11-PIPERAZINO-8,9-DIHYDRO(AND 8,9,11,12-TETRAHYDRO)-7*H*-BENZ[*b*]INDENO[5,6-*f*]THIEPINS*

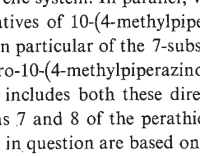
I. ČERVENÁ, E. SVÁTEK, J. METYŠOVÁ and M. PROTIVA

Research Institute of Pharmacy and Biochemistry, 130 00 Prague 3

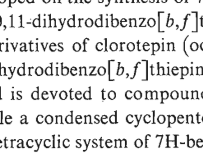
Received March 8th, 1974

2-(5-Indanylthio)phenylacetic acid (*IX*) synthesized from indane-5-thiol in five steps was cyclized with polyphosphoric acid to 7,8,9,12-tetrahydrobenz[*b*]indeno[5,6-*f*]thiepin-11-one (*X*) which was converted in two further steps to 11-chloro-8,9,11,12-tetrahydro-7*H*-benz[*b*]indeno[5,6-*f*]-thiepin (*XII*). Substitution reactions with 1-methyl and 1-ethoxycarbonylpiperazine yielded bases *I* and *II* along with the elimination product *XIII*. The carbamate *II* was hydrolyzed to the secondary amine *III*. The enamine *IV* was prepared from ketone *X* and 1-methylpiperazine by means of titanium tetrachloride. Compounds *I* and *IV* are little toxic but only slightly neuroleptically active; in their general profile they resemble rather chlorpromazine than clorotepin.

In a previous communication[1] we reported the synthesis of potential neuroleptics of the 10-piperazinodibenzo[*b*,*f*]thiepin type which contain another ring condensed to the tricyclic system. In parallel, work developed on the synthesis of 7,8-disubstitution derivatives of 10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin (perathiepin[2]), in particular of the 7-substituted derivatives of clorotepin (octoclothepin), *i.e.* 8-chloro-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b*,*f*]thiepin[3,4]. The present study includes both these directions and is devoted to compounds containing in positions 7 and 8 of the perathiepin tricycle a condensed cyclopentene ring. The derivatives in question are based on the new tetracyclic system of 7H-benz[*b*]indeno-[5,6-*f*]thiepin, in particular compounds *I*–*IV*.



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

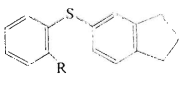


IV

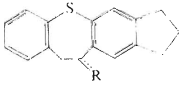
* Part LXXVIII in the series Neurotropic and Psychotropic Agents; Part LXXVII: This Journal *39*, 3548 (1974)

In the present synthesis we used procedures similar to those described before[3–6]. The parent compound, indane-5-thiol[7], was obtained by reduction of indane-5-sulfonyl chloride[7] with iodine and phosphorus in acetic acid[8]. Reaction of indane-5-thiol with 2-iodobenzoic acid[9] in an aqueous solution of potassium hydroxide resulted in acid V which was reduced with sodium bis(2-methoxyethoxy)dihydroaluminate[10] to alcohol *VI*. Action of thionyl chloride on alcohol *VI* in the presence of pyridine yielded chloride *VII* which reacted with sodium cyanide in aqueous ethanol to produce nitrile *VIII*. Hydrolysis with boiling aqueous-ethanolic solution of potassium hydroxide resulted in 2-(5-indanylthio)phenylacetic acid (*IX*). Heated with polyphosphoric acid to 115°C, this acid yields in a practically theoretical amount a product which, according to its spectrum, is 7,8,9,12-tetrahydrobenz[*b*]indeno-[5,6-*f*]thiepin-11-one (*X*). The critical arguments are IR spectral bands at 750 and 775 cm^{-1}, corresponding to 4 vicinal aromatic C—H bonds, and the band at 890 cm^{-1}, corresponding to a solitary aromatic C—H bond; the absence of the band at 800–860 cm^{-1} confirming the absence of two vicinal aromatic C—H bonds is typical. In the NMR spectrum one can see the typical singlet at 8·05 p.p.m. corresponding to a single aromatic proton. This singlet is ascribed to the proton in position 10 which lies in direct vicinity of the oxygen atom of the keto group[11]. Reduction of ketone *X* with sodium borohydride yielded the alcohol *XI* (ν_{Ar-H} 748 and 880 cm^{-1}) which was converted to the chloride *XII* under the influence of hydrogen chloride.

Heating of chloride *XII* with 1-methylpiperazine or 1-ethoxycarbonylpiperazine[12] led to the desired substitution reactions, their products being bases *I* and *II*. The IR spectra of these two bases display a weak band at 807 and 822 cm^{-1}, respectively, which suggests the presence of a small amount of the isomer *XIV*. This phenomenon may be accounted for by the fact that during cyclization of *IX* a mixture of ketone *X* and a small amount of ketone *XIV* (R = :0) is formed, the two isomers *XIV* being separated by crystallization of ketone *X* and alcohol *XI* so that the analytical samples of *X* and *XI* do not contain the isomers. On the other hand, when using crude compounds *X* and *XI*, bases *I* and *II* are obtained together with the isomers *XIV* as minor components. The observations may represent another contribution to our understanding the course of cyclization of 2-(*m*-substituted phenylthio)phenylacetic acids;

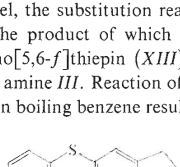


V, R = COOH
VI, R = CH_2OH
VII, R = CH_2Cl
VIII, R = CH_2CN
IX, R = CH_2COOH

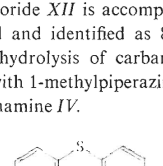


X, R = =O
XI, R = OH
XII, R = Cl

if the cyclization is permitted, both possibilities, *i.e.* formation of the 7 and the 9-substituted derivative of dibenzo[*b*,*f*]thiepin, the sterically preferred 7-substituted derivative is not formed selectively (as was assumed from earlier findings[13,14]), but rather the formation is accompanied by that of the hindered 9-substituted derivative. In parallel, the substitution reaction of chloride *XII* is accompanied by minor elimination, the product of which was isolated and identified as 8,9-dihydro-7*H*-benz[*b*]indeno[5,6-*f*]thiepin (*XIII*). Alkaline hydrolysis of carbamate *II* yielded the secondary amine *III*. Reaction of ketone *X* with 1-methylpiperazine and titanium tetrachloride in boiling benzene resulted in the enamine *IV*.



XIII



XIV

Pharmacological evaluation of the maleates of bases *I* and *IV* was done with a view to the potential neuroleptic activity of these compounds. Its results are shown as usual in Table I (data in mg/kg referring to the base). The compounds were administered *per os*. The acute toxicity for mice (mean lethal doses LD_{50}), the incoordinating effect in the rotating-rod test with mice as an indicator of central depressant activity (mean effective doses ED_{50}) and the cataleptic effect with rats as an indicator of neuroleptic activity (mean effective doses ED_{50}) were estimated (for details of pharmacological methods see ref.[15]). For the sake of comparison, the table includes clorotepin[3,4,16] and chlorpromazine as standards.

The very low toxicity of *I* and *IV* is striking. From the point of view of activity, the enamine *IV* is of greatest interest, being about three times less active sedatively and cataleptically than clorotepin but more active in both tests than chlorpromazine. In view of the very low toxicity, it possesses more favourable therapeutical indexes than chlorpromazine. The dihydro derivative *I* is less active than chlorpromazine in both tests.

Compounds *I* and *IV* were tested for antimicrobial activity *in vitro* using the following microorganisms (the minimum inhibitory concentrations in μg/ml are shown): *Streptococcus* β-*haemolyticus*, *I*, 12·5; *IV*, 12·5; *Staphylococcus pyogenes aureus*, *I*, 25; *IV*, 12·5; *Klebsiella pneumoniae*, *I*, 50; *Mycobacterium tuberculosis* H37Rv, *I*, 12·5; *IV*, 12·5; *Saccharomyces pasterianus*, *I*, 125; *IV*, 62·5; *Trichophyton mentagrophytes*, *I*, 125; *IV*, 62·5; *Candida albicans*, *IV*, 125.

EXPERIMENTAL

The melting points of the analytical preparations were estimated in Kofler's block and are not corrected. The samples were dried *in vacuo* of about 0·5 Torr over phosphorus pentoxide (at most 100°C). The UV spectra (in methanol unless stated otherwise) were recorded in a Unicam SP 700 spectrophotometer, the IR spectra (in KBr unless stated otherwise) in a Unicam SP 200G spectrophotometer or in a Hilger and Watts Infrascan, the NMR spectra (in $CDCl_3$) in a ZKR 60 (Zeiss, Jena) spectrometer. The homogeneity of the compounds was tested chromatographically on a thin layer of alumina.

Indane-5-thiol

A boiling mixture of 120 ml acetic acid, 27 g red phosphorus and 2·1 g iodine was combined over a period of 30 min with a solution of 65 g indane-5-sulfonyl chloride[7] (b.p. 177—181°C/13 Torr, m.p. 46—48°C) in 75 ml acetic acid and the mixture was refluxed for 3 h. After adding 30 ml water it was refluxed for 1·5 h, cooled, diluted with 400 ml water and extracted with chloroform. The extract was filtered through charcoal, the filtrate was washed with water, dried with $MgSO_4$ and distilled; 37·1 g (82%), b.p. 125—127°C/14 Torr. The analytical sample was redistilled, b.p. 118—119°C/13 Torr. Ref.[7] reports for a product obtained by reduction with zinc in sulfuric acid a b.p. of 184°C/17 Torr.

2-(5-Indanylthio)benzoic Acid (*V*)

A solution of 46 g KOH in 500 ml water was combined at 50°C with 38·5 g indane-5-thiol, stirred for 10 min and then 1·7 g of a copper paste and 60·7 g 2-iodobenzoic acid[9] was added. The mixture was refluxed for 7 h, partly cooled, filtered and the filtrate was cooled to room temperature and acidified with hydrochloric acid. The product was filtered, washed with water, dried at 100°C and suspended in 500 ml ethanol. The supension was briefly boiled, cooled and filtered: 51·5 g (75%), m.p. 228—230°C (ethanol). IR spectrum: 745, 822, 870 (4 and 2 adjacent and solitary Ar—H), 921, 1255, 2555, 2640 (COOH), 1562, 1587 (Ar), 1670 cm^{-1} (Ar—COOH). For $C_{16}H_{14}O_2S$ (270·3) calculated: 71·08% C, 5·22% H, 11·86% S; found: 71·26% C, 5·35% H, 11·86% S.

2-(5-Indanylthio)benzyl Alcohol (*VI*)

106 ml of a 70% benzene solution of sodium bis(2-methoxyethoxy)-dihydroaluminate[10] were added dropwise under stirring to a solution of 51·8 g *V* in 400 ml benzene. The mixture was stirred for 3 h at room temperature, diluted with 500 ml benzene, decomposed by slowly adding 250 ml 10% NaOH, the benzene phase was dried with K_2CO_3 and evaporated. A total of 41·1 g (84%) product was obtained. A sample was purified by recrystallization from hexane; m.p. 55—56·5°C. IR spectrum (Nujol): 750, 761, 770, 810, 813, 821 (4 and 2 adjacent and solitary Ar—H), 1034 (CH_2OH), 1564 and 1589 (Ar), 3290 cm^{-1} (OH). For $C_{16}H_{16}OS$ (256·4) calculated: 74·96% C, 6·29% H, 12·51% S; found: 74·73% C, 6·40% H, 12·43% S.

2-(5-Indanylthio)benzyl Chloride (*VII*)

Thionyl chloride (24·5 g) was added dropwise at 10—20°C over a period of 45 min under stirring to a solution of 38·4 g *VI* in 15 ml pyridine. The mixture was stirred for 2 h at room temperature, left to stand overnight, stirred for 1 h at 30—40°C, cooled, diluted with 100 ml benzene and decomposed with 100 ml water. Extraction with benzene yielded 35·2 g (86%) product, m.p. 63 to 65°C (acetone). NMR spectrum: δ 7·00—7·60 (m, 7 H, aromatic protons), 4·72 (s, 2 H, $ArCH_2Cl$), 2·84 (t, $J = 7·0$ Hz, 4 H, CH_2ArCH_2) 2·10 (m, 2 H, middle CH_2 of cyclopentene). For $C_{16}H_{15}$·.ClS (274·8) calculated: 69·92% C, 5·50% H, 12·90% Cl, 11·67% S; found: 70·29% C, 5·57% H, 13·20% Cl, 11·86% S.

2-(5-Indanylthio)phenylacetonitrile (*VIII*)

A mixture of solutions of 5·9 g NaCN in 10 ml water and 22·0 g *VII* in 25 ml ethanol was refluxed for 7 h. After evaporation of the ethanol it was diluted with water and the product was

isolated by extraction with benzene. After processing the extract and evaporation, the residue was crystallized from 40 ml ethanol; 18·9 g (89%), m.p. 78—80°C. IR spectrum: 2245 cm^{-1} (R—CN). For $C_{17}H_{15}NS$ (265·4) calculated: 76·94% C, 5·70% H, 5·28% N, 12·08% S; found: 77·27% C, 5·86% H, 5·24% N, 12·26% S.

2-(5-Indanylthio)phenylacetic Acid (*IX*)

A solution of 50 g KOH in 110 ml water was added to a solution of 51·7 g *VIII* in 175 ml ethanol and the mixture was refluxed for 3·5 h. After evaporation of ethanol it was diluted with 650 ml water, the turbid solution was washed with ether, cooled, and acidified with dilute hydrochloric acid. The product was filtered on the following day and recrystallized from 100 ml ethanol; 42·1 g (76%), m.p. 132—134°C. For $C_{17}H_{16}O_2S$ (284·4) calculated: 71·80% C, 5·67% H, 11·28% S; found: 72·31% C, 5·91% H, 11·21% S.

7,8,9,12-Tetrahydrobenz[*b*]indeno[5,6-*f*]thiepin-11-one (*X*)

A mixture of polyphosphoric acid (105 g P_2O_5 and 105 g 85% H_3PO_4) and 42·1 g *IX* was heated under stirring for 4 h at 110—115°C. After partial cooling, it was poured on 700 g mixture of ice and water, extracted with benzene, the extract washed with 5% NaOH and water and dried with $CaCl_2$. Evaporation yielded 39·4 g (theoretical amount) of product which was recrystallized from 200 ml ethanol; 31·0 g (79%), m.p. 109—112°C. An analytical sample melted at 110—112°C (ethanol). UV spectrum: λ_{max} 246 nm (log ε 4·36), infl. 255 nm (4·29), 334 nm (3·55). IR spectrum (Nujol): 750, 775, 890 (4 adjacent and solitary Ar—H), 1570, 1602 (Ar), 1660 cm^{-1} (Ar—CO). NMR spectrum: δ 8·05 (s, 1 H, 10-H), 6·90—7·70 (m, 5 H, remaining aromatic protons), 4·29, (s, 2 H, $ArCH_2CO$), 2·82 (t, $J = 6·0$ Hz, 4 H, CH_2ArCH_2), 2·00 (m, 2 H, middle CH_2 of cyclopentene). For $C_{17}H_{14}OS$ (266·3) calculated: 76·65% C, 5·30% H, 12·04% S; found: 76·90% C, 5·56% H, 11·99% S.

8,9,11,12-Tetrahydro-7*H*-benz[*b*]indeno[5,6-*f*]thiepin-11-ol (*XI*)

A solution of 2·0 g $NaBH_4$ in 20 ml water containing 0·3 ml 10% NaOH was added dropwise to a solution of 32·0 g *X* in 570 ml ethanol. The mixture was refluxed for 5 h and, after evapora-

TABLE I

Pharmacological Effects (mg/kg) after Oral Administration

Compound	Acute toxicity LD_{50}	Rotating rod ED_{50}	Catalepsy ED_{50}
I	>500[a]	26·0	24·5
IV	>500[b]	7·6	11·5
Clorotepin	78	2·2	4·3
Chlorpromazine	198	8·2	16·0

[a] A dose of 500 mg/kg causes the death of one mouse in ten. [b] A dose of 500 mg/kg causes the death of 2 mice in ten.

tion, the residue was divided between water and benzene. The benzene solution was washed (3% NaOH and water), dried and evaporated. The residue was recrystallized from a mixture of benzene and acetone; 22·7 g (70%), m.p. 121—122°C. IR spectrum (Nujol): 748, 880 (4 adjacent and solitary Ar—H), 1 044 (CHOH), 1 562, 1 590 (Ar), 3 340 cm^{-1} (OH). NMR spectrum: δ 6·90 to 7·60 (m, 6 H, aromatic protons), 5·25 (bs, after D_2O dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—O), 3·65 and 3·20 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$ in a seven-membered ring), 2·80 (t, J = 6·0 Hz, 4 H, CH_2ArCH_2), 2·20 (bs, disappears after D_2O, 1 H, OH), 2·00 (m, 2 H, middle CH_2 of cyclopentene). For $C_{17}H_{16}OS$ (268·4) calculated: 76·08% C, 6·01% H, 11·95% S; found: 76·02% C, 6·20% H, 11·68% S.

11-Chloro-8,9,11,12-tetrahydro-7*H*-benz[*b*]indeno[5,6-*f*]thiepin (*XII*)

A solution of 23·3 g *XI* in 200 ml benzene was combined with 20 g $CaCl_2$ powder and the suspension was saturated for 2·5 h with anhydrous hydrogen chloride at room temperature. On the following day it was filtered, the filtrate was evaporated and the residue recrystallized from 250 ml acetone; 18·5 g (71%), m.p. 116—118°C. NMR spectrum: δ 7·00—7·70 (m, 6 H, aromatic protons), 5·81 (dd, J = 9·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·91 and 3·60 (2 dd, J = 14·0; 4·0 and 14·0; 9·0 Hz, 2 H, $ArCH_2$ in a seven-membered ring), 2·78 (t, J = 7·0 Hz, 4 H, CH_2ArCH_2), 2·00 (m, 2 H, middle CH_2 of cyclopentene). For $C_{17}H_{15}ClS$ (286·8) calculated: 71·18% C, 5·27% H, 12·36% Cl, 11·18% S; found: 70·92% C, 5·10% H, 12·57% Cl, 11·04% S.

11-(4-Methylpiperazino)-8,9,11,12-tetrahydro-7*H*-benz[*b*]indeno[5,6-*f*]thiepin (*I*)

A mixture of 11·5 g *XII* and 12·0 g 1-methylpiperazine was heated for 5 h to 105—110°C. After cooling, it was diluted with water and extracted with benzene. The benzene solution was washed with water and shaken with 80 ml 3M-HCl. The precipitated hydrochloride was filtered, combined with the acid-aqueous layer of the filtrate and the suspension was made alkaline with ammonium hydroxide. The liberated base was isolated by extraction with benzene. Evaporation of the extract yielded 11·8 g (84%) crystalline base, a sample of which was purified for analysis by recrystallization from ethanol; m.p. 150—152°C. IR spectrum: 750 (4 adjacent Ar—H), 807 (weak band, 2 adjacent Ar—H), 870 (solitary Ar—H), 2770, 2800 cm^{-1} (N—CH_3). NMR spectrum: δ 6·90—7·60 (m, 6 H, aromatic protons), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·79 (t, J = 7·0 Hz, 4 H, CH_2ArCH_2), 2·63 (t, 4 H, $CH_2N^1CH_2$), 2·40 (t, 4 H, $CH_2N^4CH_2$), 2·22 (s, 3 H, NCH_3), 1·98 (m, 2 H, middle CH_2 of cyclopentene). For $C_{22}H_{26}N_2S$ (350·5) calculated: 7·99% N, 9·15% S; found: 8·24% N, 9·39% S.

Maleate (solvate with C_2H_5OH), m.p. 99—103°C and again 191—194°C (ethanol). For $C_{28}H_{36}N_2O_5S$ (512·7) calculated: 65·60% C, 7·08% H, 5·46% N, 6·26% S; found: 65·60% C, 7·00% H, 5·32% N, 6·30% S.

Evaporation of the benzene solution (from which the basic fractions had been removed) yielded 4·3 g crude neutral compound which was recrystallized several times from ethanol; m.p. 119—120°C, 8,9-dihydro-7*H*-benz[*b*]indeno[5,6-*f*]thiepin (*XIII*). UV spectrum: λ_{max} 218 nm (log ε 4·51), 267 nm (4·46), 298 nm (3·74). NMR spectrum: δ 7·05—7·70 (m, 6 H, aromatic protons), 6·97 (s, 2 H, olefinic CH=CH), 2·78 (t, 4 H, CH_2ArCH_2), 1·94 (m, 2 H, remaining CH_2 group). For $C_{17}H_{14}S$ (250·4) calculated: 81·56% C, 5·64% H, 12·80% S; found: 81·22% C, 5·78% H, 12·58% S.

11-(4-Ethoxycarbonylpiperazino)-8,9,11,12-tetrahydro-7*H*-benz[*b*]indeno[5,6-*f*]thiepin (*II*)

A mixture of 11·5 g *XII* and 15 g 1-ethoxycarbonylpiperazine[12] was heated for 6 h to 110—120°C and processed as in the preparation of *I*. A total of 16·0 g (almost the theoretical amount) crystal-

line base was obtained. Its sample was purified by repeated crystallization from acetone; m.p. 150–152°C. IR spectrum: 755 (4 adjacent Ar—H), 822 (weak band, 2 adjacent Ar—H!), 872 (solitary Ar—H), 1 236 (C—O), 1 683 (NCOOR), 2740 and 2790 cm^{-1} ($N—CH_2$). NMR spectrum: δ 7·00–7·60 (m, 6 H, aromatic protons), 4·10 (q, J = 7·0 Hz, 2 H, $COOCH_2$), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 3·42 (t, 4 H, $CH_2N^4CH_2$), 2·79 (t, J = 7·0 Hz, 4 H, CH_2ArCH_2), 2·57 (t, 4 H, $CH_2N^1CH_2$), 2·00 (m, 2 H, middle CH_2 of cyclopentene), 1·21 (t, 3 H, $C—CH_3$). For $C_{24}H_{28}N_2O_2S$ (408·6) calculated: 70·55% C, 6·91% H, 6·86% N, 7·85% S; found: 70·78% C, 7·14% H, 6·58% N, 7·96% S.

11-Piperazino-8,9,11,12-tetrahydro-7*H*-benz[*b*]indeno[5,6-*f*]thiepin (*III*)

A mixture of 4·85 g *II*, 10 ml ethanol and 5·0 g KOH was refluxed for 5 h at 120–125°C. After cooling, it was dissolved in 50 ml water and extracted with benzene. Treatment of the extract yielded 3·8 g (96%) base, a sample of which was purified by crystallization from ethanol; m.p. 147–150°C. IR spectrum: 744 and 875 (4 adjacent and solitary Ar—H), 2710 and 2790 (NCH_2), 3255 cm^{-1} (NH). NMR spectrum: δ 7·00–7·60 (m, 6 H, aromatic protons), 3·00–4·00 (m, 3 H, $ArCH_2CHAr$), 2·80 (t, J = 7·0 Hz, 4H, CH_2ArCH_2), 2·80 (t, 4 H, $CH_2N^4CH_2$), 2·67 (t, 4 H, $CH_2N^1.CH_2$), 2·00 (m, 2 H, middle CH_2 of cyclopentene), 1·47 (s, disappears after D_2O, 1 H, NH). For $C_{21}H_{24}N_2S$ (336·5) calculated: 74·95% C, 7·19% H, 8·33% N, 9·53% S; found: 75·35% C, 7·57% H, 7·88% N, 9·58% S.

11-(4-Methylpiperazino)-8,9-dihydro-7*H*-benz[*b*]indeno[5,6-*f*]thiepin (*IV*)

1-Methylpiperazine (22·0 g) was slowly added to a solution of 11·7 g *X* in 50 ml benzene, followed by a dropwise addition over a period of 5 min of 4·5 g $TiCl_4$ in 30 ml benzene. The mixture was refluxed under stirring for 30 h. After cooling, it was, decomposed by adding 170 ml water, the precipitate was filtered and washed with benzene. The filtrate was separated, the aqueous phase extracted with benzene and the benzene phases combined. Their washing with water, drying and evaporation yielded 15·0 g (almost the theoretical amount) of a base which was purified by crystallization from ethanol; m.p. 158–160°C. UV spectrum: λ_{max} 240 nm (log ε 4·29), 270 nm (4·13), 306 nm (3·92), NMR spectrum: δ 7·50 and 7·41 (2 s, 2 H, 6,10-H_2), c. 7·45 (m, 1 H, 4-H), 7·20 (m, 3 H, remaining aromatic protons), 6·29 (s, 1 H, ArCH=C), 2·95 (t, 4 H, $CH_2N^1CH_2$), 2·70 (t, J = 7·0 Hz, 4 H, CH_2ArCH_2), 2·50 (t, 4 H, $CH_2N^4CH_2$), 2·30 (s, 3 H, $N—CH_3$), 2·00 (m, 2 H, remaining CH_2 of cyclopentene). For $C_{22}H_{24}N_2S$ (348·5) calculated: 75·82% C, 6·94% H, 9·20% S; found: 75·70% C, 6·98% H, 9·22% S.

Maleate, m.p. 222–224°C (ethanol). For $C_{26}H_{28}N_2O_4S$ (464·6) calculated: 67·22% C, 6·07% H, 6·03% N, 6·90% S; found: 67·49% C, 6·10% H, 5·84% N, 6·97% S.

The authors are indebted to Mrs M. Hrubantová for skilled assistance with the preparative part of the work, to Mrs M. Jandová for technical assistance with the pharmacological tests, to Dr B. Kakáč and Dr J. Holubek for registration and interpretation of NMR spectra, to Dr J. Turinová and Dr A. Čapek for estimation of antimicrobial activity and to Mr K. Havel, Mrs J. Komancová, Mrs V. Šmídová and Mrs J. Hrdá for analytical work.

REFERENCES

1. Kopicová Z., Protiva M.: This Journal *39*, 3147 (1974).
2. Jílek J. O., Svátek E., Metyšová J., Pomykáček J., Protiva M.: This Journal *32*, 3186 (1967).
3. Jílek J. O., Metyšová J., Pomykáček J., Protiva M.: This Journal *33*, 1831 (1968).

4. Jílek J. O., Šindelář K., Pomykáček J., Horešovský O., Pelz K., Svátek E., Kakáč B., Holubek J., Metyšová J., Protiva M.: This Journal *38*, 115 (1973).
5. Jílek J. O., Šindelář K., Metyšová J., Metyš J., Pomykáček J., Protiva M.: This Journal *35*, 3721 (1970).
6. Jílek J. O., Pomykáček J., Metyšová J., Protiva M.: This Journal *36*, 2226 (1971).
7. Cagniant P.: Bull. Soc. Chim. France *1950*, 28; Chem. Abstr. *44*, 5366 (1950).
8. Wagner A. W.: Chem. Ber. *99*, 375 (1966).
9. Wachter W.: Ber. *26*, 1744 (1893).
10. Černý M., Málek J., Čapka M., Chvalovský V.: This Journal *34*, 1025 (1969).
11. Šindelář K., Kakáč B., Svátek E., Holubek J., Metyšová J., Hrubantová M., Protiva M.: This Journal *38*, 3321 (1973).
12. Moore T. S., Boyle M., Thorn V. M.: J. Chem. Soc. *1929*, 39.
13. Pelz K., Ernest I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1852 (1968).
14. Šindelář K., Kakáč B., Svátek E., Holubek J., Rajšner M., Metyšová J., Protiva M.: This Journal *39*, 333 (1974).
15. Šindelář K., Metyšová J., Protiva M.: This Journal *38*, 2137 (1973).
16. Metyš J., Metyšová J., Votava Z., Benešová O., Dlabač A., Kazdová E., Franc Z., Queisnerová M., Kraus P., Vaněček M., Hradil F., Jílek J. O., Protiva M.: Farmakoterap. zprávy *17*, 131 (1971).

Translated by A. Kotyk.