2-(TERT.AMINO)-11-(4-METHYLPIPERAZINO)DIBENZO[*b,f*]THIEPINS AND THEIR 10,11-DIHYDRO DERIVATIVES; SYNTHESIS AND NEUROLEPTIC ACTIVITY

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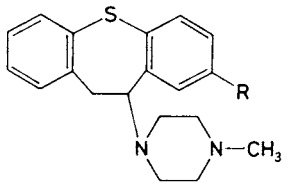
Reactions of (2-iodophenyl)acetic acid with 4-(dimethylamino)thiophenol, 4-piperidinothiophenol, and 4-morpholinothiophenol in boiling aqueous potassium hydroxide solutions in the presence of copper gave the arylacetic acids *IVabc* which were cyclized with polyphosphoric acid at 130°C to 8-(tert.amino)dibenzo[*b,f*]thiepin-10(11*H*)-ones *Vabc*. The following reactions with 1-methylpiperazine in boiling benzene in the presence of titanium tetrachloride afforded the enamines *IIabc*. Compounds *IIa* and *IIc* were reduced with diborane to the 10,11-dihydro compounds *Ia* and *Ic*. Compound *Ia* (the 8-dimethylamino derivative of perathiepin) is a typical incisive neuroleptic agent with very strong cataleptic, antiapomorphine, central depressant, and antiadrenergic activities. The morpholino derivative *Ic* and the enamines *IIb* and *IIc* are less active.

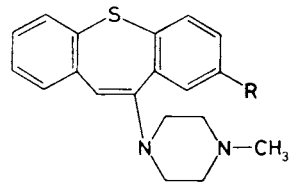
A rather long time ago[1] our research team synthesized 2-amino-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepin (the 8-amino derivative of perathiepin) which was found to be a rather strong cataleptic neuroleptic agent. In a recent communication[2], the synthesis of 2-(tert.amino)-9-(3-dimethylaminopropylidene)thioxanthenes (*i.e.* 2-tert.amino derivatives of prothixene) has been described and the products have been characterized as mild tranquillizers lacking the cataleptic potency. Because of the still incomplete information on the position of different amino groups between the "neuroleptic substituents", we considered useful to prepare and test some 8-tert.amino derivatives of perathiepin, *i.e.* 2-(tert.amino)-11-(4-methylpiperazino)-10,11-dihydrodibenzo[*b,f*]thiepins of the general formula *I*. This experimental work forms the subject of the present communication.

The synthetic work was started by an attempt to transform the known 2-(4-dimethylaminophenylthio)benzoic acid[2] to the homologous acid *IVa* by the usual four-step procedure (*cf.*[3]). The first of these steps, *i.e.* reduction of the mentioned acid with sodium dihydridobis(2-methoxyethoxo)aluminate[4,5], was successful and resulted in the amino alcohol *IIIa*. Since the following step, reaction of the alcohol *IIIa* with thionyl chloride, carried out either without solvent or in pyridine, did not lead to any characterized product, this approach to the acids *IVabc* was abandoned.

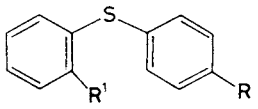
It was replaced by the direct syntheses of the acids *IVabc* by reactions of (2-iodophenyl)acetic acid[6] with 4-(dimethylamino)thiophenol[7], 4-piperidinothiophenol[2], and 4-morpholinothiophenol[2] in boiling aqueous potassium hydroxide solutions in the presence of copper (method, *cf.*[8]). The yields on the acids *IVabc* were moderate (about 50%) due to the rather low reactivity of the atom of iodine in the starting (2-iodophenyl)acetic acid[6] (this acid contaminated the crude products and purification by crystallization was necessary), and to the low quality of the thiols[2] used. The following step was the cyclization of the acids *IVabc* with polyphosphoric acid at about 130°C to the amino ketones *Vabc* whose identity was corroborated by the UV, IR, and ^{1}H NMR spectra. The synthetic method was similar to that used in the synthesis of 8-aminodibenzo[*b*,*f*]thiepin-10(11*H*)-one[1]. The amino ketone *Va* was reduced with sodium borohydride in aqueous ethanol to the amino alcohol *VI*.



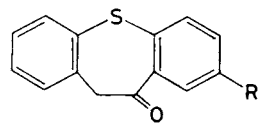
I



II



III, $R^1 = CH_2OH$
IV, $R^1 = CH_2COOH$



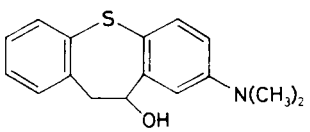
V

In formulae *I*–*V*: *a*, R = $N(CH_3)_2$ *b*, R = N⟨ ⟩ *c*, R = N⟨ ⟩O

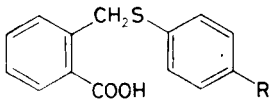
Reactions of the ketones *Vabc* with 1-methylpiperazine in boiling benzene in the presence of titanium tetrachloride gave the enamines *IIabc* (method, *cf.*[9,10]) with typical UV, IR, and ^{1}H NMR spectra. The enamines were obtained in mixtures with the starting ketones; the problem of separation was solved by crystallization or by chromatography on alumina which decreased the yields. The enamines *IIb* and *IIc* were prepared also in the form of maleates. The reduction of enamines *IIa* and *IIc* to the 10,11-dihydro compounds *Ia* and *Ic* was carried out by diborane, generated from sodium borohydride and acetic acid in tetrahydrofuran (method, *cf.*[11,12]). The resulting oily bases *Ia* and *Ic* could either be purified by chromato-

graphy or directly be transformed to the succinates which were purified by crystallization. The identity of the products was confirmed by mass spectra, in the case of compound *Ic* also by the ^{1}H NMR spectra (of the released base as well as of the succinate).

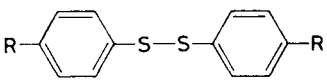
Reactions of phthalide with sodium salts of 4-(dimethylamino)thiophenol[7], 4-pyrrolidinothiophenol[2], 4-piperidinothiophenol[2], and 4-morpholinothiophenol[2] in boiling ethanol (method, *cf.*[13]) gave the 2-(4-(tert.amino)phenylthiomethyl)benzoic acids *VII*–*X* which were characterized by the UV, IR, and ^{1}H NMR spectra. The attempts to cyclize the acids *VII* and *IX* with polyphosphoric acid at 130°C led to cleavage of the benzyl CH_2—S bond. The proof of that was the islation of the disulfides *XI* (*cf.*[14,15]) and *XII* as the only characterized products. They evidently resulted from the oxidation of the corresponding thiophenols which were formed by cleavage. Mass spectra of the disulfides (*cf.*[16]) confirmed structures *XI* and *XII*. In a different connection (*cf.*[17]), 5-chloro-2-(3-methoxyphenylthio)acetophenone (*XIII*) was prepared by heating a mixture of 2,5-dichloroacetophenone[18], 3-methoxythiophenol[19], potassium carbonate, and copper to 150°C.



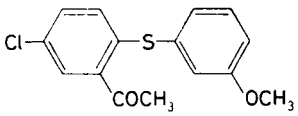
VI



VII, R = $N(CH_3)_2$
VIII, R = N⬡
IX, R = N⬡
X, R = N⬡O



XI, R = $N(CH_3)_2$
XII, R = N⬡



XIII

Compounds *Ia*, *Ic*, *IIb*, and *IIc* were pharmacologically tested in the form of salts described in the Experimental, as potential neuroleptic agents (the compounds were administered orally – unless stated otherwise – and the doses in mg/kg were calculated *per* bases). Acute toxicity in mice, LD_{50}: *Ia*, 48, *i.v.* 40; *Ic*, *i.v.* 35. Discoordinating effect in the rotarod test in mice, ED_{50}: *Ia*, 1·2 (in 24 h after the administration, the doses of 2·5 and 5·0 mg/kg elicited ataxia in 40, and 50% animals, respectively); *Ic*, 10·3 (the dose of 25 mg/kg elicited ataxia in 40% animals and exitus in 10% in the interval of 24 h after the administation); *IIb*, 8·4 (in 24 h the dose

of 25 mg/kg brought about ataxia in 30% animals, in 48 h in 20%); *IIc*, 5·3 (the effect disappeared within 24 h). Cataleptic effect in rats, ED_{50} (in 24 h the effect was over): *Ia*, 1·4; *Ic*, 12·3; *IIb*, 7·1; *IIc*, 7·5. Antiapomorphine effects in rats, D_{50} for the inhibition of chewing and of agitation given (the effects are not prolonged over 24 h): *Ia*, 3·6, 3·5; *Ic*, 27·4, 25·9; *IIb*, 3·6, 3·5; *IIc*, 14·4, 12·3. Inhibition of locomotor activity in mice evaluated by the photo-cell method (Dews): *Ia*, 0·24 (in 1 h after the administration), 1 (after 24 h). Antagonization of lethality caused by adrenaline in mice (α-adrenolytic effect), PD_{50}: *Ia*, 0·2; *Ic*, 0·14; *IIb*, 0·12; *IIc*, 0·11.

The most active dimethylamino compound *Ia* and its morpholino analogue were subjected to further tests within the general screening programme: Hypotensive effect in normotensive rats: *Ia*, long lasting drops of blood pressure by 50% after intravenous doses of 0·04–0·4 mg/kg; *Ic*, the oral dose of 25 mg/kg decreased the blood pressure by 16% in 1 h after the administration, by 10% in 3 h, and by 12% in 24 h; the oral dose of 10 mg/kg decreased the pressure in the same intervals by 11%, 10%, and 7%, respectively. Adrenolytic effect evaluated by inhibition of the adrenaline pressure reaction in rats by 50%: *Ia*, ED = 0·001 mg/kg *i.v.* Spasmolytic effects on the isolated rat duodenum: *Ia*, concentrations of 0·1–1·0 μg/ml reduced the acetylcholine contractions to 50% of the control value; 1–10 μg/ml reduced similarly the barium chloride contractions. Hypothermic effect in rats: *Ia*, the dose of 0·1 mg/kg *i.p.* decreased the rectal temperature by 1°C (comparable with chlorpromazine). Antihistamine effect in guinea-pigs evaluated by protection of 50% of the animals from the lethal effect of 5 mg/kg histamine (administered intrajugularly): *Ia*, ED = 0·1–1·0 mg/kg *s.c.*; *Ic*, 1 mg/kg *s.c.* Potentiation of the thiopental sleeping time in mice (prolongation to 200% of the control value): *Ia*, ED = 0·1 to 1·0 mg/kg *i.v.*; *Ic*, 0·5 mg/kg *i.v.* Antiarrhythmic effect evaluated by prolongation (with statistical significance) of the latency of ventricular extrasystoles in rats elicited with aconitine: *Ia*, ED = 1–2·5 mg/kg *i.v.* (5 times stronger than the quinidine effect). Antiamphetamine effect in mice evaluated by protection 100% animals from the lethal effect of a standard dose of amphetamine: *Ia*, ED = 0·05 mg/kg *i.v.*; *Ic*, 0·1–0·5 mg/kg *i.v.*

In conclusion, the dimethylamino compound *Ia* is a very potent cataleptic neuroleptic agent with strong central depressant, antiapomorphine, antiamphetamine, adrenolytic, and antiarrrhythmic activities. The compound is well comparable with the most active members of the 10-piperazino-10,11-dihydrodibenzo[*b*,*f*]thiepin series of neuroleptics, *e.g.* clorothepin[5]. The dimethylamino group appears thus as a very effective neuroleptic substituent. Its lower effect in the thioxanthene series[2] must be explained *1*) by the lower activity of the thioxanthenes in general, and *2*) the corresponding compound is a mixture of geometrical isomers out of which only one is active. The morpholino analogue *Ic* and the enamines *IIb* and *IIc* are less active.

The acids *IVb*, *IVc*, *IX*, and *X* were tested for antiinflammatory activity (carrageenan oedema and adjuvant oedema) and for analgetic activity (Haffner test) in mice. The benzoic acids *IX* and *X* were found practically inactive. The substituted phenylacetic acids *IVb* and *IVc* showed a significant antiinflammatory activity in the oral doses of 100 mg/kg in the carrageenan oedema model; compound *IVb* showed additionally some activity in the oral dose of 50 mg/kg in the adjuvant oedema model. The activities found were lower than those of ibuprofene used as the standard.

The compounds prepared were also tested for antimicrobial activity *in vitro* (microorganisms and the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml): *Streptococcus β-haemolyticus,Ia* 50, *Ic* 100, *IIb* 50; *Streptococcus faecalis*, *Ia* 100, *IIb* 25; *Staphylococcus pyogenes aureus*, *Ia* 50, *Ic* 100, *IIb* 12·5; *Saccharomyces pasterianus*, *IIb* 12·5; *Trichophyton mentagrophytes*, *IIb* 12·5.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at room temperature or at 77°C. UV spectra (in methanol) were recorded with a Unicam SP 8 000 spectrophotometer, IR spectra (mostly in Nujol) with the Perkin–Elmer 298 spectrophotometer, ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer, and the mass spectra with MCH 1 320 and Varian MAT 44S spectrometers. The homogeneity of the products and composition of the mixtures were checked by thin-layer chromatography on silica gel (Silufol). The extracts were dried with Na_2SO_4 or K_2CO_3 and evaporated under reduced pressure on a rotating evaporator.

2-(4-Dimethylaminophenylthio)benzyl Alcohol (*IIIa*)

A stirred suspension of 36·1 g 2-(4-dimethylaminophenylthio)benzoic acid[2] in 350 ml benzene was treated dropwise with 110 g 50% sodium dihydridobis(2-methoxyethoxo)aluminate in toluene with maintaining the temperature below 40°C. The mixture was stirred for 4 h at room temperature, the clear solution obtained was decomposed by a slow addition of a slight excess of 10% NaOH, the organic layer was separated, washed with water, dried and evaporated; 30·8 g (90%) *IIIa*, m.p. 75–77°C (aqueous methanol). IR spectrum: 745, 750, 809 (4 and 2 adjacent Ar—H), 1 025 (CH_2OH), 1 509, 1 592, 3 045 (Ar), 2 810 (N—CH_3), 3 465, 3 550 cm^{-1} (OH). ^{1}H NMR spectrum: δ 7·25 (d, J = 8·5 Hz, 2 H, 2′,6′-H_2), c. 7·00 (m, 4 H, 3,4,5,6-H_4), 6·61 (d, J = 8·5 Hz, 2 H, 3′,5′-H_2), 4·75 (bd, after ^2H_2O s, 2 H, $ArCH_2O$), 2·95 (s, 6 H, $N(CH_3)_2$), 2·3 (bt, disappears after ^2H_2O, 1 H, OH). For $C_{15}H_{17}NOS$ (259·4) calculated: 69·46% C, 6·61% H, 5·40% N, 12·36% S; found: 69·80% C, 6·83% H, 5·34% N, 12·30% S.

(2-(4-Dimethylaminophenylthio)phenyl)acetic Acid (*IVa*)

A solution of 4·0 g KOH in 40 ml water was made free of O_2 by the addition of 0·2 g $Na_2S_2O_4$, 5·1 g 4-(dimethylamino)thiophenol[7] were added, the solution was heated to 60°C and treated under stirring with 8·4 g (2-iodophenyl)acetic acid[6], and 0·2 g Cu catalyst. The mixture was refluxed for 20 h. filtered with charcoal while hot, the filtrate was neutralized with acetic acid to pH of 5–6, and the precipitated product was filtered after standing overnight; 6·1 g (67%), m.p. 112–116°C. Analytical sample, m.p. 114–117°C (ethanol). UV spectrum: λ_{max} 278 nm (log ε

4·37). IR spectrum (KBr): 758, 805 (4 and 2 adjacent Ar—H), 943, 1 190, 1 235, 1 700, 2 560, 2 625, 2 760, infl. 3 100 (RCOOH), 1 506, 1 600 cm^{-1} (Ar). ^1H NMR spectrum: δ 10·70 (bs, 1 H, COOH), 7·22 (d, J = 8·5 Hz, 2 H, 2′,6′-H_2), c. 7·10 (m, 4 H, 3,4,5,6-H_4), 6·58 (d, J = 8·5 Hz, 2 H, 3′,5′-H_2), 3·80 (s, 2 H, $ArCH_2CO$), 2·88 (s, 6 H, $N(CH_3)_2$). For $C_{16}H_{17}NO_2S$ (287·4) calculated: 66·87% C, 5·96% H, 4·87% N, 11·16% S; found: 66·58% C, 6·05% H, 4·88% N, 11·36% S.

(2-(4-Piperidinophenylthio)phenyl)acetic Acid (*IVb*)

4-Piperidinothiophenol[2] (6·7 g) and 7·9 g (2-iodophenyl)acetic acid[6] were similarly reacted in the solution of 8·4 g KOH in 85 ml water in the presence of 0·2 g Cu. Similar processing gave 4·1 g (42%) *IVb*, m.p. 146—148°C (aqueous ethanol). IR spectrum (KBr): 760, 810 (4 and 2 adjacent Ar—H), 920, 1 230, 1 700, 2 545, 2 620, infl. 3 100 (RCOOH), 1 495, 1 595, 3 020, 3 048, 3 080 (Ar), 2 810 cm^{-1} (N—CH_2). For $C_{19}H_{21}NO_2S$ (327·4) calculated: 69·69% C, 6·46% H, 4·28% N, 9·79% S; found: 68·98% C, 6·53% H, 4·06% N, 9·74% S.

(2-(4-Morpholinophenylthio)phenyl)acetic Acid (*IVc*)

Was prepared similarly like in the preceding two cases from 6·0 g 4-morpholinothiophenol[2], 6·0 g (2-iodophenyl)acetic acid[6], and 0·2 g Cu in a solution of 6·0 g KOH in 60 ml water; 4·0 g (40%), m.p. 164—166°C (ethanol). UV spectrum: λ_{max} 271 nm (log ε 4·33). IR spectrum: 735, 751, 817 (4 and 2 adjacent Ar—H), 925, 1 121, 1 239, 1 704, 2 720, infl. 3 160 (RCOOH), 1 497, 1 589 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·80—7·40 (m, 8 H, ArH), 3·70 (m, 4 H, CH_2OCH_2), 3·70 (s, 2 H, $ArCH_2CO$), 3·12 (m, 4·H, CH_2NCH_2). For $C_{18}H_{19}NO_3S$ (329·4) calculated: 65·63% C, 5·81% H, 4·25% N, 9·73% S; found: 65·31% C, 5·97% H, 4·19% N, 9·53% S.

8-(Dimethylamino)dibenzo[*b,f*]thiepin-10(11*H*)-one (*Va*)

A mixture of 24·0 g *IVa* and 240 g polyphosphoric acid was heated to 135°C and stirred for 3 h at this temperature. After partial cooling, it was poured on ice and neutralized with 20% NaOH to pH 7. After standing overnight, the product was filtered, washed with water, and dried *in vacuo*; 22·1 g (93%), m.p. 112—115°C. Analytical sample, m.p. 125—127°C (ethanol). UV spectrum: λ_{max} 252 nm (log ε 4·41), 285 nm (4·23), 398 nm (3·40). IR spectrum: 740, 760, 812, 865 (4 and 2 adjacent, and solitary Ar—H), 1 410, 1 540, 1 596 (Ar), 1 660 (ArCOR), 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 7·00—7·70 (m, 6 H, 1,2,3,4,6,9-H_6), 6·75 (dd, J = 9·0; 3·0 Hz, 1 H, 7-H), 4·39 (s, 2 H, $ArCH_2CO$), 2·90 (s, 6 H, $N(CH_3)_2$). For $C_{16}H_{15}NOS$ (269·4) calculated: 71·34% C, 5·61% H, 5·20% N, 11·91% S; found: 70·94% C, 5·75% H, 4·91% N, 11·94% S.

8-Piperidinodibenzo[*b,f*]thiepin-10(11*H*)-one (*Vb*)

Similar cyclization of 13·9 g *IVb* with 140 g polyphosphoric acid at 130°C (3 h) gave 12 g inhomogeneous product which was extracted with methanol (separation from the polymeric substance), the extract was evaporated and the residue crystallized from aqueous methanol; 3·5 g (27%), m.p. 105—107°C. UV spectrum: λ_{max} 250 nm (log ε 4·38), 282 nm (4·19), 430 nm (3·40). IR spectrum: 746, 763, 822, 859, 886 (4 and 2 adjacent, and solitary Ar—H), 1 480, 1 597, 3 050, 3 065, 3 090 (Ar), 1 664 cm^{-1} (ArCOR). ^1H NMR spectrum: δ 7·70 (d, J = 2·0 Hz, 1 H, 9-H), 7·05—7·60 (m, 5 H, 1,2,3,4,6-H_5), 6·95 (dd, J = 8·5; 2·0 Hz, 1 H, 7-H), 4·38 (s, 2 H, $ArCH_2CO$), 3·14 (bm, 4 H, CH_2NCH_2), 1·60 (bs, 6 H, remaining 3 CH_2 of piperidine). For $C_{19}H_{19}NOS$ (309·4) calculated: 73·75% C, 6·19% H, 4·53% N, 10·36% S; found: 73·81% C, 6·44% H, 4·12% N, 10·46% S.

8-Morpholinodibenzo[*b,f*]thiepin-10(11*H*)-one (*Vc*)

Similar cyclization of 12·4·g *IVc* with 125 g polyphosphoric acid at 125—130°C (3 h) and similar processing of the crude product like in the preceding case gave 7·0 g (60%) product melting at 135—139°C (methanol). Recrystallization for analysis from aqueous methanol gave the hemihydrate, m.p. 150—152°C. Mass spectrum, *m/z* (composition and %): 311 (M^+ corresponding to $C_{18}H_{17}NO_2S$, 100%), 312 (23), 279 (27), 278 ($C_{18}H_{16}NO_2$, 61), 253 ($C_{15}H_{11}NOS$, 24), 252 ($C_{15}H_{10}NOS$, 20), 224 ($C_{14}H_{10}NS$, 24), 220 ($C_{15}H_{10}NO$, 16), 165 ($C_{13}H_9$, 15). UV spectrum: λ_{max} 249 nm (log ε 4·46), 278 nm (4·25), 376 nm (3·58). IR spectrum: 742, 761, 807, 862, 870, 879 (4 and 2 adjacent, and solitary Ar—H), 1 480, 1 594 (Ar), 1 671 cm^{-1} (ArCOR). For $C_{18}H_{17}NO_2S + 0{\cdot}5\ H_2O$ (320·4) calculated: 67·47% C, 5·35% H, 4·37% N, 10·01% S; found: 67·84% C, 5·43% H, 4·67% N, 10·17% S.

8-(Dimethylamino)-10,11-dihydrodibenzo[*b,f*]thiepin-10-ol (*VI*)

A stirred solution of 1·35 g *Va* in 30 ml ethanol was slowly treated with a solution of 0·4 g $NaBH_4$ in 5 ml water containing 1 drop of 20% NaOH. The mixture was refluxed for 4 h, ethanol was evaporated *in vacuo*, the residue was treated with 10 ml water and extracted with benzene. The extract was washed with 5% NaOH and water, dried, and evaporated. The residue (1·25 g, 92%, m.p. 118—122°C) was recrystallized from a mixture of benzene and light petroluem, m.p. 123—125°C. IR spectrum: 755, 805, 860, 870 (4 and 2 adjacent and solitary Ar—H), 1 060 (CHOH in the ring), 1 492, 1 550, 1 600 (Ar), 3 280 cm^{-1} (OH). ^1H NMR spectrum: δ 7·00 to 7·50 (m, 5 H, 1,2,3,4,6-H_5), 6·95 (d, J = 2·5 Hz, 1 H, 9-H), 6·48 (dd, J = 8·5; 2·5 Hz, 1 H, 7-H), 5·40 (dd, J = 8·0; 4·0 Hz, 1 H, Ar—CH—O), 3·68 and 3·30 (2 dd, J = 13·0; 4·0 and 13·0; 8·0 Hz, 1 + 1 H, $ArCH_2$), 2·89 (s, 6 H, $N(CH_3)_2$), 2·59 (bs, 1 H, OH). For $C_{16}H_{17}NOS$ (271·4) calculated: 70·81% C, 6·31% H, 5·16% N, 11·82% S; found: 71·21% C, 6·36% H, 4·87% N, 11·66% S.

2-(Dimethylamino)-11-(4-methylpiperazino)dibenzo[*b,f*]thiepin (*IIa*)

A stirred solution of 4·1 g *Va* and 7·5 g 1-methylpiperazine in 90 ml benzene was slowly treated with a solution of 2·18 g $TiCl_4$ in 15 ml benzene, and the mixture was refluxed for 24 h. After cooling it was shaken with water, the separated TiO_2 was filtered off, the filtrate was washed with a saturated $NaHCO_3$ solution, dried and evaporated. The residue crystallized after trituration with light petroleum; 3·6 g (61%) crude product which was recrystallized for analysis from ethanol, m.p. 155—157°C. UV spectrum: λ_{max} 230 nm (log ε 4·41), 267 nm (4·40), infl. 323 nm (3·90). IR spectrum: 749, 800, 805, 830, 872 (4 and 2 adjacent, and solitary Ar—H), 1 487, 1 550, 1 585, 3 065 (Ar), 1 605 (C=C in conjugation), 2 690, 2 745, 2 790, 2 820 cm^{-1} (N—CH_3, N—CH_2). ^1H NMR spectrum: δ 7·00—7·50 (m, 5 H, 4,6,7,8,9-H_5), 6·98 (d, J = 2·5 Hz, 1 H, 1-H), 6·61 (dd, J = 8·5; 2·5 Hz, 1 H, 3-H), 6·25 (s, 1 H, 10-H), 3·02 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·90 (s, 6 H, $N(CH_3)_2$), 2·52 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·35 (s, 3 H, NCH_3). For $C_{21}H_{25}N_3S$ (351·5) calculated: 71·75% C, 7·17% H, 11·96% N, 9·12% S; found: 72·66% C, 7·35% H, 11·50% N, 9·14% S.

11-(4-Methylpiperazino)-2-piperidinodibenzo[*b,f*]thiepin (*IIb*)

A similar reaction of 6·9 g *Vb*, 11·5 g 1-methylpiperazine, and 2·2 g $TiCl_4$ in 170 ml benzene gave 7·4 g crude product which was chromatographed on a column of 150 g neutral Al_2O_3 (activity II). Elution with benzene afforded 2·7 g (31%) homogeneous *IIb*, m.p. 152—154°C (aqueous methanol). UV spectrum: λ_{max} 271 nm (log ε 4·38), infl. 312 nm (3·96). IR spectrum:

750, 805, 820, 886 (4 and 2 adjacent, and solitary Ar—H), 1 550, 1 585, 1 601, 3 050 (Ar and conjugated C=C), 2 790 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 7·00—7·50 (m, 6 H, 1,4,6,7, 8,9-H_6), 6·83 (dd, J = 8·5; 2·5 Hz, 1 H, 3-H), 6·25 (s, 1 H, 10-H), 3·10 (bm, 8·H, $CH_2N^1CH_2$ in piperazine and CH_2NCH_2 in piperidine), 2·50 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, NCH_3), 1·60 (bm, 6 H, remaining 3 CH_2 of piperidine). For $C_{24}H_{29}N_3S$ (391·6) calculated: 73·61% C, 7·47% H, 10·73% N, 8·19% S; found: 73·20% C, 7·55% H, 10·94% N, 8·44% S.

Maleate hemihydrate, m.p. 132·5—134·5°C (ethanol–ether). For $C_{28}H_{33}N_3O_4S + 0{\cdot}5\ H_2O$ (516·6) calculated: 65·09% C, 6·63% H, 8·13% N, 6·20% S; found: 64·98% C, 6·52% H, 8·25% N, 6·40% S.

11-(4-Methylpiperazino)-2-morpholinodibenzo[*b,f*]thiepin (*IIc*)

Preparation from 6·6 g *Vc*, 6·4 g 1-methylpiperazine, and 1·85 g $TiCl_4$ in 150 ml benzene was carried out similarly like in the synthesis of *IIa*. The crude product obtained (4·8 g, 58%) was purified by crystallization from aqueous ethanol, m.p. 180·5—182·5°C. UV spectrum: λ_{max} 251 nm (log ε 4·41), infl. 270 nm (4·36), 314 nm (3·95). IR spectrum: 750, 757, 805, 811, 884 (4 and 2 adjacent, and solitary Ar—H), 1 119, 1 220, 1 245 (R—O—R), 1 550, 1 582, 1 603, 3 040, 3 050 (Ar), 1 611 (conjugated C=C), 2 681, 2 740, 2 755 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 6·90—7·50 (m, 6 H, 1,4,6,7,8,9-H_6), 6·88 (dd, J = 8·5; 3·0 Hz, 1 H, 3-H), 6·25 (s, 1 H, 10-H), 3·80 (bt, 4 H, CH_2OCH_2), 3·00 (bm, 8 H, $CH_2N^1CH_2$ of piperazine and CH_2NCH_2 of morpholine), 2·50 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, NCH_3). For $C_{23}H_{27}N_3$·.OS (393·5) calculated: 70·19% C, 6·92% H, 10·68% N, 8·15% S; found: 70·03% C, 6·92% H, 10·58% N, 8·21% S.

Maleate hemihydrate, m.p. 171—173°C (95% ethanol–ether). For $C_{27}H_{31}N_3O_5S + 0{\cdot}5\ H_2O$ (518·7) calculated: 62·52% C, 6·22% H, 8·10% N, 6·18% S; found: 62·43% C, 6·18% H, 7·65% N, 6·03% S.

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

A stirred solution of 1·9 g *IIa* in 20 ml tetrahydrofuran was treated with 1·2 g $NaBH_4$ and then dropwise over 1·5 h with a solution of 6·3 ml acetic acid in 10 ml tetrahydrofuran. The mixture was stirred for 30 min at room temperature, refluxed for 2 h. diluted with 20 ml chloroform, washed with 20 ml 5% NaOH, and with water. After drying, the solvents were evaporated, the residue (2·4 g of the aminoborane complex) was dissolved in 40 ml ethanol and the solution was refluxed for 6 h with 20 ml 20% NaOH. After cooling the mixture was extracted with benzene, the extract was washed with water, dried and evaporated. The residue (1·7 g oily crude *Ia*) was neutralized with 0·53 g succinic acid in ethanol and the precipitated salt was crystallized from a mixture of ethanol and ether; 1·0 g (42%) succinate, m.p. 130—132°C. Mass spectrum, *m/z* (%): 353 (M^+ corresponding to $C_{21}H_{27}N_3S$, 17%), 253 ($C_{16}H_{15}NS$, 52), 222 (50), 99 (75), 72 (78), 70 (100). For $C_{25}H_{33}N_3O_4S$ (471·6) calculated: 63·67% C, 7·05% H, 8·91% N, 6·80% S; found: 63·15% C, 7·17% H, 8·44% N, 7·10% S.

11-(4-Methylpiperazino)-2-morpholino-10,11-dihydrodibenzo[*b.f*]thiepin (*Ic*)

Similar reduction of 12·4 g *IIc* with 8·0 g $NaBH_4$ and 30 ml acetic acid in 170 ml tetrahydrofuran gave 11·1 g crude *Ic* which was purified by chromatography on 200 g neutral Al_2O_3 (activity II). Elution with benzene afforded 8·1 g (65%) homogeneous oily *Ic* which was neutralized with 2·4 g succinic acid in ethanol. Crystallization of the crude succinate from ethanol–ether gave 7·5 g pure substance, m.p. 169—172°C. Mass spectrum, *m/z* (%): 395 (M^+ corresponding to $C_{23}H_{29}N_3$·.

.OS, 45%), 295 (55), 264 (40), 99 (65), 72 (75), 70 (100), 56 (55), 42 (28). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 10·30 (bs, 2 H, 2 COOH), 7·00—7·60 (m, 6 H, 1,4,6,7,8,9-H_6), 6·75 (dd, J = 8·5; 3·0 Hz, 1 H, 3-H), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·70 (bm, 4 H, CH_2OCH_2), 3·10 (bm, 4 H, CH_2NCH_2 of morpholine), 2·60 (m, 8 H, 4 CH_2N of piperazine), 2·48 (s, 4 H, CH_2CH_2 of succinic acid), 2·30 (s, 3 H, NCH_3). For $C_{27}H_{35}N_3O_5S$ (513·6) calculated: 63·13% C, 6·87% H, 8·18% N, 6·24% S; found: 62·96% C, 7·08% H, 8·15% N, 6·40% S.

A sample of the oily base was released from the succinate with NH_4OH and isolated by extraction with ether. ^{1}H NMR spectrum: δ 6·50—7·50 (m, 7 H, ArH), 3·00—4·00 (m, 3 H, $ArCH_2CHAr$), 3·80 (m, 4 H, CH_2OCH_2), 3·10 (m, 4 H, CH_2NCH_2 of morpholine), 2·70 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·25 (s, 3 H, NCH_3).

2-(4-(Dimethylamino)phenylthiomethyl)benzoic Acid (*VII*)

Sodium ethoxide solution was prepared from 200 ml ethanol and 4·1 g Na, 27·4 g (4-(dimethylamino)thiophenol[7] and 23·0 g phthalide were added, and the mixture was refluxed for 3 h. Ethanol was evaporated *in vacuo*, the residue was dissolved in 100 ml water, the solution was filtered, and the filtrate was neutralized with acetic acid to pH 6. Standing overnight led to 33·2 g (65%) crude product, m.p. 140—145°C. Analytical sample, m.p. 151—153°C (aqueous ethanol). UV spectrum: λ_{max} 274 nm (log ε 4·25), 277·5 nm (4·25). IR spectrum: 762, 769, 806 (4 and 2 adjacent Ar—H), 943, 1 269, 1 292, 1 672, 2 520, 2 645 (COOH), 2 805 (N—CH_3), 3 060, 3 080 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 11·68 (bs, 1 H, COOH), 8·00 (m, 1 H, 6-H), c. 7·30 (m, 3 H, 3,4,5-H_3), 7·12 (d, J = 8·5 Hz, 2 H, 2′,6′-H_2), 6·54 (d, J = 8·5 Hz, 2 H, 3′,5′-H_2), 4·38 (s, 2 H, $ArCH_2S$), 2·88 (s, 6 H, $N(CH_3)_2$). For $C_{16}H_{17}NO_2S$ (287·4) calculated: 66·86% C, 5·96% H, 4·87% N, 11·16% S; found: 66·46% C, 6·05% H, 4·73% N, 11·21% S.

2-(4-Pyrrolidinophenylthiomethyl)benzoic Acid (*VIII*)

The compound was prepared similarly from 12·0 g 4-pyrrolidinothiophenol[2], 8·7 g phthalide, and sodium ethoxide (1·62 g Na) in 100 ml ethanol: 10·2 g (50%), m.p. 193—195°C (ethanol). UV spectrum: λ_{max} 277 nm (log ε 4·34), infl. 310 nm (3·89). IR spectrum: 766, 810 (4 and 2 adjacent Ar—H), 930, 1 267, 1 296, 1 670, 2 640, infl. 3 100 (ArCOOH), 1 483, 1 502, 1 570, 1 596 cm^{-1} (Ar). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·80 (m, 1 H, 6-H), 6·90—7·40 (m, 3 H, 3,4,5-H_3), 7·02 (d, J = 9·0 Hz, 2 H, 2′,6′-H_2), 6·32 (d, J = 9·0 Hz, 2 H, 3′,5′-H_2), 4·30 (s, 2 H, $ArCH_2S$), 3·12 (m, 4 H, CH_2NCH_2), 1·85 (m, 4 H, remaining 2 CH_2 of pyrrolidine). For $C_{18}H_{19}NO_2S$ (313·4) calculated: 68·98% C, 6·11% H, 4·47% N, 10·23% S; found: 69·44% C, 6·38% H, 4·48% N, 10·23% S.

2-(4-Piperidinophenylthiomethyl)benzoic Acid (*IX*)

The compound was prepared similarly like *VII* and *VIII* from 19·2 g 4-piperidinothiophenol[2], 13·0 g phthalide, and sodium ethoxide (2·3 g Na) in 80 ml ethanol; 14·5 g (45%), m.p. 146—148°C (aqueous ethanol). UV spectrum: λ_{max} 275 nm (log ε 4·20). IR spectrum (KBr): 768, 815, (4 and 2 adjacent Ar—H), 915, 1 240, 1 270, 1 300, 1 675, 2 510, 2 635, infl. 3 100 (ArCOOH), 1 495, 1 590, 3 020, 3 055 (Ar), 2 820 cm^{-1} (CH_2—N). For $C_{19}H_{21}NO_2S$ (327·4) calculated: 69·69% C, 6·46% H, 4·28% N, 9·79% S; found: 69·73% C, 6·51% H, 3·86% N, 9·58% S.

2-(4-Morpholinophenylthiomethyl)benzoic Acid (*X*)

The compound was prepared similarly like *VII*—*X* from 11·7 g 4-morpholinothiophenol[2], 7·5 g phthalide, and sodium ethoxide (1·38 g Na) in 50 ml ethanol; 11·6 g (60%), m.p. 123—124°C (aqueous methanol). UV spectrum: λ_{max} 270 nm (log ε 4·25). IR spectrum: 710, 763, 815 (4 and

2 adjacent Ar—H), 925, 1 243, 1 274, 1 300, 1 680, 2 515, 2 555, 2 640, infl. 3 100 (ArCOOH), 1 123 (R—O—R), 1 498, 1 572, 1 598 cm^{-1} (Ar). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 7·85 (m, 1 H, 6-H), 7·10—7·50 (m, 3 H, 3,4,5-H_3), 7·15 (d, J = 9·0 Hz, 2 H, 2′,6′-H_2), 6·80 (d, J = = 9·0 Hz, 2 H, 3′,5′-H_2), 4·40 (s, 2 H, $ArCH_2S$), 4·28 (bm, 4 H, CH_2OCH_2), 3·05 (bm, 4 H, CH_2NCH_2). For $C_{18}H_{19}NO_3S$ (329·4) calculated: 65·62% C, 5·81% H, 4·25% N, 9·73% S; found: 65·52% C, 5·71% H, 4·50% N, 9·75% S.

Attempt to Cyclize the Acid *VII*

A stirred mixture of 155 g polyphosphoric acid and 14·4 g *VII* was heated for 4 h to 130°C. After partial cooling the mixture was poured into a mixture of ice and water, and neutralized with 20% NaOH. The product was extracted with benzene, the extract was washed with water, dried and evaporated. The residue (10·0 g) was chromatographed on a column of 200 g neutral Al_2O_3 (activity II), The first benzene eluates gave 1·12 g of bis(4-dimethylaminophenyl) disulfide (*XI*), m.p. 116—118°C (ethanol). Mass spectrum, m/z (composition, %): 304 (M^+ corresponding to $C_{16}H_{20}N_2S_2$, 12%), 152 ($C_8H_{10}NS$, 100), 136 (C_7H_6NS, 10), 120 ($C_8H_{10}N$, 3). UV spectrum: λ_{max} 537 nm (log ε 4·21), 629 nm (4·28), 605 nm (4·26), infl. 462 nm (4·15). IR spectrum: 810 (2 adjacent Ar—H), 1 505, 1 594, 3 078 (Ar), 2 805 cm^{-1} (CH_3—N). ^1H NMR spectrum: δ7·28 (d, J = 8·5 Hz, 4 H, 2,6,2′,6′-H_4), 6·55 (d, J = 8·5 Hz, 4 H, 3,5,3′,5′-H_4), 2·90 (s, 12 H, 2 $N(CH_3)_2$). Refs.[14,15], m.p. 118°C.

Attempt to Cyclize the Acid *IX*

IX (3·3 g) was heated for 1 h with 33 g stirred polyphosphoric acid to 130°C. The cooled mixture was diluted with ice and water, neutralized with 20% NaOH and Na_2CO_3,and the precipitated solid was filtered, washed with water, and dried *in vacuo*; 2·1 g bis(4-piperidinophenyl) disulfide (*XII*), m.p. 110—111°C (aqueous ethanol). Mass spectrum, m/z (%): 384·1709 (M^+ corresponding to $C_{22}H_{28}N_2S_2$, calculated 384·1694, 2·5%), 193 (67), 192 (100), 160 (13), 137 (15), 136 (19). UV spectrum: λ_{max} 269 nm (log ε 4·28), infl. 300 nm (4·16). IR spectrum (KBr): 805 (2 adjacent Ar—H), 1 491, 1 592 (Ar), 2 800 cm^{-1} (N—CH_2). ^1H NMR spectrum: δ 7·30 (d, J = 9·0 Hz, 4 H, 2,6,2′,6′-H_4), 6·78 (d, J = 9·0 Hz, 4 H, 3,5,3′,5′-H_4), 3·15 (bm, 8 H, 2 CH_2NCH_2), 1·65 (bs, 12 H, remaining 6 CH_2 of two piperidyls). For $C_{22}H_{28}N_2S_2$ (384·5) calculated: 68·72% C, 7·34% H, 7·29% N, 16·65% S; found: 68·46% C, 7·27% H, 7·29% N, 16·20% S.

5-Chloro-2-(3-methoxyphenylthio)acetophenone (*XIII*)

A mixture of 42 g 3-methoxythiophenol[19], 52 g 2,5-dichloroacetophenone[18], 66 g K_2CO_3, and 1·1 g Cu was stirred and heated for 2·5 h to 140—150°C. The mixture solidified after some time and the stirring was discontinued. After cooling, the mixture was extracted with boiling benzene, and the extract was evaporated; 60·0 g (74%), m.p. 82—84°C (ethanol). ^1H NMR spectrum: δ 7·72 (d, J = 2·5 Hz, 1 H, 6-H), 6·70—7·50 (m, 6 H, remaining ArH), 3·79 (s, 3 H, OCH_3), 2·62 (s, 3 H, $COCH_3$). For $C_{15}H_{13}ClO_2S$ (292·8) calculated: 61·53% C, 4·48% H, 12·11% Cl, 10·95% S; found: 61·31% C, 4·44% H, 12·24% Cl, 11·00% S.

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