POTENTIAL TETRACYCLIC NEUROLEPTICS: 12-(4-METHYLPIPERAZINO)BENZO[*b*]NAPHTHO[2,3-*f*]THIEPIN AND ITS 12,13-DIHYDRO DERIVATIVE*

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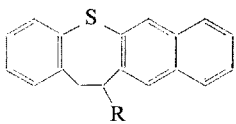
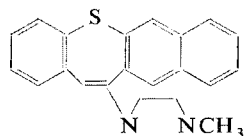
Starting from 2-(2-naphthylthio)benzoic acid (*VII*), the homologous acid *XI* was synthesized and cyclized with the aid of polyphosphoric acid. On the basis of spectra the product is assigned the linear structure *II* rather than the angular structure *VI*. Ketone *II* was converted *via* intermediates *III* and *IV* to the piperazine derivative *I*, or directly to enamine *V*. Compound *I* is a neuroleptic with about one-half the activity of chlorpromazine in two tests; in addition it shows an *in vitro* antimicrobial activity against a rather broad spectrum of microorganisms.

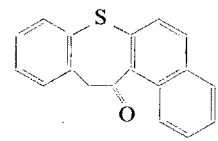
In three previous communications of this series[1-3] the derivatives of 10-piperazinodibenzo[*b*,*f*]thiepin were studied which contain a fourth ring annelated to the main tricyclic system and which have been prepared as potential neuroleptics. In the present communication the preparation of piperazine derivatives *I* and *V*, derived from the new tetracyclic system, benzo[*b*]naphtho[2,3-*f*]thiepin, is described.



I, R = N NCH$_3$



V



VI

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

In the present synthesis we proceeded from 2-(2-naphthylthio) benzoic acid[4] (*VII*) which was obtained by a reaction of 2-thionaphthol[5,6] with 2-iodobenzoic acid[7] in boiling aqueous solution of potassium hydroxide in the presence of copper. The other steps were analogous to the synthesis of benzo[*b*]naphtho[2,1-*f*]thiepin

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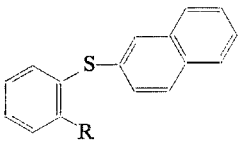
derivatives[1]. Reduction of acid *VII* with lithium aluminium hydride in ether resulted in alcohol *VIII* which reacted with thionyl chloride in boiling benzene to chloride *IX*. Reaction with sodium cyanide in dimethylformamide yielded nitrile *X* which was hydrolyzed in an alkaline medium to acid *XI*.



VII, R = COOH
VIII, R = CH_2OH
IX, R = CH_2Cl
X, R = CH_2CN
XI, R = CH_2COOH

Acid *XI* was cyclized with polyphosphoric acid in the presence of boiling toluene. A high yield of the neutral product of expected compostion was obtained which, according to IR and NMR spectra, has the structure of the linearly condensed ketone *II*. In view of the greater reactivity of the naphthalene α-position we had to consider the isomeric angular structure *VI* (for analogies see ref.[8-10]) which, however, is not compatible with the spectra of the present product (ν(Ar—H) 737, 750, 762 and 875 cm^{-1}; in the NMR spectrum there is a signal of 11-H in the form of a singlet at 8·70 p.p.m.[11]). In the present case, there is apparently a preference for the previously described[2,11-13] formation of the 9-unsubstituted dibenzo[*b*,*f*]-thiepin-10(11*H*)-one in those cases when the course of cyclization has two alternatives. Reduction of ketone *II* with sodium borohydride in aqueous ethanol led to alcohol *III* which was treated with anhydrous hydrogen chloride in benzene to convert it to chloride *IV*. A substitution reaction with 1-methylpiperazine in boiling chloroform led to base *I*. Reaction of ketone *II* with 1-methylpiperazine and titanium tetrachloride in boiling benzene led to enamine *V*.

Maleate of base *I* was tested by Dr J. Metyšová (Pharmacological department of this Institute) from the point of view of assumed neuroleptic activity. It was administered *per os* and the doses shown refer to the base. In the rotating-rod test in mice it brings about ataxia on the basis of central depression; the mean effective dose ED_{50} was 18·5 mg/kg (for chlorpromazine 8·2 mg/kg). The compound brings about catalepsy in a test on rats, the mean effective dose being 37 mg/kg (for chlorpromazine 16 mg/kg). It may be observed that the compound has the character of a weak neuroleptic, its activity in both tests being about 50% that of chlorpromazine. In comparison with perathiepin[14] (the corresponding values of ED_{50} for the tests are 2·4 and 45 mg/kg, respectively) compound *I* has an activity lower by about one order of magnitude as a central depressant and is about equally potent cataleptically. Thus, the annealing of the benzene ring to positions 7 and 8 of perathiepin has no favourable effect on the desired activity.

Compound *I* was further evaluated *in vitro* for its antimicrobial activity toward the standard set of microorganisms by Dr J. Turinová and Dr A. Čapek (Bacteriological department of this

Institute), a clear activity against cocci and mycobacteria being apparent. The organisms where an effect was observed and the minimum inhibitory concentration of *I* in μg/ml is shown: *Streptococcus β-haemolyticus*, 12·5; *Staphylococcus pyogenes aureus*, 12·5; *Mycobacterium tuberculosis* H37RV, 12·5; *Saccharomyces pasterianus*, 62·5; *Trichophyton mentagrophytes*, 62·5; *Candida albicans*, 125.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; samples were dried at about 0·5 Torr over P_2O_5 at a suitably raised temperature (at most 100°C). The UV spectra were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) in a Unicam SP 200 G or an Infrascan (Hilger and Watts) spectrophotometer, the NMR spectra (in $CDCl_3$) in a ZKR 60 (Zeiss-Jena) spectrometer. Homogeneity of the compounds was tested by chromatography on a thin layer of silicagel.

2-(2-Naphthylthio)benzoic Acid (*VII*)

2-Thionaphthol[5,6] (135 g) was added to a solution of 205 g 85% KOH in 2 litres water and the mixture was stirred for 30 min at 50°C. 2-Iodobenzoic acid[7] (208 g) and copper (6·5 g) were then added and the mixture was refluxed under stirring for 7 h. After cooling, it was filtered with charcoal, the substance on the filter was boiled with 1 litre of water and the combined aqueous filtrates were acidified with hydrochloric acid. After standing overnight, the crude product was filtered and recrystallized from 800 ml ethanol; 82 g (35%), m.p. 199–200°C. Ref.[4] reports a m.p. of 200–201°C for a product prepared in the reaction of sodium salt of 2-thionaphthol with potassium 2-chlorobenzoate.

2-(2-Naphthylthio)benzyl Alcohol (*VIII*)

Acid *VII* (26·5 g) was slowly added under stirring to a solution of 7·2 g $LiAlH_4$ in 400 ml ether and the mixture was refluxed under stirring for 5 h. After standing overnight, it was decomposed by consecutively adding dropwise 10 ml water, 10 ml 15% NaOH and 20 ml water. After standing for 30 min, it was filtered, the compound on the filter was washed with ether, the ether filtrate was washed with water, dried with $MgSO_4$ and evaporated. The residue is 21·4 g (85%) product melting at 80–84°C. The analytical product melts at 84–86°C (benzene–light petroleum). IR spectrum: 732, 805, 850 (4 and 2 adjacent and solitary Ar—H), 1032 (CH_2OH), 1500, 1570, 1588 (Ar), 3200, 3270 cm^{-1} (OH). NMR spectrum: δ 7·10–7·90 (m, 11 H, aromatic protons), 4·71 (s, 2 H, $ArCH_2O$), 2·25 (bs, disappears after D_2O, 1 H, OH). For $C_{17}H_{14}OS$ (266·4) calculated: 76·66% C, 5·30% H, 12·04% S; found: 76·86% C, 5·49% H, 12·02% S.

2-(2-Naphthylthio)benzyl Chloride (*IX*)

Thionyl chloride (9 ml) was added dropwise over 10 min to a stirred refluxed solution of 21·3 g *VIII* in 200 ml benzene. The mixture was refluxed for 3 h, the volatile fractions were distilled off *in vacuo*, the residue was dissolved in benzene, the solution filtered with charcoal and the filtrate evaporated again. A total of 20·5 g (90%) oily product was obtained, a sample of which was redistilled before analysis; b.p. 210°C/0·5 Torr, m.p. 46–48°C. NMR spectrum: δ 7·15–8·00 (m, 11 H, aromatic protons), 4·80 (s, 2 H, $ArCH_2Cl$). For $C_{17}H_{13}ClS$ (284·8) calculated: 71·69% C, 4·60% H, 12·45% Cl, 11·26% S; found: 71·78% C, 4·64% H, 12·37% Cl, 11·30% S.

o-(2-Naphthylthio)phenylacetonitrile (*X*)

NaCN (3·5 g) was added to a solution of 15·5 g *IX* in 80 ml dimethylformamide and the mixture was heated under stirring for 5 h to 100°C. Most of the Solvent was then evaporated *in vacuo*, the residue diluted with water and extracted with benzene. The benzene extract was dried with $MgSO_4$ and distilled: 6·9 g (46%), b.p. 192 – 196°C/0·5 Torr. The distillate was recrystallized from ethanol; m.p. 87·5–89·5°C. IR spectrum: 750, 760, 816, 860 (4 and 2 adjacent and solitary Ar–H), 1500, 1590 (Ar), 2260 cm^{-1} (CN). For $C_{18}H_{13}NS$ (275·4) calculated: 78·51% C, 4·76% H, 5·09% N, 11·64% S; found: 78·67% C, 4·98% H, 4·71% N, 11·60% S.

o-(2-Naphthylthio)phenylacetic Acid (*XI*)

A solution of 6·3 g KOH in 15 ml water was added to a hot solution of 6·9 g *X* in 50 ml ethanol and the mixture was refluxed for 5 h. The ethanol was distilled off at normal pressure, the residue was diluted with water and the solution washed with chloroform; the aqueous phase was acidified with hydrochloric acid. After standing overnight, the crude acid was filtered, dissolved in chloroform, the solution dried with $MgSO_4$ and evaporated; 6·3 g (85%), m.p. 131–135°C (aqueous ethanol). IR spectrum: 740, 765, 812, 858 (4 and 2 adjacent, and solitary. Ar–H), 930 (COOH), 1240 (C–O), 1500, 1588 (Ar), 1705, 2640, 2740 cm^{-1} (COOH). For $C_{18}H_{14}O_2S$ (294·4) calculated: 73·44% C, 4·79% H, 10·89% S; found: 73·57% C, 4·60% H, 10·76% S.

Benzo[*b*]naphtho[2,3-*f*]thiepin-12(13*H*)-one (*II*)

A mixture of 70 g polyphosphoric acid, 30 ml toluene, and 7·1 g acid *XI* was refluxed with stirring for 6 h on a 120°C bath. After partial cooling, it was poured onto ice, the product was extracted with toluene and the extract thoroughly washed with 5% NaOH and water. After drying with K_2CO_3 the toluene was evaporated. A total of 5·65 g (85%) product was obtained, m.p. 146 to 148°C (benzene). UV spectrum (methanol): λ_{max} 215 nm (log ε 4·54), 250 nm (4·48), 271 nm (4·62), inflexion 287 nm (4·00). IR spectrum (KBr): 737, 750, 762, 875 (4 adjacent and solitary. Ar–H), 1567, 1615 (Ar), 1672 cm^{-1} (Ar–CO). NMR spectrum: δ 8·70 (s, 1 H, 11-H), 8·00 (s, 1H, 6-H), 7·00–7·80 (m, 8 H, remaining aromatic protons), 4·35 (s, 2 H, $ArCH_2CO$). For $C_{18}H_{12}OS$ (276·3) calculated: 78·23% C, 4·28% H, 11·60% S; found: 77·82% C, 4·54% H, 11·44% S.

12,13-Dihydrobenzo[*b*]naphtho[2,3-*f*]thiepin-12-ol (*III*)

A solution of 3·0 g $NaBH_4$ in 50 ml water with 3 drops of 15% NaOH was added dropwise to a suspension of 19·6 g *II* in 600 ml ethanol. The mixture was refluxed under stirring for 3 h, ethanol was evaporated at reduced pressure, the residue was diluted with water and extracted with benzene. The extract was washed with 3% NaOH and water, filtered with charcoal and K_2CO_3 and evaporated. The crude product (19·2 g, and almost theoretical yield) is oily; it crystallizes from cyclohexane and melts at 109–112°C. IR spectrum (KBr): 737, 883 (4 adjacent and solitary Ar–H), 1042 (CHOH in a ring), 1560, 1575 (Ar), 3440 cm^{-1} (OH). NMR spectrum: δ 7·99 (s, 2 H, 6,11-H_2), 7·00–7·85 (m, 8 H, remaining aromatic protons), 5·65 (m, after D_2O dd, J = 9·0; 4·0 Hz, 1 H, Ar–CH–O), 3·72 and 3·25 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$), 2·52 (bs, disappears after D_2O, 1 H, OH). For $C_{18}H_{14}OS$ (278·4) calculated: 77·76% C, 5·07% H, 11·52% S; found: 77·17% C, 5·23% H, 11·31% S.

12-Chloro-12,13-dihydrobenzo[*b*]naphtho[2,3-*f*]thiepin (*IV*)

Powdery $CaCl_2$ (3 g) was added to a solution of 7·2 g *III* in 500 ml benzene and the suspension was saturated for 3 h with anhydrous hydrogen chloride. After 48 h of standing, it was filtered and benzene was evaporated at reduced pressure. The residue (7·6 g, an almost quantitative yield) slowly crystallizes on standing; m.p. 124—126°C (cyclohexane). For $C_{18}H_{13}ClS$ (296·8) calculated: 72·84% C, 4·41% H, 11·95% Cl, 10·80% S; found: 73·07% C, 4·39% H, 11·83% Cl, 10·96% S.

12-(4-Methylpiperazino)-12,13-dihydrobenzo[*b*]naphtho[2,3-*f*]thiepin (*I*)

1-Methylpiperazine (1·35 g) was added to a solution of 2·0 g *IV* in 30 ml chloroform and the mixture was refluxed for 7 h. After evaporation of chloroform, the residue was diluted with benzene, the solution was washed with water and shaken with dilute hydrochloric acid. The acid aqueous phase was separated, made alkaline with ammonia and the base was isolated by extraction with chloroform: 1·65 g (68%), m.p. 173—176·5°C (ethanol). IR spectrum (KBr): 750, 760, 895 (4 adjacent and solitary Ar—H), 2800 cm^{-1} (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: 76·42% C, 6·81% H, 7·46% N, 8·96% S.

Maleate, m.p. 192—193·5°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: 67·89% C, 6·17% H, 5·74% N, 6·87% S.

12-(4-Methylpiperazino)benzo[*b*]naphtho[2,3-*f*]thiepin (*V*)

1-Methylpiperazine (12 g) was added to a warm solution of 6·4 g ketone *II* in 50 ml benzene and, over a period of 20 min, a solution of 2·2 g $TiCl_4$ in 20 ml benzene was added dropwise, under stirring. The mixture was refluxed for 20 h stirring, cooled, decomposed with 130 ml water, the precipitate was filtered and washed with benzene. The benzene layer separated from the filtrate was dried with K_2CO_3, filtered with charcoal and the filtrate was evaporated. A total of 6·8 g crude product was obtained which crystallizes from ethanol: m.p. 173—177°C. UV spectrum (ethanol): λ_{max} 222 nm (log ε 4·44), 239 nm (4·46), 271 nm (4·11), 335 nm (3·63). For $C_{23}H_{22}N_2S$ (358·5) calculated: 77·05% C, 6·19% H, 7·82% N, 8·94% S; found: 77·02% C, 6·54% H, 7·75% N, 8·93% S.

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