]thiepin (*I*)

A mixture of 10·0 g chloride *X*, 100 ml chloroform and 7·0 g 1-methylpiperazine was refluxed under stirring for 7 h. The chloroform was then evaporated and the residue divided between 100 ml water and 250 ml benzene. The benzene phase was washed with water and extracted with 250 ml 10% hydrochloric acid. After 1 h of standing and cooling, the hydrochloride was filtered and added to the acid aqueous layer of the filtrate. The mixture was made alkaline with $NH_4OH$ and the base was isolated by extraction with chloroform; 7·5 g (62%) m.p. after recrystallization from ethanol 137—139·5°C. UV spectrum: $\lambda_{max}$ 229 nm (log $\varepsilon$ 4·78), 300 nm (3·83). IR spectrum (KBr): 740, 760, 795 and 810 (4 and 2 adjacent Ar—H), 1495, 1548 (Ar), 2765 (N—$CH_3$), 3030 $cm^{-1}$ (aromatic C—H). NMR spectrum: $\delta$ 8·90 (m, 1 H, 1-H), 7·00—8·00 (m, 9 H, remaining aromatic protons), 4·36 and 4·00 (2 dd, $J$ = 12·0; 4·0 and 12·0; 11·0 Hz, 2 H, $ArCH_2$), 3·31 (dd, $J$ = 11·0; 4·0 Hz, 1 H, Ar—CH—N), 2·75 (t, 4 H, $CH_2N^1CH_2$), 2·45 (t, 4 H, $CH_2N^4CH_2$), 2·27 (s, 3 H, $NCH_3$). For $C_{23}H_{24}N_2S$ (360·5) calculated: 76·62% C, 6·71% H, 7·77% N, 8·90% S; found: 76·35% C, 6·83% H, 7·30% N, 9·00% S.

*Maleate*, m.p. 193—195·5°C (ethanol). For $C_{27}H_{28}N_2O_4S$ (476·6) calculated: 68·04% C, 5·92% H, 5·88% N, 6·73% S; found: 68·40% C, 6·13% H, 5·56% N, 6·72% S.

Benzo[*b*]naphtho[2,1-*f*]thiepin (*XII*)

A solution of 2·1 g chloride *X* in 23 ml 2,4,6-collidine was refluxed for 6 h, cooled and poured into excess dilute hydrochloric acid and the neutral product was extracted with benzene. The extract was washed with dilute hydrochloric acid and with water, dried with $K_2CO_3$ and evaporated. The residue (1·7 g) which was shown chromatographically to contain chloride *X*, was chromatographed on a column of 200 g alumina. Compound *XII* (1·2 g) was eluted with benzene as the least polar product; m.p. 106—109°C (cyclohexane). UV spectrum: $\lambda_{max}$ 232 nm (log $\varepsilon$ 4·64), 254 nm (4·26), 274 nm (4·39), inflexion 308 nm (3·66), inflexion 340 nm (3·55). IR spectrum

(KBr): 756, 767 (4 adjacent Ar—H), 797 (*cis*-CH=CH), 829 (2 adjacent Ar—H), 1500, 1555, 1595 $cm^{-1}$ (Ar). For $C_{18}H_{12}S$ (260·3) calculated: 83·04% C, 4·65% H, 12·31% S; found: 83·02% C, 4·83% H, 12·04% S.

7-(4-Ethoxycarbonylpiperazino)-7,8-dihydrobenzo[*b*]naphtho[2,1-*f*]thiepin (*II*)

A mixture of 9·1 g chloride *X*, 100 ml chloroform and 9·7 g 1-ethoxycarbonylpiperazine was refluxed under stirring for 7 h. After cooling, it was washed several times with water, the chloroform solution was dried with $K_2CO_3$ and evaporated. A total of 12·0 g crude product was obtained; a sample was purified via the hydrochloride and the base then recrystallized from ethanol; m.p. 140—143°C. NMR spectrum: $\delta$ 8·98 (m, 1 H, 1-H), 7·00—8·00 (m, 9 H, remaining aromatic protons), 4·13 (q, $J$ = 7·0 Hz, 2 H, $COOCH_2$), 3·00—4·30 (m, 3 H, Ar—$CH_2$CH—Ar), 3·45 (t, $J$ = 6·0 Hz, 4 H, $CH_2N^4CH_2$), 2·65 (t, $J$ = 6·0 Hz, 4 H, $CH_2N^1CH_2$), 1·23 (t, $J$ = 7·0 Hz, 3 H, $CH_3$). For $C_{25}H_{26}N_2O_2S$ (418·5) calculated: 71·74% C, 6·26% H, 6·69% N, 7·66% S; found: 71·58% C, 6·40% H, 6·60% N, 7·46% S.

7-Piperazino-7,8-dihydrobenzo[*b*]naphtho[2,1-*f*]thiepin (*III*)

A mixture of 8·75 g crude carbamate *II*, 10 ml ethanol and 5·9 g solid KOH was refluxed for 2 h at 120°C, cooled, diluted with water and extracted with chloroform. The extract was washed with water and evaporated. The residue was dissolved in 300 ml benzene and the solution was shaken with excess dilute hydrochloric acid. The precipitated hydrochloride was filtered, combined with the aqueous phase of the filtrate and the suspension was made alkaline with $NH_4OH$. The liberated base was extracted with benzene; 2·8 g (39%), m.p. 130—134°C (ethanol). For $C_{22}H_{22}N_2S$ (346·5) calculated: 76·25% C, 6·40% H, 8·09% N, 9·26% S; found: 76·47% C, 7·07% H, 7·70% N, 9·23% S.

*Maleate* (*monohydrate*), m.p. 161–164°C (ethanol). For $C_{26}H_{28}N_2O_5S$ (480·5) calculated: 64·99% C, 5·87% H, 5·83% N, 6·66% S; found: 65·25% C, 6·26% H, 5·59% N, 6·76% S.

*The spectra were recorded and interpreted by Drs B. Kakáč, J. Holubek and E. Svátek at the physico-chemical department of this Institute. Pharmacological testing for neurotropic effects was done under the direction of Dr J. Metyšová at the pharmacological department of this Institute. The antimicrobial activity was estimated by Dr J. Turinová and Dr A. Čapek (bacteriological department of this Institute). The analyses were done by Mr K. Havel, Ms J. Komancová, Ms V. Šmídová, Ms J. Hrdá and Ms A. Slavíková at the analytical department of this Institute. The required starting compounds were prepared by Mr Z. Šedivý.*

REFERENCES

1. Protiva M.: Biul. Inform. Inst. Przem. Farm. 20 (*2*), 107 (1972).
2. Loudon J. D., Sloan A. D. B., Summers L. A.: J. Chem. Soc. *1957*, 3814.
3. Jílek J. O., Seidlová V., Svátek E., Protiva M.: Monatsh. Chem. *96*, 182 (1965).
4. Jílek J. O., Svátek E., Metyšová J., Pomykáček J., Protiva M.: This Journal *32*, 3186 (1967).
5. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1831 (1968).
6. Šindelář K., Metyšová J., Protiva M.: This Journal *34*, 3801 (1969).
7. Jílek J. O., Pelz K., Vejdělek Z. J., Protiva M.: This Journal *31*, 269 (1966).
8. Černý M., Málek J., Čapka M., Chvalovský V.: This Journal *34*, 1025 (1969).
9. Moore T. S., Boyle M., Thorn V. M.: J. Chem. Soc. *1929*, 39.

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