POTENTIAL HYPNOTICS AND ANXIOLYTICS IN THE 4*H*-*s*-TRIAZOLO[4,3-*a*]-1,4-BENZODIAZEPINE SERIES: 8-CHLORO-6-(2-CHLOROPHENYL)-1-[4-(2-METHOXYETHYL)-PIPERAZINO]-4*H*-*s*-TRIAZOLO[4,3-*a*]-1,4-BENZODIAZEPINE AND SOME RELATED COMPOUNDS*

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1-Bromo derivatives *XIIa* and *XIIb* were prepared by bromination of 8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XIa*) and its 6-(2-chlorophenyl) analogue *XIb* with bromine in chloroform in the presence of pyridine. Substitution reactions with 1-(2-methoxyethyl)-piperazine (*XIVb*), 1-(3-methoxypropyl)piperazine (*XVb*), 1-(2-ethoxyethyl)piperazine (*XVIb*) and 1-(2-methylthioethyl)piperazine (*XVIIb*) afforded the title compound *IIb* and analogues *IIa* and *IIIb*—*Vb*. A substitution reaction of the bromo derivative *XIIb* with piperazine gave the 1-piperazino derivative *VIIIb* which was alkylated with 2-phenoxyethyl bromide and 2-phenylthioethyl bromide to give compounds *VIb* and *VIIb*. The title compound *IIb* has very high anticonvulsant and discoordinating activities in mice. The enlargement of the substituent R^1 (compounds *IIIb*—*VIIb*) results in a gradual decrease of the effects mentioned.

In one of the previous communications of this series[1] we described the synthesis of S-substituted 8-chloro-6-(2-chlorophenyl)-1-(mercaptomethyl)-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepines as potential hypnotics and anxiolytics and gave a short survey about the group of the neurotropically highly potent 4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepines out of which 8-chloro-6-(2-chlorophenyl)-1-methyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine[1-3] (known under the generic name of triazolam[4]) excels as an extremely potent hypnotic agent. More recently we devoted out efforts to substances of a similar type having a piperazine residue as substituent in position 1. The literature data in this line are rather poor; 1-(4-methylpiperazino) derivatives *Ia* and *Ib* (ref.[5,6]), however, were described and compound *Ib* was found to have unusually high anticonvulsant activity towards pentetrazole and bicucullin and further in the test of potentiatioh of the sleep induced by γ-butyrolactone[5]. The main object of the present communication is the description of synthesis and properties of the piperazine derivatives *IIab* and *IIIb*—*VIIb* in whose molecules the less usual

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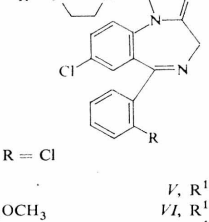
alkoxyalkyls, 2-methylthioethyl, 2-phenoxyethyl and 2-phenylthioethyl appear as the piperazine N^4-substituents.

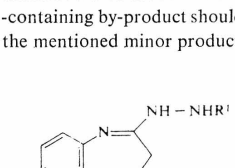


In formulae *I*—*XII* *a*, R = H; *b*, R = Cl

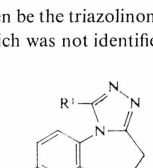
I, $R^1 = CH_3$
II, $R^1 = CH_2CH_2OCH_3$
III, $R^1 = (CH_2)_3OCH_3$
IV, $R^1 = CH_2CH_2OC_2H_5$
V, $R^1 = CH_2CH_2SCH_3$
VI, $R^1 = CH_2CH_2OC_6H_5$
VII, $R^1 = CH_2CH_2SC_6H_5$
VIII, $R^1 = H$

The work was started by synthesis of the methylpiperazino derivatives *Iab* (ref.[5]) as standards for pharmacological tests; the synthesis of these compounds served simultaneously as model experiments and was carried out by making use of novel modifications of the known preparative methods. 7-Chloro-5-phenyl-1,3-dihydro--1,4-benzodiazepine-2-thione and its 5-(2-chlorophenyl) analogue[1,2,7,8] were transformed by treatment with hydrazine hydrate in ethanol (or methanol) to the hydrazine derivatives *IXa* (ref.[9]) and *IXb* (ref.[10]) which were cyclized by reactions with ethyl orthoformate in ethanol and in the presence of sulfuric acid as and acid catalyst to give 8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XIa*) (ref.[9]) and its 6-(2-chlorophenyl) analogue *XIb* (ref.[10]). Compounds *XIab* were transformed to 1-bromo derivatives *XIIab* by treatment with bromine in boiling chloroform in the presence of pyridine which represents for this case a novel method (analogy, *cf*[11]); the literature[5,12] reported the bromination with N-bromosuccinimide and compound *XIIa* was also prepared by different procedures[13,14]. The piperazine derivatives *Iab* were obtained from the bromo derivatives *XIIab* by treatment with excessive 1-methylpiperazine[5,6]. In the case of compound *Ia* the reaction was carried out at the boiling temperature of the mixture, *i.e.* under more severe conditions than reported in the literature[5], and the crude product was separated by chromatography on silica gel. The required amine *Ia* was obtained in a yield of 76%, its identity was confirmed by the mass spectrum, and it was transformed to a crystalline fumarate (solvate with ethanol). The literature[5] reported a yield of only 55%. In the case of preparation of the compound *Ib* the conditions described[5] were approximately followed, *i.e.* the mixture was heated for 8 h to 100—110°C. A mixture was obtained which consisted, according to the thin-layer chromatography on silica gel, of three main and

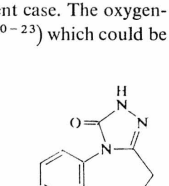
one minor components. By chromatography on aluminium oxide and by elution with benzene there was obtained a first fraction containing the less polar components, *i.e.* the starting bromo derivative *XIIb* and compound *XIb* resulting as a by-product of the reaction (the formation of this compound was noted also in the literature[5]). The more polar fractions represent the almost pure *Ib* crystallizing from a mixture of benzene and cyclohexane as a benzene solvate (the identity of the base *Ib* was corroborated by spectra) and affording a crystalline oxalate (2 : 1 solvate with ethanol). As an alternative for explaining the formation of compound *XIb* in the reaction of the bromo derivative *XIIb* with 1-methylpiperazine we propose a disproportionation reaction of a similar type we observed in four cases[15–18] of reactions of 11-bromodibenzo[*b*,*f*]thiepin-10(11*H*)-ones with 1-methylpiperazine where, in addition to the expected substitution product there resulted always the corresponding 10,11-diketone and in one case[15] we were able to isolate also the other disproportionation product, *i.e.* the debrominated 10-ketone. The reaction of 2-bromo-2-phenylacetophenone with water at elevated temperature resulting in benzil and 2-phenylacetophenone (deoxybenzoin) (ref.[19]), represents apparently a similar type of disproportionation. Commercial 1-methylpiperazine contains always a small amount of water which could be the source of this side reaction even in our present case. The oxygen-containing by-product should then be the triazolinone *XIII* (*cf.*[20–23]) which could be the mentioned minor product which was not identified.



IX, $R^1 = H$
X, $R^1 = COO(CH_2)_3CH_3$



XI, $R^1 = H$
XII, $R^1 = Br$



XIII

With regard to the fact that the most usual preparative way leading to 1-substituted 6-aryl-8-chloro-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepines is the reaction of 5-aryl-7-chloro-1,3-dihydro-1,4-benzodiazepin-2-thiones with acid hydrazides RCONH. $.NH_2$ (R is then the 1-substituent) in boiling 1-butanol[1–3], we attempted at using to the synthesis of compound *Ib* a formal analogy consisting in a reaction of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione[1,2,7] with 1-hydrazinocarbonyl-4-methylpiperazine[24] in boiling 1-butanol. The formation of hydrogen sulfide took place and a mixture was obtained which was chromatographed on silica gel. A substance was obtained as the main product for which the mass spectrum

showed the elemental composition $C_{16}H_{10}Cl_2N_4O$ (hemihydrate according to the analysis). This composition indicates that only one further carbon atom and only two further nitrogen atoms were added to the 15 carbon atoms and two nitrogens of the starting compound; the result is that not only the cleavage of hydrogen sulfide but also of 1-methylpiperazine took place. According to the IR spectrum, the oxygen function of the product is the carbonyl of a lactam group CONH while the presence of the NH group proton was confirmed by the ^{1}H NMR spectrum. All experimental data lead to formulating the product as 8-chloro-6-(2-chlorophenyl)-2,4-dihydro--1*H*-*s*-triazolo[4,3-a]-1,4-benzodiazepin-1-one(*XIII*). This compound is known[20-23] and the properties described are not at variance with those of our product. After this unexpected course of the reaction we considered useful to try a similar reaction of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione[1,2,7] with semicarbazide in boiling 1-butanol. From the three products isolated, from which the first crystallized by cooling of the reaction mixture and the further two were separated by chromatography on silica gel, only for one (the main product) a structure could be suggested. Its mass spectrum in agreement with the analysis demonstrated the elemental composition $C_{20}H_{20}Cl_2N_4O_2$. The IR spectrum showed bands at 1 645 and 1 700 cm^{-1} from which the former is ascribed to the fragment C=N and the latter to a group NHCOOR. The product is considered to be *Xb*, *i.e.* having an analogous structure like the product of reaction of the starting thione with ethyl carbazate[20]. The compound melts with decomposition at the same temperature like compound *XIII* (203–205°C) to which it is apparently transformed at this temperature (the ethyl carbazate product is similarly transformed to compound *XIII*, ref.[20]). The formation of compound *Xb* can be explained either in that way that the reaction of semicarbazide with boiling butanol yields butyl carbazate which then reacts with the thione, or a primary reaction of the thione with semicarbazide results in the corresponding "semicarbazone" which then undergoes alcoholysis with boiling butanol under the cleavage of ammonia.

For preparing the title compound *IIb* and its analogues *IIa* and *IIIb* – *VIIb* we needed the monosubstituted piperazines *XIVb* – *XIXb* which were obtained by hydrolysis of the corresponding carbamates *XIVa* – *XIXa* with boiling mixtures of equal parts of ethanol and potassium hydroxide.The literature reported the preparation of compounds *XIVa* (ref.[25]), *XIVb* (ref.[25,26]), *XVIa* (ref.[25]), *XVIb* (ref.[25,26]), *XVIIb* (ref.[27]) and *XVIIIb* (ref.[26,28]). Our preparations differed from the procedures described either in principle or at least by the conditions used; the characterization of some known compounds was completed. Compound *XIVa* was obtained by alkylation of 1-ethoxycarbonylpiperazine with 2-methoxyethyl bromide[29] in chloroform in the presence of sodium carbonate. Compound *XVa* was prepared similarly by using 3-methoxypropyl bromide[30] in dioxane at 90°C. For preparing compound *XVIa* 1-ethoxycarbonylpiperazine was alkylated with 2-ethoxyethyl bromide[31] in boiling acetone in the presence of potassium carbonate. Compound *XVIIa* was obtained

by a similar alkylation with 2-methylthioethyl chloride[32] in toluene at 100°C. Compound *XVIIIa* was prepared by reaction of phenol with 1-(2-chloroethyl)-4-ethoxycarbonylpiperazine hydrochloride[33] and potassium carbonate in boiling acetone. Finally, compound *XIXa* was obtained similarly from thiophenol.

XIV, $R^1 = OCH_3$, $n = 2$ — *XVII*, $R^1 = SCH_3$, $n = 2$
XV, $R^1 = OCH_3$, $n = 3$ — *XVIII*, $R^1 = OC_6H_5$, $n = 2$
XVI, $R^1 = OC_2H_5$, $n = 2$ — *XIX*, $R^1 = SC_6H_5$, $n = 2$

In formulae *XIV*–*XIX*: *a*, R = $COOC_2H_5$; *b*, R = H.

Reactions of bromo derivatives *XIIa* and *XIIb* with an excess of 1-(2-methoxyethyl)piperazine (*XIVb*) at 150–160°C and separation of the crude base on alumina afforded compounds *IIa* and *IIb*. Reactions of the bromo compound *XIIb* with piperazines *XVb*–*XVIIb* at 160–165°C and chromatography of the mixtures on silica gel resulted in bases *IIIb*–*Vb*. All the bases are crystalline, their identity was confirmed by spectra and neutralization reactions afforded salts for characterization and for the pharmacological tests. With regard to the fact that the bromide *XIIb* did not react with excessive 1-(2-phenyoxyethyl)piperazine (*XVIIIb*) at 160°C (starting compound recovered), we performed the reaction at 220°C. At this temperature decomposition reactions took already place (a considerable quantity of phenol was isolated) and the desired product was not obtained. Attempts at carrying out the reaction in boiling dimethylformamide (N-formylation of compound *XVIIIb* with dimethylformamide was noted) or in hexamethylphosphoric triamide at 160–170°C were also unsuccessful. For these reasons a different approach was used. The new piperazino derivative *VIIIb* was prepared by a reaction of the bromo derivative *XIIb* with anhydrous piperazine at 160–165°C. Similarly like in preparations of compounds *IIIb*–*Vb* the debrominated derivative *XIb* was obtained as a neutral by-product; it was isolated in crystalline state and identified by the melting point and by chromatographic comparison with the authentic substance. The hypothesis about its mode of formation has already been mentioned. The piperazine derivative *VIIIb* was then alkylated with 2-phenoxyethyl bromide[34] on the one hand, and with 2-phenylthioethyl bromide[35] on the other, in both cases in boiling chloroform in the presence of potassium carbonate. Chromatography of the crude products on silica gel afforded in moderate yields the desired bases *VIb* and *VIIb* which were characterized by spectra and transformed to the fumarates.

Compounds *IIa*–*VIIb* were pharmacologically evaluated by several tests in mice oriented to the acute toxicity, discoordinating activity, central depressant and anticonvulsant effects; they were administered orally. The results are assembled in Table I

which includes triazolam[4] as a standard and further the known compounds *Ia*, *Ib*, *XIa* and *XIIb*. The toxicity of the tested compounds is low but all the new compounds are more toxic than triazolam. The discoordinating activity was evaluated in the rotarod test; the Table gives the medium effective doses (ED_{50}) at the time of maximum effect which brought about ataxia in 50% animals. The inhibition of the spontaneous locomotor activity was used as a criterion of the central depressant activity and it was evaluated by the photo-cell method of Dews; the medium effective doses (D_{50}), decreasing the motility to 50% of the control value, are given. The anticonvulsant activity was evaluated by two tests: *a*) antagonization of the convulsant and lethal effects of pentetrazole (the effective doses ED had significant activity) and *b*) antagonization of the convulsant effect of the electroshock (the medium protective doses PD_{50} are given which decrease the appearence of convulsions to 50% in comparison with the control group).

The tabulated values show that the title compound *IIb* has an extremely high anticonvulsant activity and in this line it almost equals that of triazolam. On the other hand its central depressant activity is weaker and the toxicity higher. The other new compounds with more bulky N-substituents are less active. The high activity of the known methylpiperazino derivative *Ib* (ref.[5]) has been confirmed.

TABLE I

Pharmacological properties of substances *Ia*—*VIIb* and of some related compounds (all doses in mg/kg orally)

Compound	Acute toxicity LD_{50}	Rotarod ED_{50}	Inhibition of locomotor activity D_{50}	Anticonvulsant activity	
				pentetrazole ED	electroshock PD_{50}
Ia	440	11·7	—	1·0	8·7
Ib	*c.* 300	0·64	0·08	>0·01	0·036
IIa	>1 000	7·1	—	1·0	0·97
IIb	390	0·32	0·1	0·01	0·07
IIIb	> 500	0·19	—	—	0·21
IVb	> 500	0·26	—	—	0·48
Vb	> 500	0·29	—	—	0·32
VIb	—	>1·0	*c.* 1·0	—	0·54
VIIb	—	—	—	—	>1·0
XIa	*c.* 600	1·4	—	0·1	3·0
XIIb	>1 000	0·8	—	1·0	0·11
TR[a]	>1 000	0·13	0·009	0·03	0·032

[a] Triazolam[4].

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 methanol) were recored with a Unicam SP 8000 spectrophotometer, the IR spectra(mostly in Nujol) with a Unicam SP 200G spectrophotometer, the ^1H NMR spectra (in C^2HCl_3 unless stated otherwise) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra 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).

1-Ethoxycarbonyl-4-(2-methoxyethyl)piperazine (*XIVa*)

A stirred mixture of 85·4 g 1-ethoxycarbonylpiperazine, 80 g Na_2CO_3 and 170 ml chloroform was treated at 50°C with a solution of 90 g 2-methoxyethyl bromide[29] in 100 ml chloroform over 30 min. The mixture was then refluxed for 8·5 h, cooled, the solid was filtered off and washed with chloroform. The filtrate was evaporated *in vacuo* and the residue was distilled; 70·6 g (61%), b.p. 102—104°C/27 Pa. Lit.[25], b.p. 94—96°C/13 Pa.

1-Ethoxycarbonyl-4-(3-methoxypropyl)piperazine (*XVa*)

A mixture of 110 g 1-ethoxycarbonylpiperazine, 96·1 g K_2CO_3, 400 ml dioxane and 106·4 g 3-methoxypropyl bromide[30] was stirred for 5·5 h at 90°C. After standing overnight the inorganic salts were filtered off and washed with dioxane. The filtrate was evaporated under reduced pressure, the residue was made alkaline with NH_4OH and extracted with dichloromethane. The extract was dried with K_2CO_3, evaporated and the residue was distilled; 118·5 g (74%) crude product, b.p. 99—111°/27 Pa. The analytical sample was obtained by redistillation, b.p. 104°C/20 Pa. For $C_{11}H_{22}N_2O_3$ (230·3) calculated: 57·37% C, 9·63% H, 12·16% N; found: 57·36% C, 9·81% H, 12·16% N.

Hydrochloride, m.p. 144·5—145°C (chloroform–ether). For $C_{11}H_{23}ClN_2O_3$ (266·8) calculated: 49·52% C, 8·65% H, 13·29% Cl, 10·50% N; found: 48·98% C, 8·80% H, 13·30% Cl, 10·11% N.

1-Ethoxycarbonyl-4-(2-ethoxyethyl)piperazine (*XVIa*)

A stirred mixture of 95 g 1-ethoxycarbonylpiperazine, 500 ml acetone, 180 g K_2CO_3 and 92 g 2-ethoxyethyl bromide[31] was refluxed for 42 h. After cooling the salts were filtered off with suction, washed with acetone, the filtrate was evaporated at normal pressure and the residue was distilled *in vacuo*; 103 g (74%), b.p. 147—150°C/2·0 kPa. Lit.[25], b.p. 96°C/13 Pa.

1-Ethoxycarbonyl-4-(2-methylthioethyl)piperazine (*XVIIa*)

A mixture of 158 g 1-ethoxycarbonylpiperazine, 600 ml toluene and 55·3 g 2-methothioethyl chloride[32] was stirred and heated for 60 h to 100°C. The mixture was then kept for 48 h in a refrigerator and the separated 1-ethoxycarbonylpiperazine hydrochloride was filtered off. The filtrate was evaporated under reduced pressure and the residue was distilled; 100 g (86%) crude product, b.p. 114—117°C/27 Pa. Redistillation gave a product boiling at 116—117°C/27 Pa. For $C_{10}H_{20}$·N_2O_2S (232·4) calculated: 51·69% C, 8·68% H. 12·06% N, 13·80 S; found: 51·97% C, 8·76% H, 12·20% N, 13·41% S.

Hydrochloride, m.p. 183—184°C (chloroform–ether). For $C_{10}H_{21}ClN_2O_2S$ (268·8) calculated: 44·68% C, 7·88% H, 13·19% Cl, 10·42% N, 11·93% S; found: 44·85% C, 7·97% H, 13·50% Cl, 10·09% N, 12·01% S.

1-Ethoxycarbonyl-4-(2-phenoxyethyl)piperazine (*XVIIIa*)

A solution of 37·6 g phenol in 200 ml acetone and 103 g 1-(2-chloroethyl)-4-ethoxycarbonylpiperazine hydrochloride[33] were added to a suspension of 120 g K_2CO_3 in 400 ml acetone and the stirred mixture was refluxed for 28 h. After cooling the solid was filtered off and washed with acetone, the filtrate was evaporated, the residue was dissolved in 300 ml chloroform, the solution was washed with water, 1M-NaOH and water, the solvent was evaporated and the residue was distilled; 80·2 g (72%), b.p. 160–168°C/0·12 kPa. IR spectrum (film): 692, 757 (5 adjacent Ar—H), 1 131, 1 243 (ArOR and C—O in NCOOR), 1 500, 1 590, 1 600, 3 030, 3 040, 3 050 (Ar), 1 693, 1 707 cm^{-1} (NCOOR). ^1H NMR spectrum: δ 6·70–7·30 (m, 5 H, ArH), 4·03 (q, J = = 7·0 Hz, 2 H, $COOCH_2$), 4·00 (t, J = 6·0 Hz, 2 H, $ArOCH_2$), 3·40 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 2·71 (t, J = 6·0 Hz, 2 H, CH_2N^4), 2·48 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 1·20 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{15}H_{22}N_2O_3$ (278·4) calculated: 64·72% C, 7·97% H, 10·07% N; found: 64·88% C, 7·81% H, 9·96% N.

Hydrochloride, m.p. 192–195°C (ethanol). For $C_{15}H_{23}ClN_2O_3$ (314·8) calcula ted:57·22% C, 7·36% H, 11·26% Cl, 8·90% N; found: 57·15% C, 7·45% H, 11·35% Cl, 8·62% N.

1-Ethoxycarbonyl-4-(2-phenylthioethyl)piperazine (*XIXa*)

A similar reaction of 11·0 g thiophenol, 25·7 g 1-(2-chloroethyl)-4-ethoxycarbonylpiperazine hydrochloride[33] and 30 g K_2CO_3 in 150 ml acetone and a similar processing gave 29·4 g crude oily base which was dissolved in 50 ml ethanol and the solution was treated with a slight exceess of HCl in ether; 25·0 g (76%) hydrochloride, m.p. 167–168·5°C (ethanol–ether). For $C_{15}H_{23}Cl.$ $.N_2O_2S$ (330·9) calculated: 54·44% C, 7·01% H, 10·72% Cl, 8·47% N, 9·69% S; found: 54·37% C, 7·02% H, 10·80% Cl, 8·52% N, 9·63% S.

1-(2-Methoxyethyl)piperazine (*XIVb*)

A mixture of 70·6 g *XIVa*, 120 g KOH and 120 ml ethanol was stirred and heated under reflux for 4 h to 95°C (bath temperature 110°C). After cooling the mixture was diluted with 300 ml warm water, ethanol was evaporated and the cold residue was extracted with chloroform. Processing of the extract gave 40·1 g (85%) *XIVb*, b.p. 100–103°C/2·7 kPa. Lit.[25,26], b.p. 94–95°C/ /1·9 kPa, and 100–101°C/2·7 kPa, respectively.

Bis(hydrogen maleate), m.p. 155–156°C (ethanol). For $C_{15}H_{24}N_2O_9$ (376·4) calculated: 47·87% C, 6·43% H, 7·44% N; found: 47·39% C, 6·50% H, 7·62% N.

1-(3-Methoxypropyl)piperazine (*XVb*)

A similar reaction of 124·5 g *XVa* and 152 g KOH in 150 ml ethanol and a similar processing gave 66·8 g (78%) *XVb*, b.p. 94–98°C/1·6 kPa. Analytical sample, b.p. 95–96°C/1·6 kPa. For $C_8H_{18}N_2O$ (158·3). calculated: 60·72% C, 11·47% H, 17·70% N; found: 60·22% C, 11·71% H 17·20% N.

Dihydrochloride, m.p. 210–212°C (acetone–ethanol). For $C_8H_{20}Cl_2N_2O$ (231·2) calculated: 41·56% C, 8·72% H, 30·68% Cl, 12·12% N; found: 41·43% C, 8·87% H, 30·52% Cl, 12·07% N.

1-(2-Ethoxyethyl)piperazine (*XVIb*)

A similar reaction of 112·9 g *XVIa* and 180 g KOH in 180 ml ethanol gave 68·5 g (91%) *XVIb*, b.p. 94–95°C/1·6 kPa. ^1H NMR spectrum: δ 3·54 (t, J = 6·0 Hz, 2 H, CH_2O of piperazino-

ethoxy), 3·48 (q, J = 7·0 Hz, 2 H, CH_2O of ethoxy), 2·89 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·54 (t, J = 6·0 Hz, 2 H, CH_2N^1), 2·44 (bs, 4 H, $CH_2N^1CH_2$ of piperazine), 1·54 (s, 1 H, NH), 1·13 (t, J = 7·0 Hz, 3 H, CH_3). Lit.[25,26], b.p. 104–106°C/1·9 kPa, and 115–117°C/2·0 kPa, respectively.

Bis(hydrogen maleate), m.p. 157·5–158·5°C (ethanol). For $C_{16}H_{26}N_2O_9$ (390·4) calculated: 49·22% C, 6·71% H, 7·18% N; found: 48·92% C, 7·04% H, 7·17% N.

1-(2-Methylthioethyl)piperazine (*XVIIb*)

XVIIa (79·6 g) was heated with a solution of 96·2 g KOH in 100 ml ethanol for 2 h to 95–100°C without stirring, and after the addition of 5 ml water the heating was continued for 1 h with stirring. Similar processing like in the preceding cases (extraction with dichloromethane) gave 43·3 g (79·%) *XVIIb*, b.p. 116–120°C/1·7 kPa. The redistilled product, b.p. 117·5–118°C/1·7 kPa. Lit.[27], b.p. 125–128°C/2·0 kPa.

Dihydrochloride, m.p. 233–236°C (99% ethanol). For $C_7H_{18}Cl_2N_2S$ (233·2) calculated: 36·05% C, 7·78% H, 30·41% Cl, 12·01% N, 13·75% S; found: 36·09% C, 7·88% H, 30·26% Cl, 12·08% N, 13·55% S.

1-(2-Phenoxyethyl)piperazine (*XVIIIb*)

A reaction of 85 g *XVIIIa*.HCl with a solution of 210 g KOH in 210 ml ethanol was carried out similarly like in the preparation of *XIVb* and gave 46·0 g (81%) *XVIIIb*, b.p. 133–134°C/70 Pa. ^{1}H NMR spectrum: δ 6·70–7·40 (m, 5 H, ArH), 4·10 (t, J = 6·0 Hz, 2 H, CH_2O), 2·88 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·75 (t, J = 6·0 Hz, 2 H, CH_2N^1), 2·50 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 1·70 (s, 1 H, NH). Lit.[26,28], b.p. 182–185°C/2·7 kPa, and 143 to 144°C/0·13 kPa, respectively.

1-(2-Phenylthioethyl)piperazine (*XIXb*)

A similar reaction of 51·1 g *XIXa*.HCl with 120 g KOH in 120 ml ethanol gave 29·3 g (85%) *XIXb*, b.p. 136–138°C/50 Pa. Analytical sample, b.p. 140–141°C/67 Pa. ^{1}H NMR spectrum: δ *c.* 7·25 (m, 5 H, ArH), 3·10 (m, 2 H, CH_2S), 2·88 (bt, 4 H, $CH_2N^4CH_2$ of piperazine), 2·65 (m, 2 H, CH_2N^1), 2·45 (bt, 4 H, $CH_2N^1CH_2$ of piperazine), 1·56 (s, 1 H, NH). For $C_{12}H_{18}N_2S$ (222·4) calculated: 64·82% C, 8·16% H, 12·60% N, 14·42% S; found: 65·54% C, 8·62% H, 12·62% N, 14·61% S.

Bis(hydrogen maleate), m.p. 147–149°C (ethanol). For $C_{20}H_{26}N_2O_8S$ (454·5) calculated: 52·85% C, 5·77% H, 6·17% N, 7·06% S; found: 52·61% C, 5·86% H, 5·97% N, 6·82% S.

1-Bromo-8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XIIa*)

A solution of 14·1 g 8-chloro-6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XIa*) (ref.[9]) in 140 ml chloroform and 5·7 g pyridine was stirred and treated at 60°C with a solution of 10·4 g bromine in 50 ml chloroform over 30 min. The mixture was then stirred and refluxed for another 30 min. After cooling it was washed with water, 150 ml 1 : 1 diluted NH_4OH and water, dried with $MgSO_4$ and the solution was filtered through a column of silica gel (10 cm, diameter of 3 cm). The column was washed with 80 ml chloroform, the filtrate was evaporated under reduced pressure and the residue was crystallized from 250 ml ethyl acetate; 9·8 g (55%), m.p. 205–208°C. Lit.[5,13,14], m.p. 202–203·5°C, and 205–207°C, respectively.

1-Bromo-8-chloro-6-(2-chlorophenyl)-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XIIb*)

A similar bromination of 49·4 g 8-chloro-6-(2-chlorophenyl)-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*XIb*) (ref.[10]) with 28·8 g bromine in a mixture of 600 ml chloroform and 18 g pyridine gave 64·5 g crude product which was crystallized from a mixture of 750 ml benzene and 150 ml hexane; 52·0 g (82%) 6 : 1 solvate with benzene, m.p. 211—213°C. Analytical sample, m.p. 214 to 215°C (benzene). UV spectrum: λ_{max} 222 nm (log ε 4·58), inflex at 250 nm (4·06). IR spectrum: 755, 775, 830, 892 (4 and 2 adjacent and solitary Ar—H), 1 490, 1 535, 1 570, 1 592, 1 600, 3 050 (Ar), 1 611 cm^{-1} (ArC=N). ^1H NMR spectrum: δ 7·78 (d, J = 9·0 Hz, 1 H, 10-H), 7·25—7·60 (m, 5 H, 9-H and 4 ArH of 2-chlorophenyl), 7·18 (d, J = 2·5 Hz, 1 H, 7-H), 5·54 and 4·22 (ABq, J = 13·0 Hz, 1 + 1 H, 4,4-H_2). For $C_{16}H_9BrCl_2N_4$ + 1/6 C_6H_6 (421·1) calculated: 48·47% C, 2·39% H, 18·98% Br, 16·84% Cl, 13·31% N; found: 48·61% C, 2·36% H, 18·84% Br, 16·72% Cl, 13·38% N. Lit[5], m.p. 208·5—210·5°C for the nonsolvated product.

8-Chloro-1-(4-methylpiperazino)-6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*Ia*)

A mixture of 1·9 g *XIIa* and 11 ml 1-methylpiperazine was stirred and refluxed under nitrogen for 7 h. After standing for 48 h at room temperature it was diluted with 35 ml water and extracted with dichloromethane. The exctract was washed with water and the bases were transferred by shaking with 60 ml 2M-HCl into the aqueous layer. The bases were released with NH_4OH and isolated by extraction with dichloromethane. The extract was dried with K_2CO_3, evaporated and the residue was chromatographed on a column of silica gel (5 cm, diameter of 2·5 cm). Elution with dichloromethane containing 2% methanol gave 1·5 g (76%) homogeneous product crystallizing from a mixture of hexane, ethyl acetate and ethanol, m.p. 236—239°C. Mass spectrum, m/z (%): 392 (M^+ corresponding to $C_{21}H_{21}ClN_6$, 1·2%), 322 (35·2), 310 (5·6), 98 (17·6), 84 (40·8), 83 (76·8), 71 (100), 70 (20·8), Lit[5,6], m.p. 238—239·5°C, and 239·5—240·5°C, respectively.

Fumarate, solvate 1 : 1 with ethanol, m.p. 143—146°C (ethanol–ether). For $C_{25}H_{25}ClN_6O_4$ + + C_2H_6O (555·0) calculated: 58·42% C, 5·63% H, 6·39% Cl, 15·14% N; found: 57·69% C, 5·27% H, 6·79% Cl, 14·92% N.

8-Chloro-6-(2-chlorophenyl)-1-(4-methylpiperazino)-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*Ib*)

A mixture of 5·0 g *XIIb* and 23·6 g 1-methylpiperazine was heated under nitrogen over 3 h to 100—110°C and then kept for 8 h at this temperature. It was poured into 100 ml saturated $NaHCO_3$ solution and extracted with dichloromethane. The extract was dried with K_2CO_3, evaporated under reduced pressure and the residue was chromatographed on a column of neutral Al_2O_3 (activity II) (20 cm, diameter of 2·5 cm). Benzene eluted first 3·0 g mixture consisting according to TLC of the desired *Ib*, the starting *XIIb*, further *XIb* (*cf.*[5]) and a minor nonidentified by-product. Further elution with benzene, dichloromethane and finally with dichloromethane containing 2% methanol resulted in 2·45 g (48%) almost homogeneous *Ib* which crystallized from ethyl acetate, m.p. 223—226°C. Lit.[5], m.p. 224—226°C. Crystallization from a mixture of benzene and cyclohexane gave a 6 : 1 solvate with benzene, m.p. 226—227·5°C. Mass spectrum, m/z (%): 426 (M^+ corresponding to $C_{21}H_{20}Cl_2N_6$, 4·4%), 369 (6·8), 356 (90·8), 344 (23·2), 328 (5·6), 321 (9·6), 84 (50·8), 83 (74·4), 71 (100), 70 (22·0), 56 (13·2). UV spectrum: λ_{max} 210 nm (log ε 4·63), inflex at 245 nm (4·17). IR spectrum: 750, 819, 849, 892, 899 (4 and 2 adjacent and solitary Ar—H), 1 470, 1 533, 1 552, 1 563, 1 590, 3 045 (Ar), 1 602 (Ar—C=N), 2 780 cm^{-1} (N—CH_3). ^1H NMR spectrum: δ 7·90 (d, J = 8·5 Hz, 1 H, 10-H), 7·20—7·70 (m, 6 H, 9-H, 4 ArH of 2-chlorophenyl and 1 H of benzene), 7·05 (*d*, J = 2·0 Hz, 1 H, 7-H), 5·35 and 4·03

(ABq, J = 13·0 Hz, 1 + 1 H, 4,4-H_2), 3·20 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·40 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 2·21 (s, 3 H, NCH_3). For $C_{21}H_{20}Cl_2N_6 + 1/6\ C_6H_6$ (440·4) calculated: 60·00% C, 4·81% H, 16·10% Cl, 19·09% N; found: 60·34% C, 4·98% H, 16·43% Cl, 18·53% N.

Oxalate, 2 : 1 solvate with ethanol, m.p. 239—241°C (aqueous ethanol). For $C_{24}H_{22}Cl_2N_6O_4 + 1/2\ C_2H_6O$ (540·4) calculated: 53·34% C, 4·66% H, 13·12% Cl, 15·55% N; found: 52·98% C, 4·92% H, 13·00% Cl, 15·39% N.

8-Chloro-6-(2-chlorophenyl)-2,4-dihydro-1*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepin-1-one (*XIII*)

A mixture of 6·4 g 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione[1,2,7], 4·0 g 1-hydrazinocarbonyl-4-methylpiperazine[24] and 70 ml 1-butanol was stirred and refluxed for 8 h. The solution was evaporated *in vacuo* and after the addition of 30 ml xylene, the evaporation was repeated. The residue was dissolved in 50 ml chloroform and the solution was chromatographed on a column of 80 g silica gel (silpearl). The first fraction to be eluted (1·0 g) consisted of a mixture, the following chloroform eluates and the first fraction obtained with chloroform containing 2% methanol were almost homogeneous (7·9 g). Crystallization from 5 ml ethyl acetate and the processing of the mother liquor gave 5·2 g (75%) *XIII*, m.p. 206—208°C. Lit.[20,23], m.p. 204—205°C for a 2 : 1 solvate with ethanol. Further crystallization of our product from ethyl acetate gave a substance melting at 208—210°C, corresponding analytically to a hemihydrate. Mass spectrum, m/z (%): 344 (M^+ corresponding to $C_{16}H_{10}Cl_2N_4O$, 100%), 309 ($C_{16}H_{10}ClN_4O$, 75), 207 ($C_9H_6ClN_3O$, 25), 172 ($C_9H_6N_3O$, 70). UV spectrum: λ_{max} 307 nm (log ε 3·14), inflex at 237 nm (4·27). IR spectrum (KBr): 736, 750, 821, 878, 885 (4 and 2 adjacent and solitary Ar—H), 1 490, 1 567, 1 590, 3 060 (Ar), 1 612 (Ar—C=N), 1 715 (CONH), 3 185, 3 410 cm^{-1} (OH of the tautomer of *XIII*, H_2O). ^1H NMR spectrum ($C^2H_3SOC^2H_3$): δ 12·05 (bs, 1 H, CONH), 8·00 (d, J = 8·5 Hz, 1 H, 10-H), 7·80 (dd, J = 8·5; 2·5 Hz, 1 H, 9-H), *c.* 7·45 (m, 4 H, 4 ArH of 2-chlorophenyl), 6·98 (d, J = 2·5 Hz, 1 H, 7-H), 4·60 (bs, 2 H, 4,4-H_2). For $C_{16}H_{10}Cl_2N_4O + 1/2\ H_2O$ (354·2) calculated: 54·26% C, 3·13% H, 20·02% Cl, 15·82% N; found: 54·76% C, 3·08% H, 20·11% Cl, 15·92% N.

2-[N^2-(Butoxycarbonyl)hydrazino]-7-chloro-5-(2-chlorophenyl)-3*H*-1,4-benzodiazepine (*Xb*)

A mixture of 6·4 g 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-1,4-benzodiazepin-2-thione[1,2,7], 1·9 g semicarbazide and 70 ml 1-butanol was stirred and refluxed for 10 h and allowed to stand overnight at room temperature. The precipitated solid (2·7 g, m.p. 180—183°C and after resolidification 219—223°C, crystallized from ethanol) was filtered off, the filtrate was evaporated *in vacuo* and the residue was dissolved in 30 ml benzene and chromatographed on a column of 50 g silica gel (Merck 60). The first fraction (0·4 g, m.p. 231—234°C), eluted with benzene, was identified as the starting thione. Chloroform eluted then 1·6 g another homogeneous compound (m.p. 266—269°C) which was not identified. Continued elution with chloroform and chloroform containing 2% methanol yielded 3·6 g (43%) main product to which the structure *Xb* was ascribed, m.p. 203—205°C with decomposition (ethanol–chloroform). Mass spectrum, m/z: 418 (M^+ corresponding to $C_{20}H_{20}Cl_2N_4O_2$). UV spectrum: λ_{max} 240 nm (log ε 4·42), 344 nm (3·29), inflexes at 255 nm (4·33) and 275 nm (4·22). IR spectrum: 738, 752, 765, 830, 889 (4 and 2 adjacent and solitary Ar—H), 1 270 (C—O in COOR), 1 475, 1 490, 1 550, 3 058 (Ar), 1 645 (C=N), 1 700 (NHCOOR), 3 110, 3 170, 3 215 cm^{-1} (C=O...HN). For $C_{20}H_{20}Cl_2N_4O_2$ (419·3) calculated: 57·28% C, 4·81% H, 16·91% Cl, 13·36% N; found: 57·40% C, 5·01% H, 16·82% Cl, 13·08% N.

8-Chloro-1-[4-(2-methoxyethyl)piperazino]-6-phenyl-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*IIa*)

A mixture of 2·8 g *XIIa* and 5·0 g *XIVb* was stirred and heated to 150—160°C for 1 h under nitrogen. After cooling it was poured into a solution of 1 g $NaHCO_3$ in 50 ml water and extracted with dichloromethane. By shaking with an excess of 5% hydrochloric acid the bases were transferred into the aqueous layer, released with NH_4OH and isolated by extraction with dichloromethane. The extract was dried with K_2CO_3, evaporated under reduced pressure and the residue was chromatographed on a column of 150 g neutral Al_2O_3 (activity II). The first fractions (eluted with a mixture of benzene and chloroform) were discarded. Chloroform eluted then 3·2 g crystalline product which was recrystallized from ethanol; 2·1 g (64%), m.p. 194—195°C. Analytical sample, m.p. 195—196°C (ethanol). UV spectrum: λ_{max} 220 nm (log ε 4·58), infl. 245 nm (4·23). IR spectrum: 698, 748, 780, 821, 831, 842, 893 (5 and 2 adjacent and solitary Ar—H), 1 110, 1 160 (ROR'), 1 477, 1 488, 1 532, 1 546, 1 553 (Ar), 1 610 (Ar—C=N), 2 755, 2 791, 2 830, 2 890 cm^{-1} ($ROCH_3$, N—CH_2). ^1H NMR spectrum: δ 8·00 (d, J = 9·0 Hz, 1 H, 10-H), 7·20 to 7·70 (m, 7 H, remaining ArH), 5·38 and 4·08 (ABq, J = 13·0 Hz, 1 + 1 H, 4,4-H_2), 3·53 (t, J = = 7·0 Hz, 2 H, CH_2O), 3·38 (s, 3 H, OCH_3), 3·25 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·60 (bm, 6 H, $CH_2N^4CH_2$ of piperazine and further CH_2N^4). For $C_{23}H_{25}ClN_6O$ (437·0) calculated, 63·22% C, 5·77% H, 8·11% Cl, 19·24% N; found: 63·37% C, 5·98% H, 8·13% Cl, 19·19% N.

Difumarate, m.p. 144—146°C (aqueous ethanol). For $C_{31}H_{33}ClN_6O_9$ (669·1) calculated: 55·65% C, 4·97% H, 5·30% Cl, 12·56% N; found: 55·17% C, 5·00% H, 5·60% Cl, 13·15% N.

8-Chloro-6-(2-chlorophenyl)-1-[4-(2-methoxyethyl)piperazino]-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*IIb*)

A mixture of 6·12 g *XIIb* and 10·75 g *XIVb* was processed similarly like in the preceding case. The crude product (7·5 g) was chromatographed on a column of 250 g neutral Al_2O_3 (activity II). Elution with a mixture of benzene and chloroform recovered 2·6 g *XIIb* (m.p. 213—215°C, ethanol). Elution with chloroform yielded 3·95 g (97% per conversion) crude *IIb* which was crystallized from ethanol, m.p. 192—194°C. UV spectrum: λ_{max} 218 nm (log ε 4·61), infl. 245 nm (4·15). IR spectrum (KBr): 732, 752, 770, 822, 833, 892 (4 and 2 adjacent and solitary Ar—H), 1 108 (ROR'), 1 487, 1 530, 1 557, 1 569 (Ar), 1 613 (Ar—C=N), 2 740, 2 790, 2 825 cm^{-1} ($ROCH_3$, CH_2—N). ^1H NMR spectrum: δ 7·98 (d, J = 9·0 Hz, 1 H, 10-H), 7·20—7·70 (m, 5 H, 9-H and 4 ArH of 2-chlorophenyl), 7·11 (d, J = 2·5 Hz, 1 H, 7-H), 5·42 and 4·13 (ABq, J = = 13·0 Hz, 1 + 1 H, 4,4-H_2), 3·54 (t, J = 7·0 Hz, 2 H, CH_2O), 3·38 (s, 3 H, OCH_3), 3·25 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·60 (bm, 6 H, $CH_2N^4CH_2$ of piperazine and further CH_2N^4). For $C_{23}H_{24}Cl_2N_6O$ (471·4) calculated: 58·60% C, 5·13% H, 15·04% Cl, 17·83% N; found: 58·44% C, 5·26% H, 14·94% Cl, 17·94% N.

Difumarate, m.p. 231—234°C with decomposition (ethanol). For $C_{31}H_{32}Cl_2N_6O_9$ (703·6) calculated: 52·92% C, 4·59% H, 10·08% Cl, 11·95% N; found: 53·03% C, 4·87% H, 10·55% Cl, 12·15% N.

8-Chloro-6-(2-chlorophenyl)-1-[4-(3-methoxypropyl)piperazino]-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*IIIb*)

A mixture of 6·1 g *XIIb* and 11·9 g *XVb* was stirred for 2 h at 160—165°C (nitrogen atmosphere). After cooling it was diluted with 100 ml dichloromethane, the solution was washed with water, the bases were extracted with 75 ml 5% hydrochloric acid, the aqueous solution was made alkaline with NH_4OH and the bases isolated by extraction with chloroform. Processing of the extract

gave 6·8 g crude product which was chromatographed on a column of 250 g silica gel (Merck 60). Chloroform containing 2% methanol was used as eluent. The first fractions (0·5 g) proved to be *XIb*, m.p. 263–266°C (ethanol) (no depression of the melting point in mixture with authentic *XIb*). It was followed by 4·6 g (79%) almost homogeneous *IIIb* which was purified by crystallization from ethanol; hemihydrate, m.p. 173–175°C. Mass spectrum, *m/z* (%): 484 (M^+ corresponding to $C_{24}H_{26}Cl_2N_6O$, <1%), 358, 356 (54), 142 (32), 141 (98), 116 (22), 114 (53), 111 (34), 71 (100), 70 (73), 56 (23), 45 (36). UV spectrum: λ_{max} 215 nm (log ε 4·64), infl. 245 nm (4·13). IR spectrum: 752, 828, 886, 898 (4 and 2 adjacent and solitary Ar—H), 1 110, 1 138 (ROR'), 1 482, 1 529, 1 550, 1 568, 1 590, 3 010 (Ar), 1 610, 1 618 ($Ar_2C{=}N$, N=C—N=C), 2 770 (N—CH_2), 3 340, 3 470 cm^{-1} (H_2O). ^1H NMR spectrum: δ 7·95 (d, J = 8·5 Hz, 1 H, 10-H), 7·20–7·70 (m, 5 H, 9-H and 4 ArH of 2-chlorophenyl), 7·09 (d, J = 2·5 Hz, 1 H, 7-H), 5·39 and 4·10 (ABq, J = 13·0 Hz, 1 + 1 H, 4,4-H_2), 3·40 (t, J = 6·0 Hz, 2 H, CH_2O), 3·30 (s, 3 H, OCH_3), 3·20 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·50 (bm, 7 H, $CH_2N^4CH_2$ of piperazine, further CH_2N^4 and 0·5 H_2O), 1·70 (m, 2 H, CH_2 in the middle of the propane chain). For $C_{24}H_{26}Cl_2N_6O + 1/2\ H_2O$ (494·3) calculated: 58·30% C, 5·50% H, 14·34% Cl, 17·00% N; found: 58·45% C, 5·22% H, 14·35% Cl, 16·90% N.

Fumarate, m.p. 159–161°C (ethanol). For $C_{28}H_{30}Cl_2N_6O_5$ (601·5) calculated: 55·91% C, 5·03% H, 11·79% Cl, 13·97% N; found: 55·77% C, 4·97% H, 11·92% Cl, 13·77% N.

8-Chloro-6-(2-chlorophenyl)-1-[4-(2-ethoxyethyl)piperazino]-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*IVb*)

A mixture of 6·1 g *XIIb* and 11·9 g *XVIb* was heated for 2 h to 160–165°C, after cooling diluted with 100 ml dichloromethane, the solution washed with 100 ml 5% NH_4OH and several times with water, dried with K_2CO_3 and evaporated. The residue was chromatographed on a column of 280 g silica gel (Merck 60). Elution with chloroform containing 1% methanol gave first 0·9 g *XIb* (m.p. 263–266°C; lit[10], m.p. 259–259·5°C). Continued elution with chloroform containing 1% and then 2% methanol gave the desired *IVb* which was recrystallized from ethanol (or from ethanol–hexane and ethanol–chloroform), 3·5 g (48%), m.p. 173–176°C. UV spectrum: λ_{max} 243 nm (log ε 4·11). IR spectrum: 733, 754, 775, 828, 894 (4 and 2 adjacent and solitary Ar—H), 1 104 (ROR'), 1 435, 1 530, 1 555, 1 568, 1 590 (Ar). 1 608 (C=N), 2 725, 2 750, 2 770 cm^{-1} (N—CH_2). ^1H NMR spectrum: δ 7·99 (d, J = 8·5 Hz, 1 H, 10-H), 7·52 (q, J = 8·5; 2·5 Hz, 1 H, 9-H), 7·20–7·70 (m, 4 H, 4 ArH of 2-chlorophenyl), 7·10 (d, J = 2·5 Hz, 1 H, 7-H), 5·40 and 4·10 (ABq, J = 13·0 Hz, 1 + 1 H, 4,4-H_2), 3·58 (t, J = 5·5 Hz, 2 H, CH_2O of aminoethoxy), 3·50 (q, J = 7·0 Hz, 2 H, CH_2O of ethoxy), 3·22 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·60 (bm, 6 H, $CH_2N^4CH_2$ of piperazine and further CH_2N^4), 1·20 (t, J = 7·0 Hz, 3 H, CH_3). For $C_{24}H_{26}Cl_2N_6O$ (485·4) calculated: 59·38% C, 5·40% H, 14·60% Cl, 17·31% N; found: 59·31% C, 5·57% H, 14·59% Cl, 17·55% N.

Difumarate, m.p. 205–207°C with decomposition (ethanol). For $C_{32}H_{34}Cl_2N_6O_9$ (717·6) calculated: 53·56% C, 4·78% H, 9·88% Cl, 11·71% N; found: 53·57% C, 5·12% H, 9·80% Cl, 11·88% N.

8-Chloro-6-(2-chlorophenyl)-1-[4-(2-methylthioethyl)piperazino]-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*Vb*)

Similarly like in the preceding case 7·0 g *XIIb* were reacted with 13·75 g *XVIIb* and the mixture was similarly processed. Chromatography on 220 g silica gel gave first 1·3 g *XIb* (m.p. 263–266°C) and then 3·9 g (47%) *Vb*, m.p. 217–218°C (ethanol–chloroform). UV spectrum: λ_{max} 214 nm (log ε 4·65), infl. 244 nm (4·15). IR spectrum: 772, 831, 881 (4 and 2 adjacent and solitary Ar—H),

1 480, 1 528, 1 548, 1 564, 1 588, 3 000, 3 015, 3 035 (Ar), 1 620 (C=N), 2 780 cm^{-1} (CH_2—N). ^1H NMR spectrum: δ 7·95 (d, J = 8·5 Hz, 1 H, 10-H), 7·20—7·70 (m, 5 H, 9-H and 4 ArH of 2-chlorophenyl), 7·10 (d, J = 2·0 Hz, 1 H, 7-H), 5·40 and 4·10 (ABq, J = 13·0 Hz, 1 + 1 H, 4,4-H_2), 3·20 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), *c.* 2·52 (bm, 8 H, SCH_2CH_2N and CH_2N^4. .CH_2 of piperazine), 2·11 (s, 3 H, SCH_3). For $C_{23}H_{24}Cl_2N_6S$ (487·5) calculated: 56·67% C, 4·96% H, 14·55% Cl, 17·24% N, 6·58% S; found: 56·49% C, 4·97% H, 14·81% Cl, 17·01% N, 6·71% S.

(+)-*Tartrate*, m.p. 211—213°C (aqueous ethanol). For $C_{27}H_{30}Cl_2N_6O_6S$ (637·6) calculated: 50·87% C, 4·74% H, 11·12% Cl, 13·18% N, 5·03% S; found: 50·73% C, 5·02% H, 11·16% Cl, 13·44% N, 5·22% S.

Hemioxalate hemihydrate, m.p. 231—232°C with decomposition (aqueous ethanol). For $C_{23}H_{24}Cl_2N_6S + 1/2\ C_2H_2O_4 + 1/2\ H_2O$ (541·5) calculated: 53·23% C, 4·84% H, 13·10% Cl, 15·52% N, 5·92% S; found: 53·60% C, 4·75% H, 12·88% Cl, 15·57% N, 5·55% S.

8-Chloro-6-(2-chlorophenyl)-1-piperazino-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*VIIIb*)

A mixture of 8·2 g *XIIb* and 6·9 g anhydrous piperazine was heated for 2 h to 160—165°C, after cooling diluted with 100 ml water and extracted with dichloromethane. The extract was washed with water and the strong bases were transferred by shaking with 5% hydrochloric acid into the aqueous layer. The organic layer was evaporated and gave 1·9 g crude *XIb* which was recrystallized from ethanol, m.p. 260—262°C. The acid aqueous layer was made alkaline with NH_4OH, the bases were isolated by extraction with dichloromethane and after the usual processing of the extract the residue was separated by chromatography on a column of 300 g neutral Al_2O_3 (activity II). Elution with chloroform gave 6·2 g (75%) homogeneous *VIIIb* which crystallized from cyclohexane as a 2 : 1 solvate with cyclohexane, m.p. 172—180°C and after resolidification again at 201—205°C. Mass spectrum, *m/z*: 412 (M^+ corresponding to $C_{20}H_{18}Cl_2N_6$), 355, 344. ^1H NMR spectrum: δ 8·00 (d, J = 8·0 Hz, 1 H, 10-H), 7·20—7·70 (m, 5 H, 9-H and 4 ArH of 2-chlorophenyl), 7·10 (d, J = 2·0 Hz, 1 H, 7-H), 5·40 and 4·10 (ABq, J = 13·0 Hz, 1 + 1 H, 4,4-H_2), 3·10 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·95 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 1·70 (bs, 1 H, NH), 1·40 (s, 6 H, 3 CH_2 of cyclohexane). For $C_{20}H_{18}Cl_2N_6 + 1/2\ C_6H_{12}$ (455·4) calculated: 60·66% C, 5·31% H, 15·57% Cl, 18·46% N; found: 60·57% C, 5·33% H, 15·50% Cl, 18·66% N.

8-Chloro-6-(2-chlorophenyl)-1-[4-(2-phenoxyethyl)piperazino]-4*H*-*s*-triazolo[4,3-a]-1,4-benzodiazepine (*VIb*)

A mixture of 6·0 g *VIIIb*, 3·5 g 2-phenoxyethyl bromide[34], 2·5 g K_2CO_3 and 12 ml chloroform was stirred and refluxed for 12·5 h under nitrogen. After standing overnight it was poured into 100 ml water and extracted with chlorofom. The extract was dried with $MgSO_4$, evaporated and the residue was chromatographed on a column of 220 g silica gel (Silpearl). The fractions eluted with chloroform were discarded and the product was eluted with chloroform containing 2% methanol; 2·1 g (27%), m.p. 110—115°C and after resolidification at 204—206°C (ethanol). IR spectrum: 693, 754, 840, 880 (5, 4 and 2 adjacent and solitary Ar—H), 1 010, 1 042, 1 250 (ArOR), 1 485, 1 520, 1 595 (Ar), 1 610 cm^{-1} (C=N). ^1H NMR spectrum: δ 7·98 (d, J = 8·5 Hz, 1 H, 10-H), 6·80—7·70 (m, 11 H remaining ArH), 5·40 and 4·11 (ABq, J = 13·0 Hz, 1 + 1 H, 4,4-H_2), 4·10 (t, J = 7·0 Hz, 2 H, CH_2O), 3·20 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·82 (t, J = 7·0 Hz, 2 H, CH_2N^4), 2·70 (bm, 4 H, $CH_2N^4CH_2$ of piperazine). For $C_{28}H_{26}Cl_2N_6O$ (533·5) calculated: 63·04% C, 4·91% H, 13·29% Cl, 15·75% N; found: 62·50% C, 4·87% H, 13·52% Cl, 15·67% N.

Fumarate, m.p. 125—127°C (ethanol). For $C_{32}H_{30}Cl_2N_6O_5$ (649·6) calculated: 59·17% C, 4·66% H, 10·92% Cl, 12·94% N; found: 58·66% C, 4·73% H, 10·81% Cl, 12·61% N.

8-Chloro-6-(2-chlorophenyl)-1-[4-(2-phenylthioethyl)piperazino]-4*H*-*s*-triazolo[4,3-*a*]-1,4-benzodiazepine (*VIIb*)

A mixture of 4·9 g *VIIIb*, 3·9 g 2-phenylthioethyl bromide[35], 2·55 g K_2CO_3 and 8 ml chloroform was processed similarly like in the preceding case. The crude product was chromatographed on a column of 200 g silica gel (Merck 60). After some less polar fractions eluted with a mixture of benzene and chloroform, the product was eluted with chloroform containing 1·5—3% methanol, 2·6 g (40%). It was purified by crystallization from a mixture of ethanol and chloroform and proved to be a 2 : 1 solvate with ethanol, m.p. 124—127°C. Mass spectrum, *m/z* (%): 548 (M^+ corresponding to $C_{28}H_{26}Cl_2N_6S$, 0·5%), 441 (65), 439 ($M-SC_6H_5$, 95), 427 (23), 425 ($M-CH_2SC_6H_5$, 35), 370 (20), 358 (50), 356 (70), 345 (37), 343 (60), 137 (55), 136 (85), 110 (30), 109 (45), 95 (43), 82 (100), 70 (90), 56 (48), 42 (78). UV spectrum: λ_{max} 245 nm (log ε 4·26), infl. 302 nm (3·16). IR spectrum: 697, 755, 842, 880 (5, 4 and 2 adjacent and solitary Ar—H), 1 480, 1 530, 1 555, 1 585 (Ar), 1 610 cm^{-1} (Ar—C=N). ^1H NMR spectrum: δ 7·90 (d, J = = 8·5 Hz, 1 H, 10-H), 7·10 (d, J = 2·0 Hz, 1 H, 7-H), 7·10—7·60 (m, 10 H, remaining ArH), 5·40 and 4·10 (ABq, J = 13·0 Hz, 1 + 1 H, 4,4-H_2), 3·20 (bm, 4 H, $CH_2N^1CH_2$ of piperazine), 2·70—3·10 (m, 4 H, SCH_2CH_2N), 2·60 (bm, 4 H, $CH_2N^4CH_2$ of piperazine), 3·70 (q), 2·18 (bs) and 1·21 (t) (signals corresponding to 1/2 CH_3CH_2OH). For $C_{28}H_{26}Cl_2N_6S + 1/2\ C_2H_6O$ (572·6) calculated: 60·83% C, 5·10% H, 12·39% Cl, 14·68% N, 5·60% S; found: 60·65% C, 5·00% H, 12·77% Cl, 14·53% N, 5·89% S.

Hemifumarate hemihydrate, m.p. 110—114°C (aqueous ethanol). For $C_{28}H_{26}Cl_2N_6S + 1/2\ C_4H_4O_4 + 1/2\ H_2O$ (616·6) calculated: 58·43% C, 4·74% H, 11·50% Cl, 13·63% N, 5·20% S; found: 58·76% C, 5·00% H, 11·74% Cl, 13·38% N, 5·47% S.

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