3-(4-METHYLPIPERAZINO)DIBENZO[*b,f*]-1,2,4-TRIAZOLO[4,3-*d*]-1,4-THIAZEPINE AND ITS 6-CHLORO AND 12-CHLORO DERIVATIVES; SYNTHESIS AND PHARMACOLOGY*

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Dibenzo[*b,f*]-1,4-thiazepin-11(10*H*)-ones *IIa*—*IIc* reacted with phosphorus pentasulfide in pyridine under the formation of the thiones *IIIa*—*IIIc* which were transformed by treatment with hydrazine hydrate in 1-butanol to the hydrazine derivatives *IVa*—*IVc*. Reactions with triethyl orthoformate in ethanol in the presence of sulfuric acid effected cyclization to dibenzo[*b,f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine (*Va*) and its chloro derivatives *Vb*, *Vc* which were treated with bromine in a boiling mixture of chloroform and pyridine and gave the 3-bromo derivatives *VIa*—*VIc*. The title compounds *Ia*—*Ic* were obtained by substitution reactions with an excess of boiling 1-methylpiperazine. An attempt at preparing an analogous 14*H*-dibenzo[*b,g*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazocine derivative was discontinued in the stage of reaction of the thione *X* with hydrazine hydrate which resulted in the azine *XI*. Compounds *Ia*—*Ic* on intravenous administration are highly toxic and inactive in tests for CNS effects; compound *Ic* showed a clear anticholinergic activity.

Annelation of the 1,2,4-triazole ring to the 1,4-benzodiazepine or thieno[2,3-*e*]-1,4-diazepine system, in which the nitrogen atom in position 1 of the bicycle is common to both anellated systems, led to the discovery of very potent central neurotropic agents[1,2] and it was established that substitution in position 3 of the triazole fragment with a piperazine residue influences favourably the activity[3–6]. These facts led us to design the structures of compounds *Ia*—*Ic* in whose molecules the 1,2,4-triazole ring is anellated in a similar manner to 10,11-dihydrodibenzo[*b,f*]-1,4-thiazepine which is known as a carrier system of compounds with antihistamine, tranquillizing, antiserotonin and local anaesthetic activity[7–10]. These compounds are included in patents (or applications) of the Upjohn company[11]. A closer examination of these documents, however, led to the recognition that we are dealing here with a fictitious invention, in which out of an enormous number of claimed dibenzo-[*b,f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine derivatives not a single one is really described, *i.e.* at least characterized by the melting point. The Upjohn team proved indeed experimental activity in series of similar compounds[12,13] which, however,

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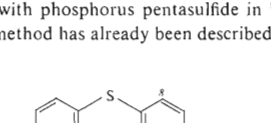
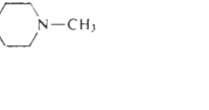
cannot change anything in our conclusion that compounds *Ia–Ic* must be considered new. We are describing in the present communication the synthesis of compounds *Ia–Ic*, as well as results of their pharmacological examination.

Starting compounds of our syntheses were dibenzo[*b*,*f*]-1,4-thiazepin-11(10*H*)-one (*IIa*) (refs[8,14,15]), its 8-chloro derivative *IIb* (refs[9,15]) and 2-chloro derivative *IIc* (ref.[15]) which are accessible by the thermic cyclization of methyl esters of 2-(2-aminophenylthio)benzoic acid and its corresponding chloro derivatives[8,9,15]. In this way we obtained the lactam *IIb* (refs[9,15]) while lactams *IIa* and *IIc* were prepared by cyclization of 2-(2-aminophenylthio)benzoic acid[16] and 2-(2-aminophenylthio)-5-chlorobenzoic acid[17] effected by heating with polyphosphoric acid to 140°C. We prefered this method after our recent experience with reactions of the homologous [2-(2-aminophenylthio)phenyl]acetic acid (*VII*) and its 2-amino-5-chlorophenyl analogue with polyphosphoric acid which did not afford the seven-membered cyclic ketones but the eight-membered lactams[16]. The lactams *IIa–IIc* were transformed to thiolactams *IIIa–IIIc* by reactions with phosphorus pentasulfide in boiling pyridine. The preparation of *IIIa* by this method has already been described[11,12].



I

II, R = O
III, R = S
IV, R = N—NH₂



V, R = H
VI, R = Br

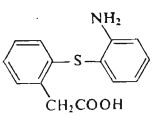
In formulae *I–VI*: *a*, $R^1 = R^2 = H$; *b*, $R^1 = Cl$, $R^2 = H$; *c*, $R^1 = H$, $R^2 = Cl$

With regard to the fact that an attempt at a direct synthesis of dibenzo[*b*,*f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine (*Va*) by a reaction of the thione *IIIa* with formic acid hydrazide in boiling 1-butanol[11] was unsuccessful and led to complete recovery of the starting thione *IIIa*, we used an analogy with the two-step synthesis of 8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine starting from 7-chloro-5-phenyl-

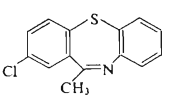
-1,2-dihydro-1,4-benzodiazepine-2-thione and proceeding *via* 7-chloro-2-hydrazino-5-phenyl-3*H*-1,4-benzodiazepine which affords the desired product by a reaction with triethyl orthoformate in ethanol in the presence of sulfuric acid[18,19]. In this case the mentioned hydrazine derivative is formed already by a reaction of the thione with hydrazine hydrate in methanol or ethanol at room temperature. These conditions are not sufficient for our thiones *IIIa*–*IIIc* which do not react with hydrazine hydrate at room temperature. The reactions proceed, however, in boiling ethanol or even better in boiling 1-butanol as reaction media. In this manner the hydrazine derivatives *IVa*–*IVc* were obtained in yields of 70–100%. We formulate these products as lactam hydrazones but it is possible to formulate them as well as the tautomeric 11-hydrazinodibenzo[*b*,*f*]-1,4-thiazepines; the spectra recorded do not enable anyway the differentiation. The reactions of the hydrazine derivatives *IVa*–*IVc* with triethyl orthoformate in ethanol in the presence of sulfuric acid proceed without external heating as mildly exothermic ones and in precise analogy with the cases mentioned[18,19]. In this way dibenzo[*b*,*f*]-1,2,4-triazolo-[4,3-*d*]-1,4-thiazepine (*Va*), its 6-chloro derivative *Vb* and 12-chloro derivative *Vc* were obtained in high yields; in their ^{1}H NMR spectra the proton in position 3 of the triazole ring is differentiated from the other aromatic protons by a signal (singlet) at δ 8·55 ppm (*Va*), and 9·23 ppm (*Vb*), respectively. By bromination carried out with bromine in boiling chloroform and in the presence of pyridine, the monobromo derivatives are formed in good yields, which were purified by column chromatography on silica gel. Their ^{1}H NMR spectra lack the mentioned signal, typical for the proton in position 3, which proves for the products the structures of the expected 3-bromo derivatives *VIa*–*VIc*. The bromine atom in these products is sufficiently reactive which enables a satisfactory course of the final nucleophilic substitution with an excess of boiling 1-methylpiperazine resulting in 3-(4-methylpiperazino) derivatives *Ia*–*Ic*. Neutralization of the bases with methanesulfonic acid afforded crystalline dimethanesulfonates which were used for pharmacological testing.

There was further carried out an attempt directed to the unknown homologous system of 14*H*-dibenzo[*b*,*g*]-1,2,4-triazolo-[4,3-*d*]-1,4-thiazocine which, however, had to be discontinued because of failure in the stage of the hydrazine intermediate. The preparation of the starting [2-(2-aminophenylthio)phenyl]acetic acid (*VII*) was repeating of our previous experiment[16]; the result was different in that point that we have now obtained the non-solvated product (benzene solvate previously[16]). In the effort to prepare also the analogous acid chlorinated in position 5 of the phenylacetic fragment we carried out a reaction of 2,5-dichloroacetophenone[20] with 2-aminothiophenol at 130°C in the presence of potassium carbonate and copper with the aim for obtaining 2-(2-aminophenylthio)-5-chloroacetophenone as the starting compound for the Willgerodt reaction[20–22]. Instead of the desired product an oxygen-free substance was isolated in a rather high yield which could be identi-

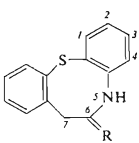
fied on the basis of analysis and spectra as 2-chloro-11-methyldibenzo[*b*,*f*]-1,4-thiazepine (*VIII*). The wanted reaction took evidently place but the amino ketone formed was transformed under the reaction conditions to the cyclic Schiff base *VIII*. The amino acid *VII* was cyclized to the eight-membered lactam *IX* by heating with polyphosphoric acid in the way reported previously[16]. The following reaction with phosphorus pentasulfide in boiling pyridine led in a satisfactory manner to the 5,7-dihydrodibenzo[*b*,*g*]-1,4-thiazocin-6-thione (*X*). This compound reacts with hydrazine hydrate in boiling methanol already under the formation of a high-melting substance, according to the mass spectrum and analysis $C_{28}H_{22}N_4S_2$. Instead of the hydrazine derivative homologous to compound *IVa* there was thus formed the azine *XI*. The tendency to form the 1,2-disubstituted hydrazine derivative prevails in this case completely over the tendency to form the monosubstituted hydrazine even in the case when a large excess of hydrazine was used.



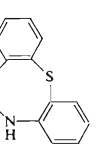
VII



VIII



IX, R = O
X, R = S
XI, R = N—N=



The pharmacological testing indicated a high acute toxicity of compounds *Ia*–*Ic*, especially on the intravenous administration (doses calculated per bases). LD_{50} values in mice (*i.v.*): *Ia*, 1·4 mg/kg; *Ib*, 0·4 mg/kg; *Ic*, 12·5 mg/kg. In rats the LD_{50} values (*i.v.*) are similar: *Ia*, 1·35 mg/kg; *Ib*, 0·26 mg/kg; *Ic*, 7·8 mg/kg. On oral administration a dose of 100 mg/kg of compound *Ia* was lethal for 100% mice; 50 mg/kg was lethal for less than 50% animals. An oral dose of 60 mg/kg of compound *Ib* was lethal for 60% mice. The toxic doses of compounds *Ia* and *Ib* bring about tonic-

-extensor convulsions of a similar type like after pentetrazole; the convulsions after toxic doses of compound *Ic* were more tryptamine-like (clonic convulsions with rolling). The effects of nontoxic doses were mostly not significant.

Compound Ia: An oral dose of 10 mg/kg did not influence the levels of dopamine, homovanillic acid or 5-hydroxyindoleacetic acid in the rat brain striatum and the level of noradrenaline in the rat hypothalamus. The same dose had not influence on the apomorphine stereotypies in rats. The reserpine ptosis in mice was not influenced by an oral dose of 1 mg/kg.

Compound Ib: An oral dose of 50 mg/kg was not cataleptogenic for rats (within 1 h after the administration 80% of the animals perished and the remaining were not cataleptic). The oral dose of 10 mg/kg did not influence the apomorphine stereotypies in rats and the reserpine ptosis in mice was not altered by 1 mg/kg *p.o.* A dose of 0·08 mg/kg *i.v.* brought about brief and deep drops of the blood pressure of normotensive rats. Concentrations of 1 – 10 μg/ml were spasmolytic on the isolated rat duodenum towards the acetylcholine, as well as barium chloride contractions. Concentrations of 10 – 25 μg/ml had a positively inotropic effect on the isolated rabbit heart atrium. An oral dose of 0·2 mg/kg decreased the blood sugar level of rats by 18% (estimated 2 h after the administration). The *i.v.* dose of 0·08 mg/kg did not alter the effects of pentetrazole, thiopental and amphetamine in mice, of histamine in guinea-pigs, and was inactive in tests for analgesic, sympathomimetic, β-adrenolytic, peripheral vasodilating, mydriatic, hypo (or hyper)thermic and diuretic activity.

Compound Ic: An oral dose of 50 mg/kg was not cataleptogenic in rats and had not antiapomorphine activity. In the photo-cell method of Dews, an oral dose of 40 mg/kg brought about a decrease of spontaneous locomotor activity below 50% of that of the control group. Doses of 20 and 40 mg/kg *p.o.* elicited discoordination in 20, and in 30% mice, respectively. The reserpine ptosis in mice was not altered by 10 mg/kg *p.o.* Doses of 1·0 – 2·5 mg/kg *i.p.* had mydriatic effect in mice. In concentrations of 0·1 – 1·0 μg/ml it had spasmolytic effect on the isolated rat duodenum which was selective towards acetylcholine (the same concentration was inactive towards barium chloride). Together with the mydriatic effect it indicates the anticholinergic character of the effects. An *i.v.* dose of 2·5 mg/kg elicited brief and sharp rises of the blood pressure in rats. The same dose was inactive in tests for analgesic, convulsant, antiarrhythmic, peripheral vasodilating, sympathomimetic and β-adrenolytic activity, it did not influence the effects of histamine and amphetamine and was without effect on diuresis, blood sugar level, body temperature and hemocoagulation.

EXPERIMENTAL

The melting points of analytical samples were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* of about 60 Pa over P_2O_5 at 77°C. The UV spectra (in me-

thanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (mostly in Nujol) with the Perkin Elmer 298 spectrophotometer, the ^{1}H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectrum with MCH-1320 and Varian MAT 44S spectrometers. The homogeneity of the compounds and composition of the reaction mixtures and crude products were checked by thin-layer chromatography on silica gel (Silufol).

[2-(2-Aminophenylthio)phenyl]acetic Acid (*VII*)

A mixture of 26·2 g 2-(2-iodophenyl)acetic acid[23], 13·8 g 2-aminothiophenol, 17 g KOH in 170 ml water and 1 g Cu was processed similarly like in our previous work[16]. There were obtained 21·6 g (84%) crude product melting at 112–114°C. A sample was crystallized from 50% aqueous ethanol, m.p. 114–115°C and after resolidification again at 126–127°C. After drying at 77°C the sample proved to be solvent-free. IR spectrum: 758, 786 (4 adjacent Ar—H), 1 225, 1 250, 1 696 (RCOOH), 1 469, 1 480, 1 571, 1 589, 3 050 (Ar), 2 560, 2 730 (NH_3^+), 3 305, 3 383 cm^{-1} (NH_2). ^{1}H NMR spectrum ($C^2H_3SOC^2H_3$): δ 6·40–7·50 (m, 8 H, ArH), 5·30 (bs, 2 H, NH_2), 3·79 (s, 2 H, $ArCH_2CO$). For $C_{14}H_{13}NO_2S$ (259·2) calculated: 64·86% C, 5·05% H, 5·40% N, 12·35% S; found: 64·75% C, 5·06% H, 5·12% N, 12·30% S. Lit.[16] gave for a benzene solvate a m.p. of 129–129·5°C.

2-Chloro-11-methyldibenzo[*b*,*f*]-1,4-thiazepine (*VIII*)

A mixture of 18·9 g 2,5-dichloroacetophenone[20], 13·7 g 2-aminothiophenol, 27·6 g K_2CO_3, 1·0 g Cu and 10 ml dimethylformamide was stirred and heated for 6 h to 130°C. After cooling the mixture was diluted with 100 ml water, stirred for 10 min and extracted with benzene. The extract was dried with $MgSO_4$, filtered with charcoal and evaporated under reduced pressure. The residue was chromatographed on a column of 500 g neutral Al_2O_3 (activity II). A 1 : 4 mixture of benzene and light petroleum eluted 19·2 g (74%) yellow crystals melting at 93–94°C. The analytical sample, m.p. 95–96°C (ethanol); the sample was dried *in vacuo* at room temperature. UV spectrum: inflex at 240 nm (log ε 4·23). IR spectrum (KBr): 765, 811, 826, 885 (4 and 2 adjacent and solitary Ar—H), 1 546, 1 571, 1 580, 3 045 (Ar), 1 630 cm^{-1} (Ar—C=N—Ar). ^{1}H NMR spectrum: δ 6·80–7·30 (m, 7 H, ArH), 2·62 (s, 3 H, CH_3). For $C_{14}H_{10}ClNS$ (259·7) calculated: 64·73% C, 3·88% H, 13·65% Cl, 5·39% N, 12·35% S; found: 65·11% C, 3·95% H, 13·38% Cl, 5·31% N, 12·41% S.

Dibenzo[*b*,*f*]-1,4-thiazepin-11(10*H*)-one (*IIa*)

A mixture of 10·0 g 2-(2-aminophenylthio)benzoic acid[16] and 100 g polyphosphoric acid was stirred and heated for 2 h to 140°C. It was then poured into 500 g ice and water, the precipitated product was filtered, washed with water and dried *in vacuo*; 8·9 g (95%), m.p. 258–260°C. Lit.[15], m.p. 258–260°C.

2-Chlorodibenzo[*b*,*f*]-1,4-thiazepin-11(10*H*)-one (*IIc*)

A mixture of 99 g 2-(2-aminophenylthio)-5-chlorobenzoic acid[17] and 1 kg polyphosphoric acid was stirred and heated for 2·5 h to 140°C and processed similarly like in the preceding case. The crude product was crystallized from 1·2 l acetic acid; 65·8 g (71%), m.p. 260–261°C Lit.[15,24], m.p. 255–257°C, and 260–262°C, respectively.

Dibenzo[*b,f*]-1,4-thiazepin-11(10*H*)-thione (*IIIa*)

A mixture of 22·7 g *IIa*, 39 g P_2S_5 and 450 ml pyridine was stirred and refluxed for 6·5 h in the atmosphere of nitrogen. Pyridine was evaporated *in vacuo*, the residue was diluted with 100 ml benzene and the evaporation of the solvents was repeated. The residue was then separated between 300 ml water and 900 ml chloroform, the chloroform solution was dried with $MgSO_4$ and filtered through a column of 80 g neutral Al_2O_3 (activity II). The column was washed with 100 ml chloroform and the filtrates were evaporated under reduced pressure; 15·1 g (65%), m.p. 244–248°C. Lit.[11,12], m.p. 246–247·5°C.

8-Chlorodibenzo[*b,f*]-1,4-thiazepin-11(10*H*)-thione (*IIIb*)

A mixture of 65·4 g *IIb* (ref.[9,15]), 44·4 g P_2S_5 and 900 ml pyridine was stirred and refluxed under nitrogen for 4·5 h. It was then poured into a solution of 1·3 kg NaCl in 5 l water and the suspension was stirred for 1·5 h. The precipitate was filtered, washed with 5 l water and crystallized from a mixture of 160 ml dimethylformamide and 150 ml ethanol; 50 g (72%), m.p. 267–270°C. Analytical sample, m.p. 272–272·5°C (dimethylformamide–ethanol). UV spectrum: λ_{max} 245 nm (log ε 4·34), 326 nm (4·17). IR spectrum: 753, 769, 816, 870 (4 and 2 adjacent and solitary Ar—H), 1 389, 1 465, 1 525 (N—C=S), 1 580 (Ar), 3 053, 3 120 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 12·87 (bs, 1 H, NH), 7·90 (m, 1 H, 1-H), 7·20–7·70 (m, 6 H, remaining ArH). For $C_{13}H_8ClNS_2$ (277·8) calculated: 56·21% C, 2·90% H, 12·76% Cl, 5·04% N, 23·09% S; found: 56·41% C, 2·94% H, 12·80% Cl, 5·05% N, 22·78% S.

2-Chlorodibenzo[*b,f*]-1,4-thiazepin-11(10*H*)-thione (*IIIc*)

A mixture of 65·4 g *IIc*, 44·4 g P_2S_5 and 800 ml pyridine was stirred and refluxed under nitrogen for 4·5 h. After standing for 48 h at room temperature it was poured into a stirred solution of 1·3 kg NaCl in 4·4 l water at 5°C. It was stirred for 2·5 h, the precipitate was filtered, washed with 5 l water and dried. The crude product was placed on a column of 300 g neutral Al_2O_3 (activity II) and successively eluted with 8 l chloroform. The eluates were evaporated, the residue was refluxed for a short time with 300 ml ethanol, after cooling the precipitate was filtered, washed with ethanol and dried; 58·7 g (85%), m.p. 263–267°C. Analytical sample, m.p. 265–267°C (chloroform). UV spectrum: λ_{max} 247 nm (log ε 4·39), 331 nm (4·10). IR spectrum: 753, 813, 880 (4 and 2 adjacent and solitary Ar—H), 1 470, 1 543 (NH—C=S), 3 060, 3 090, 3 130 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 13·00 (bs, 1 H, NH), 7·90 (d, 1 H, 1-H), 7·10–7·70 (m, 6 H, remaining ArH). For $C_{13}H_8ClNS_2$ (277·8) calculated: 56·21% C, 2·90% H, 12·76% Cl, 5·04% N, 23·09% S; found: 56·19% C, 2·88% H, 12·84% Cl, 4·96% N, 22·95% S.

5,7-Dihydrodibenzo[*b,g*]-1,4-thiazocin-6-thione (*X*)

A mixture of 12·0 g *IX* (ref.[16]), 8·8 g P_2S_5 and 150 ml pyridine was stirred and refluxed under nitrogen for 2·5 h. After cooling to 20°C it was poured into a solution of 260 g NaCl in 880 ml water at 0–3°C. The suspension was stirred for 30 min, the precipitated product was filtered, washed with 1 l water and dried. This crude product was dissolved in 400 ml dichloromethane and the solution was filtered through a column of 50 g neutral Al_2O_3 (activity II), the column was washed with 250 ml dichloromethane and the combined filtrates were evaporated. The residue was heated under reflux with 30 ml ethanol to boil, the suspension was cooled in a refrigerator, the product was filtered and washed with 20 ml hexane; 7·8 g (61%), m.p. 234–238°C. Analytical sample, m.p. 235–239°C (ethanol). UV spectrum: λ_{max} 250 nm (log ε 4·12), 300 nm (4·24). IR spectrum: 748, 750, 760, 768 (4 adjacent Ar—H), 1 110, 1 119 (C=S), 1 523 (NHC=S),

1 583, 3 050 (Ar), 3 115 cm^{-1} (NH). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 12·50 (bs, 1 H, NH), 7·00–8·00 (m, 8 H, ArH), 3·75 (s, 2 H, $ArCH_2$). For $C_{14}H_{11}NS_2$ (257·4) calculated: 65·33% C, 4·31% H, 5·44% N, 24·92% S; found: 65·44% C, 4·29% H, 5·18% N, 24·21% S.

11-Hydrazinodibenzo[*b,f*]-1,4-thiazepine (*IVa*)

A mixture of 15·8 g *IIIa*, 11·4 g 100% $N_2H_4.H_2O$ and 450 ml 1-butanol was stirred and refluxed for 30 min. After cooling it was filtered and the filtrate was evaporated *in vacuo*. The residue was treated with 200 ml water and extracted with dichloromethane. The extract was washed with water, dried with Na_2SO_4 and evaporated. The residue was crystallized by dissolving in 40 ml boiling dichloromethane and by treating the filtered solution with 150 ml hexane. After cooling overnight in a refrigerator the product was filtered and washed with hexane; 10·1 g (65%), m.p. 119–123°C. Analytical sample, m.p. 121–123°C (chloroform–hexane). UV spectrum: inflexes at 230 5 nm (log ε 4·24), 253·5 nm (4·13), 285 nm (3·90). IR spectrum: 767 (4 adjacent Ar–H), 1 320 (NHAr), 1 476, 1 573, 1 586, 3 015, 3 030 (Ar), 1 626 (NH_2, C=N), 3 115, 3 205, 3 230 cm^{-1} (NH, NH_2). ^1H NMR spectrum: δ 7·00–8·00 (m, 8 H, ArH), 5·50 (bs, 3 H, NH_2 and NH). For $C_{13}H_{11}N_3S$ (241·3) calculated: 64·70% C, 4·60% H, 17·41% N, 13·29% S; found: 64·57% C, 4·70% H, 17·11% N, 13·40% S.

8-Chloro-11-hydrazinodibenzo[*b,f*]-1,4-thiazepine (*IVb*)

A solution of 38 g *IIIb* in 570 ml ethanol was treated with 27·5 g 100% $N_2H_4.H_2O$ and the mixture was refluxed for 5 h. After standing overnight ethanol was evaporated under reduced pressure, the crude product was dissolved in 350 ml dichloromethane, the solution was washed with water, dried (Na_2SO_4) and evaporated. The residue was crystallized from a mixture of chloroform and hexane; 32·7 g (87%), m.p. 134–136°C. Analytical sample, m.p. 136·5–138°C (chloroform–hexane). UV spectrum: inflexes at 239 nm (log ε 4·23), 255·5 nm (4·14), 289 nm (3·93). IR spectrum: 740, 760, 770, 800, 868, 893 (4 and 2 adjacent and solitary Ar–H), 1 500, 1 570, 3 045 (Ar), 1 619 (NH_2, C=N), 3 175, 3 280, 3 320 cm^{-1} (NH, NH_2). ^1H NMR spectrum: δ 6·70–7·60 (m, 7 H, ArH), 5·20 (bs, 3 H, NH and NH_2). For $C_{13}H_{10}ClN_3S$ (275·8) calculated: 56·62% C, 3·66% H, 12·86% Cl, 15·24% N, 11·63% S; found: 56·60% C, 3·72% H, 13·26% Cl, 15·39% N, 11·95% S.

2-Chloro-11-hydrazinodibenzo[*b,f*]-1,4-thiazepine (*IVc*)

The reaction of 33·3 g *IIIc* with 24 g $N_2H_4.H_2O$ in 500 ml ethanol was carried out similarly like in the preceding case. Similar processing gave 32·8 g (98%) product melting at 135–140°C. Analytical sample, m.p. 142–144°C (chloroform–hexane). UV spectrum: inflexes at 230 nm (log ε 4·30), 265 nm (4·05), 290 nm (3·85). IR spectrum: 730, 748, 760, 805, 812, 824, 882 (4 and 2 adjacent and solitary Ar–H), 1 470, 1 550, 1 588 (Ar), 1 622, 1 640 (NH_2, C=N), 3 148, 3 250, 3 336, 3 358 cm^{-1} (NH, NH_2). For $C_{13}H_{10}ClN_3S$ (275·8) calculated: 56·62% C, 3·66% H, 12·86% Cl, 15·24% N, 11·63% S; found: 56·61% C, 3·67% H, 12·92% Cl, 15·85% N, 11·46% S.

1,2-Bis(5,7-dihydrodibenzo[*b,g*]-1,4-thiazocin-6-ylidene)hydrazine (*XI*)

A mixture of 7·2 g *X*, 14·2 g $N_2H_4.H_2O$ and 140 ml methanol was stirred for 30 min at room temperature and then refluxed for 30 min. The clear solution formed was evaporated *in vacuo*, the residue was diluted with 250 ml water and extracted with dichloromethane. The extract

was washed with water, dried (Na_2SO_4) and evaporated. The residue crystallized after heating with 15 ml ethanol. Filtration, washing with hexane and drying gave 4·3 g (64%) product melting at 222–230°C. Analytical sample, m.p. 232–234·5°C (chloroform–ethanol–hexane). Mass spectrum, *m/z* (%): 478 (M^+ corresponding to $C_{28}H_{22}N_4S_2$, 100%), 461 ($C_{28}H_{19}N_3S_2$, 28), 281 ($C_{15}H_{13}N_4S$, 50), 280 ($C_{15}H_{12}N_4S$, 34), 279 ($C_{15}H_{11}N_4S$, 55), 278 ($C_{15}H_{10}N_4S$, 39), 224 ($C_{14}H_{10}NS$, 31), 223 ($C_{14}H_9NS$, 30), 197 ($C_{13}H_9S$, 38). UV spectrum: λ_{max} 245 nm (log ε 4·43), 280 nm (3·75). IR spectrum: 750, 766 (4 adjacent Ar—H), 1 480, 1 516, 1 560, 1 587, 3 053 (Ar), 1 613 (C=N), 3 185, 3 300, 3 435 cm^{-1} (NH). For $C_{28}H_{22}N_4S_2$ (478·5) calculated: 70·28% C, 4·63% H, 11·71% N, 13·38% S; found: 69·25% C, 4·72% H, 11·60% N, 13·10% S.

Dibenzo[*b*,*f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine (*Va*)

A stirred solution of 3·6 g *IVa* in 160 ml ethanol was treated with 8·9 g triethyl orthoformate and then slowly with 1·7 ml H_2SO_4. The temperature rose spontaneously from 22 to 36°C and the mixture was stirred for 30 min. Then it was treated dropwise with a solution of 5·5 g $NaHCO_3$ in 60 ml water. Ethanol was evaporated *in vacuo*, the residue was diluted with 100 ml water and extracted with dichloromethane. The extract was dried with Na_2SO_4 and chromatographed on a 25 cm column of silica gel (diameter of 2·5 cm). Dichloromethane eluted only some by-products. The desired *Va* was eluted with chloroform containing 2% methanol and crystallized from 90 ml ethanol; 2·8 g (67%), m.p. 214–215°C. Analytical sample, m.p. 215–216°C (ethanol). UV spectrum: λ_{max} 242·5 nm (log ε 4·28). IR spectrum: 731, 753 (4 adjacent Ar—H), 1 529, 1 559, 1 580, 1 590, 3 060 cm^{-1} (Ar). ^1H NMR spectrum: δ 8·55 (s, 1 H, 3-H), 8·00 (m, 1 H, 13-H), 7·20–7·80 (m, 7 H, remaining ArH). For $C_{14}H_9N_3S$ (251·3) calculated: 66·91% C, 3·61% H, 16·72% N, 12·76% S; found: 66·75% C, 3·61% H, 16·83% N, 12·92% S.

6-Chlorodibenzo[*b*,*f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine (*Vb*)

A stirred solution of 30·9 g *IVb* in 1·2 l ethanol was treated with 58·2 g triethyl orthoformate and then dropwise over 15 min with 12·7 ml H_2SO_4. The mixture was stirred for 1·5 h without heating and neutralized with a solution of 41·1 g $NaHCO_3$ in 450 ml water. Ethanol was evaporated and the residue was extracted with 1 l dichloromethane. The extract was dried with K_2CO_3 and evaporated. The residue was crystallized from a mixture of 500 ml ethanol and 300 ml chloroform and the mother liquor was processed by evaporation and treatment with hexane; total amount of *Vb* was 28·6 g (89%), m.p. 239–242°C. Analytical sample, m.p. 242–244°C (chloroform–hexane). UV spectrum: inflex at 243 nm (log ε 4·30). IR spectrum: 770, 800, 843, 861, 871 (4 and 2 adjacent and solitary Ar—H), 1 490, 1 565, 1 578, 1 590, 3 068, 3 120 (Ar), 1 652 cm^{-1} (C=N). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 9·23 (s, 1 H, 3-H), 7·40–8·00 (m, 7 H, ArH). For $C_{14}H_8ClN_3S$ (285·8) calculated: 58·84% C, 2·82% H, 12·41% Cl, 14·71% N, 11·22% S; found: 58·48% C, 2·80% H, 13·12% Cl, 14·45% N, 10·96% S.

12-Chlorodibenzo[*b*,*f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine (*Vc*)

The reaction of 30·3 g *IVc* with 57·1 g triethyl orthoformate and 12·5 ml H_2SO_4 in 1·2 l ethanol was carried out similarly like in the preceding case (1 h stirring at room temperature). Similar processing gave 25·6 g (81%) crude *Vc* melting at 238–240·5°C. Analytical sample, m.p. 240 to 241°C (ethanol–chloroform). UV spectrum: λ_{max} 245 nm (log ε 4·33). IR spectrum: 760, 849, 886, 899 (4 and 2 adjacent and solitary Ar—H), 1 500, 1 554, 1 570, 3 079 cm^{-1} (Ar). For $C_{14}H_8ClN_3S$ (285·8) calculated: 58·84% C, 2·82% H, 12·41% Cl, 14·71% N, 11·22% S; found: 58·92% C, 2·76% H, 12·66% Cl, 14·79% N, 11·22% S.

3-Bromodibenzo[*b*,*f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine (*VIa*)

A refluxing solution of 5·2 g *Va* in a mixture of 50 ml chloroform and 6·4 ml pyridine was stirred and treated dropwise over 15 min with a solution of 6·7 g Br_2 in 20 ml chloroform. The mixture was refluxed for 1 h, allowed to stand for 2 days at room temperature, washed with 50 ml 5% $Na_2S_2O_3$ and water, dried with K_2CO_3 and evaporated under reduced pressure. The residue was chromatographed on a column of 65 g silica gel. Chloroform eluted an almost homogeneous product which was crystallized from a mixture of ethanol and chloroform; 4·9 g (74%), m.p. 190–194°C. Analytical sample, m.p. 192·5–193·5°C (ethanol–chloroform). UV spectrum: λ_{max} 244 nm (log ε 4·24). IR spectrum: 760, 770 (4 adjacent Ar—H), 1 565, 1 590, 3 048 cm^{-1} (Ar). ^{1}H NMR spectrum: δ 7·20—8·00 (m, ArH). For $C_{14}H_8BrN_3S$ (330·2) calculated: 50·92% C, 2·44% H, 24·20% Br, 12·73% N, 9·71% S; found: 51·21% C, 2·44% H, 24·52% Br, 12·61% N, 9·90% S.

3-Bromo-6-chlorodibenzo[*b*,*f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine (*VIb*)

A refluxing solution of 25·2 g *Vb* and 30 g pyridine in 220 ml chloroform was treated over 45 min with a solution of 28·2 g Br_2 in 90 ml chloroform and the mixture was refluxed for 1·5 h. After cooling it was washed with 200 ml water, 200 ml 2% NH_4OH and 150 ml 5% $Na_2S_2O_3$, dried and evaporated. The residue was chromatographed on a column of 150 g silica gel. The product was eluted by the first chloroform fractions and crystallized from a mixture of 40 ml chloroform and 40 ml hexane; 26·7 g (83%), m.p. 195—200°C. Analytical sample, m.p. 199—200°C (ethanol). UV spectrum: inflex at 247·5 nm (log ε 4·20). IR spectrum: 730, 770, 800, 839, 880 (4 and 2 adjacent and solitary Ar—H), 1 474, 1 519, 1 563, 1 577, 1 590, 3 088 (Ar), 1 650, 1 670 cm^{-1} (C=N). ^{1}H NMR spectrum: δ 7·92 (m, 1 H, 13-H), 7·65 (d, J = 8·0 Hz, 1 H, 8-H), 7·20—7·50 (m, 5 H, remaining ArH). For $C_{14}H_7BrClN_3S$ (364·7) calculated: 46·12% C, 1·93% H, 21·91% Br, 9·72% Cl, 11·52% N, 8·79% S; found: 45·93% C, 1·95% H, 21·77% Br, 9·66% Cl, 11·63% N, 8·98% S.

3-Bromo-12-chlorodibenzo[*b*,*f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine (*VIc*)

Vc (24·3 g) was similarly brominated with 27·2 g Br_2 in 300 ml boiling chloroform in the presence of 27 g pyridine. Similar processing including chromatography on 150 g silica gel and finally crystallization from ethanol–chloroform and chloroform–hexane gave 24·3 g (78%) *VIc* melting at 225—227°C. UV spectrum: inflexes at 246 nm (log ε 4·26) and 296·5 nm (3·07). IR spectrum (KBr): 758, 770, 805, 820, 832, 889, 902 (4 and 2 adjacent and solitary Ar—H), 1 430, 1 450, 1 476, 1 513, 1 553, 3 080 (Ar), 1 625 cm^{-1} (C=N). ^{1}H NMR spectrum: δ 7·90 (d, J = 2·0 Hz, 1 H, 13-H), 7·20—7·80 (m, 6 H, remaining ArH). For $C_{14}H_7BrClN_3S$ (364·7) calculated: 46·11% C, 1·94% H, 21·91% Br, 8·72% Cl, 11·52% N, 8·79% S; found: 45·45% C, 1·94% H, 22·76% Br, 10·10% Cl, 11·43% N, 8·88% S.

3-(4-Methylpiperazino)dibenzo[*b*,*f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine (*Ia*)

A mixture of 4·95 g *VIa* and 12 g 1-methylpiperazine was refluxed for 8 h in a bath of 160—170°C. After standing overnight the mixture was diluted with 120 ml water, made alkaline with 5 ml NH_4OH and extracted with dichloromethane. The extract was shaken with excessive 5% hydrochloric acid, the acid aqueous layer was made alkaline with NH_4OH and the base was extracted with dichloromethane. The extract was washed with water, dried with K_2CO_3, evaporated and the residue was crystallized from 30 ml ethanol; 2·25 g (43%), m.p. 240—241°C. Analytical sample, m.p. 242—243°C (ethanol). UV spectrum: λ_{max} 260 nm (log ε 4·03), inflexes at 285 nm (3·88), 238 nm (4·16), 217 nm (4·46). IR spectrum: 765 (4 adjacent Ar—H), 1 470, 1 540 (Ar), 2 790 cm^{-1}

(N—CH_2, N—CH_3). ^{1}H NMR spectrum: δ 7·10—8·20 (m, 8 H, ArH), 3·20 (bm, 4 H, CH_2 .N^1CH_2 of piperazine), 2·40 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·22 (s, 3 H, NCH_3). For $C_{19}H_{19}N_5S$ (349·5) calculated: 65·30% C, 5·48% H, 20·04% N, 9·18% S; found: 65·01% C, 5·47% H, 20·33% N, 9·59% S.

Dimethanesulfonate, m.p. 242—244°C (aqueous ethanol). For $C_{21}H_{27}N_5O_6S_3$ (541·7) calculated: 46·56% C, 5·02% H, 12·93% N, 17·76% S; found: 46·67% C, 5·07% H, 13·20% N, 17·79% S.

6-Chloro-3-(4-methylpiperazino)dibenzo[*b*,*f*]-1,2,4-triazolo[4,3-*d*]-1,4-thiazepine (*Ib*)

A similar reaction of 15·0 g *VIb* with 33 g 1-methylpiperazine and a similar processing gave the crude base which was chromatographed on a column of 15 g silica gel. The desired product was eluted with dichloromethane and then with chloroform containing 2% methanol; it was recrystallized from ethanol: 12·7 g (80%), m.p. 203—205·5°C. UV spectrum: λ_{max} 261 nm (log ε 4·06), inflex at 282 nm (3·90). IR spectrum: 749, 770, 790, 804, 832, 890, 904 (4 and 2 adjacent and solitary Ar—H), 1 528, 1 565, 1 578, 3 015, 3 055, 3 080 (Ar), 1 562 (C=N), 2 695, 2 745, 2 765, 2 785 cm^{-1} (N—CH_2, N—CH_3). ^{1}H NMR spectrum: δ 8·00 (m, 1 H, 13-H), 7·80 (d, J = 3·0 Hz, 1 H, 5-H), 7·20—7·70 (m, 5 H, remaining ArH), 3·20 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·30 (s, 3 H, NCH_3). For $C_{19}H_{18}$. .ClN_5S (383·9) calculated: 59·44% C, 4·73% H, 9·24% Cl, 18·24% N, 8·35% S; found: 59·42% C, 4·81% H, 8·90% Cl, 18·61% N, 8·16% S.

Dimethanesulfonate, m.p. 231·5—233°C (aqueous ethanol). For $C_{21}H_{26}ClN_5O_6S_3$ (576·1) calculated: 43·78% C, 4·55% H, 6·15% Cl, 12·16% N, 16·70% S; found: 43·74% C, 4·67% H, 6·30% Cl, 12·29% N, 16·47% S.

12-Chloro-3-(4-methylpiperazino)dibenzo[*b*,*f*]-1,2,4-traizolo[4,3-*d*]-1,4-thiazepine (*Ic*)

Was prepared similarly like compound *Ib* from 14·6 g *VIc* and 32 g 1-methylpiperazine; 11·0 g (72%) crude base *Ic*, m.p. 233—235°C. Analytical sample, m.p. 235—236·5°C (ethanol). UV spectrum: λ_{max} 263 nm (log ε 4·06). IR spectrum: 780, 803, 838, 906, 916 (4 and 2 adjacent and solitary Ar—H), 1 475, 1 530, 1 570, 3 040 (Ar), 2 680, 2 740, 2 785 cm^{-1} (N—CH_2, N—CH_3). ^{1}H NMR spectrum: δ 8·00 (d, J = 3·0 Hz, 1 H, 13-H), 7·80 (m, 1 H, 5-H), 7·20—7·75 (m, 5 H, remaining ArH), 3·20 (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). For $C_{19}H_{18}ClN_5S$ (383·9) calculated: 59·44% C, 4·73% H, 9·24% Cl, 18·24% N, 8·35% S; found: 59·38% C, 4·83% H, 9·55% Cl, 18·65% N, 8·62% S.

Dimethanesulfonate, m.p. 262—263·5°C (aqueous ethanol). For $C_{21}H_{26}ClN_5O_6S_3$ (576·1) calculated: 43·78% C, 4·55% H, 6·15% Cl, 12·16% N, 16·70% S; found: 43·80% C, 4·62% H, 6·30% Cl, 12·28% N, 16·78% S.

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