NONCATALEPTIC POTENTIAL NEUROLEPTICS: 2-METHYL-10-(4-METHYLPIPERAZINO)- AND -10-[4-(2-HYDROXYETHYL)PIPERAZINO]--10,11-DIHYDRODIBENZO[*b*,*f*]THIEPIN*

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[5-Methyl-2-(phenylthio)phenyl]acetic acid (*XV*) was synthesized on the one hand from the acid *VIII* using the known homologization technique *via* the alcohol *X*, chloride *XI* and nitrile *XII*, on the other from 5-methyl-2-(phenylthio)acetophenone (*XIII*) by means of the Willgerodt reaction. *Via* the intermediates *XIX* and *XX*, the synthesis led to 10-chloro-2-methyl-10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXI*), giving by treatment with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine the title compounds *III* and *IV*. These compounds have low cataleptic and high central depressant activity; on the other hand, they do not influence the levels of dopamine metabolites in the rat brain which is considered an indication of their lacking the neuroleptic character.

In several communications of this series[1-4], we described our efforts at finding noncataleptic neuroleptics in the series of 2-substituted 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepins. All of the compounds prepared were practically inactive or very little active in the test of catalepsy in rats. According to the degree of their central depressant effects, it was possible to divide them into substances with high and low activity; this type of activity proved dependent on the character of the substituent in position 2. High activity was exhibited by all of the halogen derivatives[3,5], further by the amino and acetamido derivative[2]. Low activity was shown by the methoxy, methylthio, trifluoromethyl, dimethylsulfamoyl[1], acetyl[2], nitro and hydroxy derivative[4]. Closer attention was then paid to the sedatively highly active substances, especially to the halogen derivatives, from which docloxythepin (VÚFB-10032), *i.e.* 2-chloro-10-[4-(2-hydroxyethyl)piperazino]-10,11-dihydrodibenzo[*b*,*f*]thiepin[4,6-8], was selected for preclinical studies; it showed a similar influence on the metabolism of dopamine in the rat brain (increase of the 3,4-dihydroxyphenylacetic and homovanillic acid levels in *corpus striatum*) like clozapine[9]. Until now, we did not check the influence of alkyl as the 2-substituent, especially methyl, on the pharmaco-

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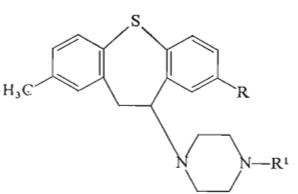
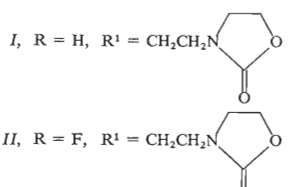
logical profile, evaluated from the point of view of requirements used for noncataleptic neuroleptics. Patents of Hoffmann-La Roche[10-12] indicated that this influence is positive and reported for compound *I* with an atypical substituent in the side chain a low cataleptic activity (10% of the chlorpromazine activity) and a rather important influence on the dopamine metabolism in the rat brain. Compound *II*, containing in addition an atom of fluorine in position 8, was then submitted to more detailed investigations as a potential noncataleptic neuroleptic[13-15]. Even after these investigations, the basic 2-methyl derivatives *III* and *IV* with simple and typical N-substituents, *i.e.* methyl and 2-hydroxyethyl, remained unknown. The present paper deals with their synthesis. Its carrying out was necessary because it was not possible to judge how far the overall activity of compounds *I* and *II* was modulated by the presence of the atypical side chain. On the other hand, it was sure that properties of substance *II* are at least partly determined by the presence of the fluorine atom in position 8; this substituent in the said position was characterized[16] as bearing the function of a "weak neuroleptic substituent".



I, R = H, $R^1 = CH_2CH_2N$ (O, O)



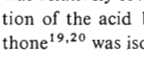
II, R = F, $R^1 = CH_2CH_2N$ (O, O)

III, R = H, $R^1 = CH_3$
IV, R = H, $R^1 = CH_2CH_2OH$

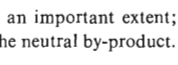
An intermediate of the preparation of amines *III* and *IV* was 10-chloro-2-methyl--10,11-dihydrodibenzo[*b*,*f*]thiepin (*XXI*), the synthesis of which was described in the mentioned patents[10-12] starting from 5-methylanthranilic acid and proceeding further *via* compounds *V*, *VIII*, *X*, *XI*, *XII*, *XV*, *XIX* and *XX*. Because compound *XXI* and four of the mentioned intermediates were not characterized at all and in no

case the yield was reported, we carried out a reinvestigation of the whole procedure. In some cases, we used alternative methods for preparing the mentioned intermediates.

2-Iodo-5-methylbenzoic acid (*V*) (ref.[15]) was transformed by treatment with thiophenol in a boiling potassium hydroxide solution in the presence of copper to 5-methyl-2-(phenylthio)benzoic acid (*VIII*) (ref.[10-12]). An alternative synthesis of this compound started from 4-iodo-3-nitrotoluene[17] which was reduced with ferrous hydroxide to 3-amino-4-iodotoluene (*VI*). Sandmeyer reaction afforded 2-iodo-5-methylbenzonitrile (*VII*), the preparation of which by a different method was already described[18]. Reaction of the iodonitrile *VII* with thiophenol in dimethylformamide at 130–145°C in the presence of potassium carbonate and cuprous chloride resulted in 5-methyl-2-(phenylthio)benzonitrile (*IX*) which was hydrolyzed with 50% sulfuric acid at 100°C to the required acid *VIII*. The yield in the last step was relatively low (56%) due to the fact that under the conditions used, the cyclization of the acid *VIII* takes already place in an important extent; 2-methylthioxanthone[19,20] was isolated in a yield of 25% as the neutral by-product.



V, R = COOH
VI, R = NH_2
VII, R = CN



VIII, R = COOH
IX, R = CN
X, R = CH_2OH
XI, R = CH_2Cl

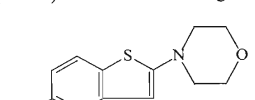
XII, R = CH_2CN
XIII, R = $COCH_3$

XIV, R = CH_2CSN

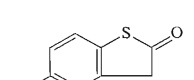
XV, CH_2COOH

Reduction of the acid *VIII* with lithium aluminium hydride in ether gave the alcohol *X*; Gerecke and coworkers[10-12] reduced the non-characterized methyl ester of the acid *VIII* with sodium dihydridobis (2-methoxyethoxy)aluminate. Transformation to the chloride *XI* was carried out by treatment with thionyl chloride in benzene[10-12]. The following reaction with sodium cyanide in dimethylformamide resulted in the nitrile *XII* which was hydrolyzed with potassium hydroxide in aqueous ethanol to [5-methyl-2-(phenylthio)phenyl]acetic acid (*XV*) (ref.[10-12]). The synthesis of this acid was carried out also by a new procedure which started from 2-chloro-5-methylacetophenone, obtained by the Friedel–Crafts reaction of 4-chlorotoluene with acetyl chloride[21,22]. It has been established that the product, obtained in this way, is not homogeneous and for further work, we used the compound purified by chromatography on aluminium oxide. Heating with thiophenol, potassium carbonate and copper to 165–175°C gave 5-methyl-2-(phenylthio)acetophenone (*XIII*), characterized also in the form of semicarbazone. The following Willgerodt reaction with sulfur and morpholine (for analogy, *cf.*[23]) resulted in the thiomorpholide *XIV*

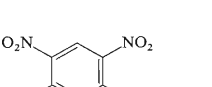
which was transformed by alkaline hydrolysis to the acid *XV*. Similarly like in the case of the 5-chloro analogue[23], the thiomorpholide *XIV* was subjected to treatment with polyphosphoric acid at 145°C. Under the cleavage of thiophenol, a substance $C_{13}H_{15}NOS$ was obtained which was identified as 5-methyl-2-morpholinobenzo[*b*]-thiophene (*XVI*). This result indicates that the reaction, observed earlier[23], is of a more general character. Acid hydrolysis of compound *XVI* gave 5-methyl-3*H*-benzo[*b*]-thiophen-2-one (*XVII*). An additional attempt at an alternative synthesis of the acid *XV* was unsuccessful. It started from 3-methylphenylacetonitrile[24] which is accessible from 3-methylbenzyl chloride[24,25]. Without experimental data, a statement was published[26] that 3-methylphenylacetonitrile can be transformed by nitration to 5-methyl-2-nitrophenylacetonitrile; this compound would be a very useful intermediate in the synthesis of the acid *XV*. In our hands, nitration of 3-methylphenylacetonitrile (for analogy, *cf.*[27]) gave an inhomogeneous product, consisting according to thin-layer chromatography of four components with two of them predominating. Acid hydrolysis (for analogy, *cf.*[28]) resulted in a crystalline mixture from which one homogeneous component was isolated in a yield of 25% by repeated crystallization; it was identified by analysis and spectra as (5-methyl-2,4-dinitrophenyl)acetic acid (*XVIII*). Further work along this line was the discontinued.



XVI

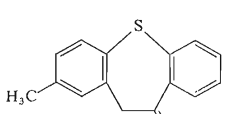


XVII

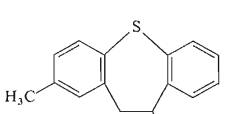


XVIII

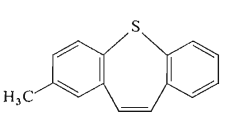
Cyclization of the acid *XV* by heating with polyphosphoric acid to 120°C gave 2-methyldibenzo[*b*,*f*]thiepin-10(11*H*)-one (*XIX*) (ref.[10-12]) which was reduced with sodium borohydride in aqueous ethanol to give the alcohol *XX*. Reaction with anhydrous hydrogen chloride in benzene afforded in an almost quantitative yield the chloro compound *XXI*. Final steps in the syntheses of compounds *III* and *IV* were substitution reactions with 1-methylpiperazine and 1-(2-hydroxyethyl)-piperazine, carried out in boiling chloroform. Bases *III* and *IV* resulted in yields of about 75%; 2-methyldibenzo[*b*,*f*]thiepin (*XXII*) (ref.[29]) was isolated and characterized as the expected neutral by-product, formed by the simultaneous elimination reaction. For pharmacological tests, bases *III* and *IV* were transformed to maleates.



XIX



XX, R = OH
XXI, R = Cl



XXII

Maleates of bases *III* and *IV* (VÚFB-13.752 and 13.753) were tested pharmacologically after oral administration (their dosage refer to the base). Their toxicities in mice were relatively low: LD_{50} = 240 and 180 mg/kg, respectively. They revealed a pronounced incoordinating action (corresponding to depressant action) in mice; their medium effective doses (inducing ataxia) in the rota-rod test were 4·0 and 5·2 mg/kg, respectively. After a dose of 10 mg/kg, catalepsy was observed in 30% rats (compound *III*) and in 10% rats (compound *IV*), respectively. After higher dosage, their depressant action interfered with the determination of catalepsy in rats. Both of the substances tested possessed only a mild cataleptogenic action in rats being, however, more active than docloxythepin[3,7]. In the dose of 50 mg/kg, both compounds failed to influence apomorphine-induced stereotypies in rats. They increased the cataleptogenic action of perphenazine in rats, whereas they did not change its anti-apomorphine action.

The effect of both substances (80 mg/kg orally, interval of 3 h) on the metabolism of dopamine in the *corpus striatum* and *tuberculum olfactorium* in the rat brain was evaluated by measuring the levels of 3-methoxy-4-hydroxy- and 3,4-dihydroxyphenylacetic acid. Whereas docloxythepin significantly increased the level of 3--methoxy-4-hydroxyphenylacetic acid in the same dose and this elevation was comparable with the effect of clozapine[30], its methyl analogues *III* and *IV* were without any effect. The elevation of dopamine turnover in the rat brain is the common feature of all neuroleptic agents and our results indicate that the evaluated substances have not the quality of neuroleptics.

Electroencephalographic studies in rats have led to similar conclusions. The interaction with apomorphine in unanesthetized rats was investigated, *i.e.* the influence of the compounds *III* and *IV* on EEG-arousal reaction and on behavioural activation induced by apomorphine. The compounds were injected in a subcutaneous dose of 10 mg/kg to rats (groups of 6 animals) with electrodes implanted into cortical and subcortical brain structures; apomorphine was administered in a dose of 0·3 mg/kg *s.c.* Administration of compounds *III* and *IV* 90 min afterwards induced mild behavioural depression, slight ptosis, increase in muscular tonus; no signs of motor coordination disturbances were observed. Native EEG-recordings were only slightly changed (resting pattern approximately in 50% of animals). Apomorphine

induced behavioural activation (in duration of 37·5 min), elicited chewing (39·2 min) and EEG-arousal reaction (41·6 min). After the administration of compound *III*, behavioural activation was reduced to approximately one quarter (11·7 min), it was almost fully blocked after the injection of compound *IV* (2·5 min). Apomorphine-induced chewing was inhibited by both substances intensively and approximately to the same extent (4·2 and 5·8 min, respectively). Both compounds exhibited only a mild antagonism against the EEG-arousal reaction (17·5 and 20·0 min, respectively). In conclusion, it is necessary to mention that the used dosage of compounds *III* and *IV* (induced definite anti-apomorphine effects) was relatively high. Compound *IV* is in this respect more active than compound *III*; it antagonizes, however, in the dosage used the apomorphine-induced EEG-arousal reaction only partially.

EXPERIMENTAL

The melting points of analytical preparations were determined partly in an automatic Mettler FP-5 melting point recorder, partly in Kofler block (these are not corrected); the samples were dried *in vacuo* at 70 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked by chromatography on thin layers of alumina or silica gel (Silufol).

3-Amino-4-iodotoluene (*VI*)

4-Iodo-3-nitrotoluene[17] (10·5 g, m.p. 50—53°C) was added to a solution of 112 g $FeSO_4.7\,H_2O$ in 200 ml H_2O and the stirred mixture was treated over 20 min with 200 ml NH_4OH, added dropwise. It was then stirred for 3 h at 50°C, cooled, diluted with 100 ml water and extracted with ether. Processing of the extract gave 8·1 g (87%) crude oily product which was used for further work. For characterization, the hydrochloride was prepared, m.p. 188—190·5°C (Kofler) (ethanol). For C_7H_9ClIN (269·5) calculated: 31·19% C, 3·36% H, 13·15% Cl, 47·09% I, 5·20% N; found: 31·29% C, 3·48% H, 13·33% Cl, 47·07% I, 5·15% N.

2-Iodo-5-methylbenzonitrile (*VII*)

A suspension of 33·6 g *VI* in 135 ml H_2O and 15 ml hydrochloric acid was heated to 80°C, cooled to 0°C and diazotized over 30 min under stirring by treatment with a solution of 9·5 g $NaNO_2$ in 125 ml H_2O, added dropwise. The mixture was stirred for another 30 min at 0°C, neutralized by a slow addition of 7·0 g Na_2CO_3 and treated at 0°C over 25 min with 160 ml 1M-CuCN solution, added dropwise. Toluene (200 ml) was added and the mixture stirred for 30 min at 0°C, for 1 h at 5°C, for 3 h at 20°C and for a short time at 50°C. It was allowed to stand overnight at room temperature, extracted with toluene, the extract was washed with H_2O, dilute hydrochloric acid, 5% $Na_2S_2O_5$ solution and 5% NaOH, dried (Na_2SO_4) and distilled; 10·1 g (33%), b.p. 112—113°C/13 Pa. The distillate crystallized from light petroleum and melted at 55—57°C (Kofler). IR spectrum (KBr): 824, 887 (2 adjacent and solitary Ar—H), 1565, 1590 (Ar), 2235 (Ar—CN), 3095 cm^{-1} (Ar). For a product prepared differently, the literature[18] reported the m.p. of 53—54°C.

5-Methyl-2-(phenylthio)benzonitrile (*IX*)

A mixture of 6·1 g *VII*, 5·5 ml dimethylformamide, 3·3 g thiophenol, 3·8 g K_2CO_3 and 1·0 g Cu was stirred for 5 h at 130—145°C. After cooling, it was diluted with water and extracted with chloroform. The extract was filtered, washed with H_2O, dried (Na_2SO_4) and distilled; 4·3 g (77%), b.p. 146—148°C/13 Pa. Analytical sample was redistilled, b.p. 144°C/11 Pa, and after solidification crystallized from a mixture of benzene and light petroleum, m.p. 38°C (Kofler). UV spectrum: λ_{max} 225 nm (log ε 4·11), 255 nm (3·94), infl. 280 nm (3·62), 318 nm (3·52). IR spectrum (KBr): 693, 757, 831, 880 (5 and 2 adjacent and solitary Ar—H), 1470, 1575, 1580, 1597, 3050, 3075 (Ar), 2232 cm^{-1} (Ar—CN). ^{1}H-NMR spectrum: δ 7·00—7·80 (m, 8 H, Ar—H), 2·28 (s, 3 H, CH_3). For $C_{14}H_{11}NS$ (225·3) calculated: 74·63% C, 4·92% H, 6·22% N, 14·23% S; found: 74·92% C, 5·06% H, 6·08% N, 14·07% S.

5-Methyl-2-(phenylthio)benzoic Acid (*VIII*)

A) Thiophenol (5·82 g), 13·1 g *V* (ref.[15]) and 0·33 g Cu were added to a solution of 9·5 g KOH in 100 ml H_2O and the mixture was stirred and refluxed for 8 h. It was filtered while hot and the filtrate acidified with hydrochloric acid. After cooling, the precipitated product was filtered, washed with water and crystallized from aqueous ethanol; 10·1 g (83%), m.p. 159—161°C (Kofler). Gerecke and coworkers[10–12] described a similar procedure and reported a m.p. of 156—157°C.

B) A mixture of 2·8 g *IX*, 10 ml H_2O and 10 ml H_2SO_4 was stirred for 5 h at 100°C. After cooling, it was diluted with H_2O, made alkaline with 5M-NaOH and the neutral by-product extracted with ether. Processing of the extract gave 0·7 g (25%) 2-methylthioxanthone, m.p. 123·5—124·5°C (benzene–light petroleum, Kofler). Literature[19,20] reported for this compound m.p. values of 123°C, and 125—127°C, respectively. The alkaline aqueous solution was filtered with charcoal and the filtrate acidified with hydrochloric acid. After standing overnight, the precipitated product was filtered, washed with water, dried *in vacuo* and recrystallized from a mixture of benzene and light petroleum; 1·7 g (56%) acid *VIII*, m.p. 159—161°C (Kofler). The product is identical with that obtained according to *A*.

5-Methyl-2-(phenylthio)benzyl Alcohol (*X*)

VIII (19·6 g) was added over 40 min to a stirred suspension of 6·1 g $LiAlH_4$ in 200 ml ether and the mixture was refluxed for 3 h. It was diluted with ether, decomposed dropwise with 50 ml water, treated with 15 g K_2CO_3, the organic layer was dried and evaporated. The residue (17·1 g, 93%) is the crude oily alcohol *X*. For analysis, a sample was distilled, b.p. 162°C/50 Pa. IR spectrum: 702, 762, 830, 899 (5 and 2 adjacent and solitary Ar—H), 1037 (CH_2OH), 1487, 1590, 1609, 3020 (Ar), 3350 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 8 H, Ar—H), 4·65 (bs, 2 H, $ArCH_2O$), 2·28 (s, 3 H, CH_3), 2·22 (bs, 1 H, OH). For $C_{14}H_{14}OS$ (230·3) calculated: 73·00% C, 6·12% H, 13·92% S; found: 73·19% C, 6·25% H, 13·93% S. Gerecke and coworkers[10–12] described the reduction of methyl 5-methyl-2-(phenylthio)benzoate with sodium dihydridobis(2-methoxyethoxy)aluminate in a mixture of tetrahydrofuran and benzene and characterized the product *X* as a red-brown oil.

5-Methyl-2-(phenylthio)benzyl Chloride (*XI*)

A mixture of 4·6 g *X*, 14 ml benzene and 6·0 g $SOCl_2$ was refluxed for 1·5 h (*cf.*[10–12]) and distilled; 4·3 g (87%), b.p. 148—149°C/70 Pa. ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 8 H, Ar—H),

4·69 (s, 2 H, $ArCH_2Cl$), 2·25 (s, 3 H, CH_3). For $C_{14}H_{13}ClS$ (248·8) calculated: 67·59% C, 5·26% H, 14·25% Cl, 12·89% S; found: 67·82% C, 5·36% H, 14·22% Cl, 12·68% S. Gerecke and coworkers[10-12] did not distil the product and characterized it as a red-brown oil.

[5-Methyl-2-(phenylthio)phenyl]acetonitrile (*XII*)

A mixture of 40·1 g *XI*, 80 ml dimethylformamide and 11·5 g NaCN was stirred for 1 h without heating and for 4 h at 55°C. After cooling, it was diluted with chloroform, the mixture was washed with water, dried with $MgSO_4$, filtered with charcoal and evaporated; 37·5 g (100%) crude *XII*. For analysis, a sample was distilled; b.p. 170—172°C/50 Pa. IR spectrum: 703, 753, 832, 888 (5 and 2 adjacent and solitary Ar—H), 1488, 1580, 1611, 3020, 3060 (Ar), 2260 cm^{-1} (R—CN). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 8 H, Ar—H), 3·80 (s, 2 H, $ArCH_2CN$), 2·35 (s, 3 H, CH_3). For $C_{15}H_{13}NS$ (239·3) calculated: 75·27% C, 5·47% H, 5·85% N, 13·40% S; found: 75·31% C, 5·28% H, 5·56% N, 13·01% S. The compound *XII* prepared from *XI* and KCN in aqueous ethanol was characterized as an oil[10-12].

2-Chloro-5-methylacetophenone

A reaction of 130 g 4-chlorotoluene, 100 g acetyl chloride and 150 g $AlCl_3$ in 150 ml CS_2 was carried out according to Mayer and Freund[21] and 97 g (56%) product boiling at 112—116°C/1·2 kPa were obtained. Redistillation gave 91 g product, b.p. 113—114°C/1·3 kPa. This was chromatographed on a column of 1 kg neutral Al_2O_3 (activity II). Light petroleum eluted 79 g (46%) homogeneous product which was used for further work. A more polar fraction (8·3 g), eluted with benzene, was discarded. The literature[21,22] reported a b.p. of 245—246°C/100 kPa, and 80—83°C/0·27 kPa, respectively.

5-Methyl-2-(phenylthio)acetophenone (*XIII*)

A mixture of 42·7 g 2-chloro-5-methylacetophenone, 30·5 g thiophenol, 65 g K_2CO_3 and 1·5 g Cu was stirred and heated for 12 h to 165—175°C. After cooling, the melt was extracted with boiling benzene, the mixture was filtered and the filtrate distilled; 24·7 g (40%), b.p. 152—157°C/65 Pa. This product was chromatographed on a column of 500 g alumina. Elution with light petroleum removed the least polar components and benzene eluted 14·7 g (24%) product, m.p. 34·5°C (light petroleum). UV spectrum: λ_{max} 211 nm (log ε 4·33), 235 nm (4·34), infl. 260 nm (3·89), 342 nm (3·59). IR spectrum: 682, 700, 743, 821, 875 (5 and 2 adjacent and solitary Ar—H), 1548, 1582 (Ar), 1660 cm^{-1} (ArCO). ^{1}H-NMR spectrum: δ 7·58 (mcs, 1 H, 6-H), 7·20—7·50 (m, 5 H, C_6H_5), 7·08 (mcd, J = 2·5; 8·5 Hz, 1 H, 4-H), 6·83 (d, J = 8·5 Hz, 1 H, 3-H), 2·61 (s, 3 H, $COCH_3$), 2·30 (s, 3 H, Ar—CH_3). For $C_{15}H_{14}OS$ (242·3) calculated: 74·34% C, 5·82% H, 13·23% S; found: 74·87% C, 5·90% H, 12·75% S.

Semicarbazone, m.p. 152—153°C (benzene, Mettler). UV spectrum: λ_{max} 247·5 nm (log ε 4·33) infl. 285 nm (3·94), infl. 325 nm (3·28). IR spectrum: 700, 760, 820, 829, 903 (5 and 2 adjacent and solitary Ar-H), 1476, 1589 (Ar), 1716 ($CONH_2$), 3060, 3180, 3270, 3435 cm^{-1} (HN, NH_2). ^{1}H-NMR spectrum: δ 8·78 (bs, 1 H, NH), 6·90—7·40 (m, 8 H, Ar—H), 5·70 (bs, 2H, NH_2), 2·29 (s, 3 H, Ar—CH_3), 2·19 (s, 3 H, =C—CH_3). For $C_{16}H_{17}N_3OS$ (299·4) calculated: 64·19% C, 5·72% H, 14·04% N, 10·71% S; found: 64·48% C, 5·75% H, 14·04% N, 10·69% S.

[5-Methyl-2-(phenylthio)phenyl]acetothiomorpholide (*XIV*)

A mixture of 12·9 g crystalline *XIII*, 9·3 g morpholine and 2·6 g sulfur was stirred and refluxed for 5 h (bath temperature of 150°C). After cooling, it was diluted with chloroform, the solution

washed with H_2O, 1M-HCl and H_2O, dried with K_2CO_3 and evaporated. The residue (18·3 g) was chromatographed on 500 g alumina. Elution with benzene gave only 5·9 g (32%) product, m.p. 83°C (cyclohexane). The majority of the product are noncrystalline mixtures of *XIV* with the corresponding oxothiomorpholide. Only the crystalline product was used for further work. IR spectrum: 689, 740, 819, 881 (5 and 2 adjacent and solitary Ar—H), 1480 (CSN), 1580, 1600, 3025, 3045 (Ar), 1252, 1282 cm^{-1} (R—O—R in a ring). ^{1}H-NMR spectrum: δ 6·90—7·50 (m, 8 H, Ar—H), 4·31 (s, 2 H, $ArCH_2CS$), 3·30—4·20 (m, 8 H, 4 CH_2 of morpholine), 2·31 (s, 3 H, CH_3). For $C_{19}H_{21}NOS_2$ (343·5) calculated: 66·46% C, 6·16% H, 4·08% N, 18·64% S; found: 66·29% C, 6·38% H, 3·96% N, 18·52% S.

[5-Methyl-2-(phenylthio)phenyl]acetict Acid (*XV*)

A) Hydrolysis of 37·5 g crude *XII* with 40 g KOH in 140 ml boiling ethanol and 85 ml H_2O (*cf.*[10-12]) gave 32·1 g (80%) crude *XV*, m.p. 130—134·5°C (Kofler). Gerecke and co-workers[10-12] reported for a crystallized product a m.p. of 132—135°C.

B) A mixture of 39 g *XIV*, 35 g KOH and 55 ml ethanol was stirred and refluxed for 4 h in a bath of 120°C, diluted with H_2O, washed with benzene, filtered with charcoal and acidified with 3M-HCl. The separated product was extracted with chloroform, the extract was dried ($MgSO_4$) and evaporated; 24·5 g (84%), m.p. 130—133°C (benzene–light petroleum). Analytical sample, m.p. 134—135°C (aqueous ethanol, Mettler). IR spectrum: 701, 756, 835, 890 (5 and 2 adjacent and solitary Ar—H), 956, 1236, 1252, 1710 (R—COOH), 1488, 1576, 1589, 1609 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 11·05 (bs, 1 H, COOH), 6·90—7·50 (m, 3 H, 3,4,6-H_3), 7·10 (s, 5 H, C_6H_5), 3·78 (s, 2 H, $ArCH_2CO$), 2·30 (s, 3 H, CH_3). For $C_{15}H_{14}O_2S$ (258·3) calculated: 69·74% C, 5·46% H, 12·41% S; found: 69·40% C, 5·39% H, 12·13% S.

5-Methyl-2-morpholinobenzo[*b*]thiophene (*XVI*)

A mixture of 4·0 g *XIV* and 50 g polyphosphoric acid was stirred and heated for 2·5 h to 145°C. After standing overnight, it was decomposed with 250 ml H_2O and extracted with benzene. The extract was washed with 5% NaOH and H_2O, dried with K_2CO_3 and evaporated. The residue was crystallized from 18 ml ethanol; 1·7 g (63%), m.p. 113—113·5°C. Analytical sample, m.p. 114—114·5°C (ethanol, Mettler). Mass spectrum, *m/e* (%): 233 (M^+ corresponding to $C_{13}H_{15}$.NOS, 100), 218 (5), 189 (9), 176 (19), 175 (90), 174 (27), 161 (18), 160 (20), 148 (14), 147 (27). UV spectrum: λ_{max} 233 nm (log ε 4·40), 287 nm (4·27). IR spectrum: 794, 804, 885 (2 adjacent and solitary Ar—H), 1116 (R—O—R), 1532, 1560, 1598, 3020 cm^{-1} (Ar). ^{1}H-NMR spectrum: δ 7·42 (d, J = 8·0 Hz, 1 H, 7-H), 7·21 (mcs, J = 1·5 Hz, 1 H, 4-H), 6·88 (mcd, J = 8·0; 1·5 Hz, 1 H, 6-H), 6·10 (bs, 1 H, partly disappears after D_2O probably due to an 3-OH impurity present, 1 H, 3-H), 3·80 (t, 4 H, CH_2OCH_2), 3·14 (t, 4 H, CH_2NCH_2), 2·35 (s, 3 H, CH_3). For $C_{13}H_{15}$.NOS (233·3) calculated: 66·92% C, 6·48% H, 6·00% N, 13·74% S; found: 67·20% C, 6·77% H, 5·80% N, 13·47% S.

5-Methyl-3*H*-benzo[*b*]thiophen-2-one (*XVII*)

A mixture of 2·3 g *XVI*, 12 ml acetic acid and 30 ml hydrochloric acid was stirred and refluxed for 3 h (bath temperature of 135°C), diluted with 150 ml H_2O and extracted with chloroform. The extract was washed with H_2O, dried with $MgSO_4$ and evaporated; 1·55 g (96%) residue which was crystallized from cyclohexane, m.p. 77·5°C (Mettler). IR spectrum: 800, 863 (2 adjacent and solitary Ar—H), 1710 cm^{-1} (RCO—S—Ar). ^{1}H-NMR spectrum: δ 6·90—7·30 (m, 3 H, Ar—H),

3·85 (s, 2 H, $ArCH_2CO$), 2·30 (s, 3 H, CH_3). For C_9H_8OS (164·2) calculated: 65·83% C, 4·91% H, 19·52% S; found: 66·20% C, 5·02% H, 19·08% S.

3-Methylphenylacetonitrile

A mixture of 28 g 3-methylbenzyl chloride[24,25], 12·5 g NaCN and 40 ml dimethylformamide was stirred and warmed to 45°C. An exothermic reaction took place and the temperature was maintained for 1 h at 50—60°C (occasional cooling) and for 2·5 h at 30—40°C (mild warming). It was then diluted with chloroform, washed with H_2O, dried with $MgSO_4$ and evaporated. The residue was distilled; 22·9 g (88%), b.p. 114—116°C/0·93 kPa. The literature[24] described the reaction in aqueous ethanol and reported a b.p. of 125—130°C/1·33 kPa.

(5-Methyl-2,4-dinitrophenyl)acetic Acid (*XVIII*)

3-Methylphenylacetonitrile (12·0 g) was added over 45 min dropwise to a stirred mixture of 30 ml 72% HNO_3 (d 1·422) and 30 ml H_2SO_4 at 12—15°C (cooling). The mixture was then stirred for 1 h without cooling and poured into a mixture of ice and water. The separated oil was extracted with chloroform, the extract was washed with H_2O, dried ($MgSO_4$) and evaporated; 15·3 g oily mixture (according to TLC on Silufol consisting of 4 components). The mixture (11·0 g) was stirred for 20 min with 30 ml H_2O and 33 ml H_2SO_4 at 110—130°C. After cooling, the mixture was diluted with H_2O and the precipitated solid was filtered, washed with H_2O, dried *in vacuo*, and precipitated from a solution in benzene by addition of light petroleum; 8·9 g mixture, m.p. 88—102°C. Repeated crystallization from benzene led to 0·6 g (3%) individual compound, m.p. 167—172°C (Kofler). UV spectrum: λ_{max} 251 nm (log ε 4·19). IR spectrum (KBr): 835, 857 (solitary Ar—H), 917, 1230, 1718 (COOH), 1348, 1530 ($ArNO_2$), 1598, 1619 cm^{-1} (Ar). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 8·62 (s, 1 H, 3-H), 7·70 (s, 1 H, 6-H), 2·58 (s, 5 H, CH_3 and $ArCH_2CO$). For $C_9H_8N_2O_6$ (240·2) calculated: 45·01% C, 3·36% H, 11·67% N; found: 45·22% C, 3·30% H, 11·92% N.

2-Methyldibenzo[*b,f*]thiepin-10(11*H*)-one (*XIX*)

Polyphosphoric acid, prepared from 156 g P_2O_5 and 95 ml 85% H_3PO_4, and 51·6 g *XV* were stirred for 1 h at 120°C. Processing gave 35·8 g (75%) ketone, m.p. 85—86·5°C (ethanol–cyclohexane, Kofler). Gerecke and coworkers[10-12] used a greater excess of polyphosphoric acid and cyclized at 100—103°C; they reported a m.p. of 83—84°C.

2-Methyl-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*XX*)

A mixture of 13·0 g *XIX*, 130 ml ethanol and 4·0 g $NaBH_4$ was refluxed for 3·5 h. Ethanol was partly distilled off, the residue diluted with H_2O and the product extracted with benzene. The extract was filtered with charcoal, dried ($MgSO_4$) and evaporated; 13·0 g (99%) crude *XX* crystallizing from a mixture of cyclohexane and light petroleum, m.p. 76—78°C (Kofler). IR spectrum: 765, 771, 824, 896 (4 and 2 adjacent and solitary Ar—H), 1046, 1070 (CHOH in a ring), 1569, 1594, 1607, 3048, 3083 (Ar), 3250 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·80—7·60 (m, 7 H, Ar—H) 5·20 (dt, after D_2O dd, 1 H, Ar—CH—O), 3·65 and 3·21 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·25 (d, J = 8·0 Hz, disappears after D_2O, OH), 2·20 (s, 3 H, CH_3). For $C_{15}H_{14}OS$ (242·3) calculated: 74·34% C, 5·82% H, 13·24% S; found: 74·54% C, 5·94% H, 13·36% S. Gerecke and coworkers[10-12] carried out a similar reduction in aqueous dioxane and characterized the product as a colourless oil.

11-Chloro-2-methyl-10,11-dihydrodibenzo[*b,f*]thiepin (*XXI*)

A solution of 12·1 g *XX* in 120 ml benzene was saturated for 4 h with anhydrous HCl in the presence of 5·0 g $CaCl_2$ at room temperature. Processing gave 12·6 g (97%) crude product which was crystallized from a mixture of cyclohexane and light petroleum, m.p. 83—85°C (Kofler). ^{1}H-NMR spectrum: δ 6·70—7·60 (m, 7 H, Ar—H), 5·72 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—Cl), 3·90 and 3·58 (2 dd, J = 14·0; 4·0 and 14·0; 8·0 Hz, 2 H, $ArCH_2$), 2·25 (s, 3 H, CH_3). For $C_{15}H_{13}$·.ClS (260·8) calculated: 69·08% C, 5·02% H, 13·60% Cl, 12·30% S; found: 69·36% C, 5·04% H, 13·36% Cl, 12·25% S. Gerecke and coworkers[10–12] used the same procedure and characterized the product as a yellow oil which crystallizes on standing.

2-Methyl-10-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (*III*)

A mixture of 11·4 g *XXI*, 20 g 1-methylpiperazine and 20 ml chloroform was stirred and refluxed for 5·5 h, diluted with chloroform, washed with H_2O and the basic product transferred by shaking with an excess of diluted H_2SO_4 into the aqueous phase. The organic layer was dried with K_2CO_3 and evaporated. The residue crystallized from a mixture of cyclohexane and light petroleum; 1·1 g (12%) 2-methyldibenzo[*b,f*]thiepin (*XXII*), m.p. 69—73°C. Pure substance was obtained by crystallization from light petroleum, m.p. 75—77°C (Kofler). UV spectrum: λ_{max} 260·5 nm (log ε 4·41), infl. 297 nm (3·95), infl. 340 nm (2·87). ^{1}H-NMR spectrum: δ 6·90—7·60 (m, 9 H, Ar—H and CH=CH), 2·30 (s, 3 H, CH_3). For this substance, prepared differently, the literature[29] reported a m.p. of 76·5—77·5°C. The aqueous layer, containing the sulfate of *III*, was filtered with charcoal, the filtrate was made alkaline with NH_4OH and extracted with chloroform. Processing of the extract gave 10·4 g (74%) oily base *III*. It was dissolved in 25 ml ethanol and the solution was neutralized with 3·74 g maleic acid in another 25 ml ethanol; 11·8 g maleate hemihydrate, m.p. 146—149·5°C (2-propanol–ether). Mass spectrum, *m/e*: 324 (M^+, corresponding to $C_{20}H_{24}N_2S$). For $C_{24}H_{28}N_2O_4S + 0{\cdot}5\ H_2O$ (449·6) calculated: 64·11% C, 6·50% H, 6·23% N, 7·13% S; found: 64·07% C, 6·57% H, 6·31% N, 7·31% S.

A sample of the maleate was decomposed with NH_4OH and the pure base *III* isolated by extraction with ether (oil). It was used for measuring the ^{1}H-NMR spectrum: δ 7·60 (m, 1 H, 9-H), 6·70—7·40 (m, 5 H, 1,3,6,7,8-H_5), 7·35 (d, 1 H, 4-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 2·58 and 2·35 (2 def. t, 8 H, 4 NCH_2 of piperazine), 2·20 (s, 6 H, NCH_3 and Ar-CH_3).

10-[4-(2-Hydroxyethyl)piperazino]-2-methyl-10,11-dihydrodibenzo[*b,f*]thiepin (*IV*)

A mixture of 4·4 g *XXI*, 4·4 1-(2-hydroxyethyl)piperazine and 5 ml chloroform was refluxed for 8 h and processed like in the preceding case; 4·7 g (78%) oily base *IV*.

Maleate, m.p. 136·5°C (acetone, Mettler). For $C_{25}H_{30}N_2O_5S$ (470·6) calculated: 63·81% C, 6·43% H, 5·95% N, 6·81% S; found: 63·86% C, 6·37% H, 5·83% N, 6·67% S.

Bis(hydrogen maleate) m.p. 141—142°C (acetone–ether, Mettler). For $C_{29}H_{34}N_2O_9S$ (586·6) calculated: 59·37% C, 5·84% H, 4·77% N, 5·47% S; found: 59·14% C, 5·88% H, 4·55% N, 5·70% S.

A sample of this salt was decomposed with NH_4OH and the pure oily base *IV* isolated by extraction with ether. ^{1}H-NMR spectrum: δ 6·80—7·70 (m, 7 H, Ar—H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·58 (t, J = 6·0 Hz, 2 H, CH_2O), 2·90 (bs, 1 H, OH), 2·60 and 2·48 (2 def. t, 8 H, 4 NCH_2 of piperazine), 2·50 (t, 2 H, NCH_2 in the side chain), 2·25 (s, 3 H, CH_3).

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REFERENCES

1. Šindelář K., Dlabač A., Metyšová J., Kakáč B., Holubek J., Svátek E., Šedivý Z., Protiva M.: This Journal *40*, 1940 (1975).
2. Šindelář K., Dlabač A., Kakáč B., Svátek E., Holubek J., Šedivý Z., Princová E., Protiva M.: This Journal *40*, 2649 (1975).
3. Jílek J. O., Šindelář K., Rajšner M., Dlabač A., Metyšová J., Votava Z., Pomykáček J., Protiva M.: This Journal *40*, 2887 (1975).
4. Šindelář K., Holubek J., Dlabač A., Bartošová M., Protiva M.: This Journal *42*, 2231 (1977).
5. Pelz K., Ernest I., Adlerová E., Metyšová J., Protiva M.: This Journal *33*, 1852 (1968).
6. Šindelář K., Holubek J., Protiva M.: This Journal *42*, 3605 (1977).
7. Dlabač A., Metyšová J., Kazdová E., Metyš J.: Activ. Nerv. Super. *17*, 217 (1975); Chem. Abstr. *85*, 72 227 (1976).
8. Votava Z., Metyš J., Dlabač A.: Activ. Nerv. Super. *17*, 216 (1975).
9. Valchář M., Dlabač A.: Česk. Fysiol. *25*, 277 (1976).
10. Gerecke M., Kaplan J.-P., Kyburz E. (F. Hoffmann-La Roche & Co.): Ger. Offen. 2,336.130 (Swiss Appl. 21.07.72); U.S. 3,929.791; Chem. Abstr. *80*, 108 576 (1974).
11. Gerecke M., Kaplan J.-P., Kyburz E. (Hoffmann-La Roche Inc.): U.S. 4,006.144 (Appl. 03.10.75).
12. Gerecke M., Kaplan J.-P., Kyburz E. (Hoffmann-La Roche Inc.): U.S. 4,006.145 (Appl. 03.10.75).
13. Gerecke M., Kaplan J.-P., Kyburz E. (F. Hoffmann-La Roche & Co).: Ger. Offen. 2 412 522 (Swiss Appl. 30.03.73); Chem. Abstr. *82*, 43 462 (1975).
14. Kyburz E., Aschwanden W. (F. Hoffmann-La Roche & Co.): Ger. Offen. 2,625.258 (Swiss Appl. 06.06.75).
15. Aschwanden W., Kyburz E., Schönholzer P.: Helv. Chim. Acta *59*, 1245 (1976).
16. Protiva M., Metyšová J.: Activ. Nerv. Super. 20, 270 (1978).
17. Willgerodt C., Simons M.: Ber. Deut. Chem. Ges. *39*, 269 (1906).
18. Gore P. H., Thorburn S., Weyell D. J.: J. Chem. Soc., Perkin Trans. 1, *1973*, 2940.
19. Mayer F.: Ber. Deut. Chem. Ges. *43*, 587 (1910).
20. Pelz K., Protiva M.: This Journal *32*, 2161 (1967).
21. Mayer F., Freund W.: Ber. Deut. Chem. Ges. *55*, 2052 (1922).
22. Dokukina A. F., Koton M. M., Mineeva O. K., Paribok V. A.: Zh. Obshch. Khim. *26*, 1651 (1956); Chem. Abstr. *51*, 1885 (1957).
23. Rajšner M., Mikšík F., Protiva M.: This Journal *43*, 1276 (1978).
24. Zanten B. van, Nauta W. T.: Rec. Trav. Chim. Pays-Bas *79*, 1211 (1960).
25. Kharasch N. S., Brown H. C.: J. Amer. Chem. Soc. *61*, 2142 (1939).
26. Chamberlain V. K., Wain R. L.: Ann. Appl. Biol. *69*, 65 (1971); Chem. Abstr. *77*, 15 433 (1972).
27. Robertson G. R.: Org. Syn., Coll. Vol. *1*, 396 (1946).
28. Robertson G. R.: Org. Syn., Coll. Vol. *1*, 406 (1946).
29. Urberg M. M., Kaiser E. T.: J. Amer. Chem. Soc. *89*, 5931 (1967).
30. Valchář M., Dlabač A.: 7th Congr. Neurol. Bohemoslov. & Symp. Neurochem., Bratislava 1976; Abstr., p. 192.

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