

POTENTIAL HYPNOTICS AND ANXIOLYTICS:

SYNTHESIS

OF 2-BROMO-4-(2-CHLOROPHENYL)-9-[4-(2-METHOXYETHYL)-PIPERAZINO]-6H-THIENO[3,2-*f*]-1,2,4-TRIAZOLO[4,3-*a*]-1,4-DIAZEPINE AND OF SOME RELATED COMPOUNDS

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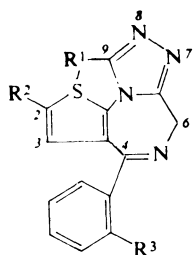
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The synthesis of 2,9-dibromo-4-(2-chlorophenyl)-6H-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (XX) has been carried out. The substitution reactions of XX with 1-(2-methoxyethyl)piperazine, 1-(3-methoxypropyl)piperazine, 1-(2-ethoxyethyl)piperazine and 1-(2-methylthioethyl)piperazine afforded the title compound XXIV and its analogues XXV–XXVII. N-Alkylations of 2-bromo-4-(2-chlorophenyl)-9-piperazino-6H-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (XXIII) with 2-phenoxyethyl bromide and 2-phenylthioethyl bromide gave compounds XXVIII and XXIX. Cyclization of 5-(2-chlorophenyl)-2-hydrazino-3H-thieno[2,3-*e*]-1,4-diazepine (XVIIIa) by treatment with triethyl orthoformate resulted in 4-(2-chlorophenyl)-6H-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (XIX) which could be brominated only to the 9-bromo derivative XXI; attempts at further bromination to position 2 were unsuccessful. Some contributions to the syntheses of etizolam (I) and its dechloro analogue V in the stage of intermediates are being described. Compounds XXIV–XXIX were pharmacologically tested from the point of view of discoordinating and anticonvulsant activities; they proved less active than the analogous 8-chloro-6-(2-chlorophenyl)-1-piperazino-4H-s-triazolo[4,3-*a*]-1,4-benzodiazepines.

1-Substituted derivatives of 4H-s-triazolo[4,3-*a*]-1,4-benzodiazepine represent a new class of extremely potent anxiolytics, hypnotics and anticonvulsants¹. Our recent contributions in this line related to the synthesis and activity of some 1-(alkylthio-methyl) derivatives^{2,3}, N-substituted 1-piperazino derivatives⁴ and 1-(piperazino-methyl) derivatives⁵. More recently the chemistry of analogous 9-substituted derivatives of 4-aryl-6H-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine has been developed. The most practically important results are the anxiolytic agent etizolam (I, Y-7131, Depas^R) (ref.^{6–9}), the hypnotic agent brotizolam (II, WE-941, Ladormin^R, Lendormin^R) (ref.^{10–12}) and the experimental anxiolytics ciclotizolam (III, WE-973) (ref.^{13,14}) and substance Ro 11-7800 (IV) (ref.^{15–17}). The syntheses of these compounds proceeded *via* the corresponding 5-aryl-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-ones^{18,19}, and *via* 4-aryl-4H,6H-thieno[2,3-*e*]-1,2,4-triazolo[3,4-*c*]-1,4-oxazepines^{20,21}, respectively. Starting compounds of these syntheses are the corresponding 2-amino-3-benzoylthiophenes which were obtained by making use of one of the two

Gewald's methods^{22,23}, the first of which consisting in a reaction of α -mercaptoaldehydes or α -mercaptoketones (or the respective 2,5-dihydroxy-1,4-dithianes which are their dimeric equivalents) with nitriles like cyanoacetic esters or benzoylacetonitriles²², and the second in a reaction of aldehydes or ketones with sulfur and nitriles of the mentioned type in the presence of tertiary amines (triethylamine) as catalysts²³. The present paper describes the synthesis of some new N-substituted derivatives of 2-bromo-4-(2-chlorophenyl)-9-piperazino-6H-thieno[3,2-f]-1,2,4-triazolo[4,3-a]-1,4-diazepine. This work was preceded by syntheses of compounds *I* and *V* as standards in which we attempted to apply some modified procedures in the stage of intermediates; in this way we wanted to use the results of our previous investigations^{3,24,25}.



I, $R^1 = \text{CH}_3$, $R^2 = \text{C}_2\text{H}_5$, $R^3 = \text{Cl}$

II, $R^1 = \text{CH}_3$, $R^2 = \text{Br}$, $R^3 = \text{Cl}$

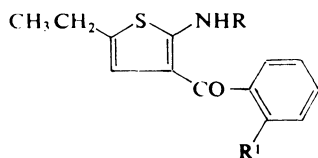
III, $R^1 = \text{—C}_6\text{H}_{10}\text{—}$, $R^2 = \text{Br}$, $R^3 = \text{Cl}$

IV, $R^1 = \text{CH}_2\text{NH}_2$, $R^2 = R^3 = \text{Cl}$

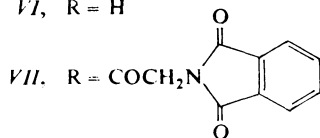
V, $R^1 = \text{CH}_3$, $R^2 = \text{C}_2\text{H}_5$, $R^3 = \text{H}$

The starting ketones *VIa* and *VIb* were prepared using the published procedures¹⁹. Benzoylacetonitrile^{26–29} has now been prepared from methyl benzoate with acetonitrile in the presence of sodium hydride in tetrahydrofuran (method³⁰) or from benzonitrile with acetonitrile in ether in the presence of sodium hydride and tert-butyl alcohol and by the following acid hydrolysis of the β -aminocinnamonnitrile formed (method³¹). 2-Chlorobenzoylacetonitrile^{31,32} was obtained from methyl 2-chlorobenzoate³³ and acetonitrile in a substantially better yield (60%) by modification of a procedure described previously²⁴. In continuing the syntheses *via* the thienodiazepinones *Xa* and *Xb* we attempted at using the Podešva's approach³⁴, used in several cases previously^{3,25}. By reactions of the amino ketones *VIa* and *VIb* with phthalimidoacetyl chloride^{35–37} in boiling chloroform we obtained in high yields the derivatives *VIIa* and *VIIb* which were subjected to hydrazinolysis in aqueous methanol or ethanol at 60°C. In the hydrazinolysis of *VIIa* about 80% of phthalylhydrazine crystallized after cooling of the methanolic solution. The remaining phthalylhydrazine was removed by extraction with aqueous ammonia and the inhomogeneous residue was separated by chromatography. After the elution of the less polar components, 7-ethyl-5-phenyl-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-one (*Xa*) was obtained in a low yield (*cf.*³⁸); its preparation by a different procedure was described¹⁹. Our product showed a lower melting point than the literature value¹⁹, but because it did not change by recrystallizations, it is considered a crystal

modification of the described substance; analytical and spectral characterization confirmed the identity of our product as being *Xa*. When repeating this preparation, we carried out the hydrazinolysis of compound *VIIa* by heating with hydrazine hydrate in aqueous ethanol to 60°C in the presence of chloroform. The inhomogeneous product obtained was characterized by thin-layer chromatography as consisting mainly of the lactam *Xa* and the noncyclized aminoacetamido ketone *VIIIa*. It was heated with a mixture of benzene, pyridine and a small quantity of acetic acid (method¹⁹). In this way, lactam *Xa* was obtained in a yield of 35%. In an attempt at the analogous hydrazinolysis of the sterically hindered phthalimido derivative *VIIb* (in aqueous ethanol at 60°C), the cyclization of the aminoacetamido ketone *VIIIb* formed did not take place at all and the attempt at crystallization of the product from acetone (*cf.*³⁸) resulted in a reaction with this solvent; the crystalline product was characterized as the ketimine *IXb*. By hydrolysis of this compound with an ethanolic solution of hydrogen chloride and by the addition of water the hydrochloride of *VIIIb* was obtained. Its decomposition with an aqueous potassium carbonate solution gave the free base *VIIIb*, which proved identical with the product, prepared by a published procedure¹⁹. The omitting of the treatment of the crude product with acetone gave the amine *VIIIb* in a yield of 83%. Its cyclization to the lactam *Xb* was then carried out by making use of the procedure described¹⁹. The Podešva's approach³⁴ in the thienodiazepine series seems to be less advantageous than in the benzodiazepine series.



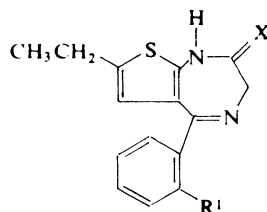
VI, $R = H$



VII, $R = COCH_2N$

VIII, $R = COCH_2NH_2$

IX, $R = COCH_2N=C(CH_3)_2$



X, $X = O$

XI, $X = S$

XII, $X = N-NH_2$

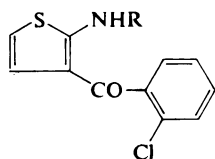
In formulae *VI*–*XII*: *a*, $R^1 = H$; *b*, $R^1 = Cl$.

The lactams *Xa* and *Xb* were then transformed to thiolactams *XIa* and *XIb* by treatment with phosphorus pentasulfide in pyridine by known procedures^{6,7}.

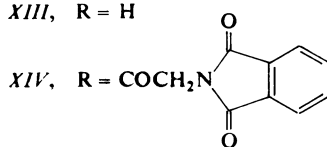
Reaction of the thiolactam *XIa* with acethydrazide³⁹ in boiling butanol and the following cyclization of the acetylhydrazine derivative afforded the compound *V*.

In the synthesis of compound *I* the thiolactam *XIb* was first transformed by a reaction with hydrazine hydrate in methanol to the hydrazine derivative *XIIb*, which was acetylated with acetic anhydride and cyclized by refluxing with a mixture of benzene and acetic acid⁶.

For the synthesis of the title compounds it was necessary to prepare 2-amino-3-(2-chlorobenzoyl)thiophene (*XIII*) (ref.¹⁸). We did verify that for the synthesis of this compound the second Gewald's method^{19,23} is of no use because by a reaction of 2-chlorobenzoylacetonitrile with acetaldehyde and sulfur in dimethylformamide and in the presence of trimethylamine *XIII* is not formed at all. It is necessary to use a modification of the first Gewald's method²² working with 2,5-dihydroxy-1,4-dithiane⁴⁰ as the dimer equivalent of mercaptoacetaldehyde. The use of this substance, prepared by the Hromatka's team⁴⁰ earlier than used by the same team^{18,41-43} in the syntheses of 2-amino-3-benzoylthiophenes, unsubstituted in positions 4 and 5, represented the solution of a problem of great practical and economical importance. Apparently for this reason, the use of 2,5-dihydroxy-1,4-dithiane in the first paper, mentioning 2-amino-3-benzoylthiophene⁴⁴, was concealed⁴⁵. Reaction of *XIII* (ref.¹⁸) with phthalimidoacetyl chloride³⁵⁻³⁷ in boiling chloroform resulted in the phthalimido derivative *XIV* in a moderate yield. Its hydrazinolysis in a mixture of methanol and chloroform at 60°C stops (due to the steric hindrance) in the stage of the aminoacetamido derivative *XV* which is obtained in a yield of 58%. This way of preparing compound *XV* is comparable — so far as the yield is concerned — with the described procedure^{10,18}.



XIII, R = H

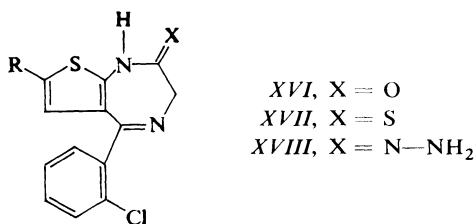


XIV, R = COCH₂N

XV, R = COCH₂NH₂

With regard to the fact that the described method¹⁸ for cyclization of compound *XV* to 5-(2-chlorophenyl)-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-one (*XVIa*) by refluxing with ethanol in the presence of a small amount of formic acid afforded only 23% of the crystalline product, we carried out the cyclization by heating with benzene and pyridine in the presence of acetic acid (method¹⁹). A mixture was obtained which was separated by chromatography on silica gel. As the less polar component, the amino ketone *XIII* was isolated in a high yield; we try to explain its formation by an intramolecular aminolysis of compound *XV*. According to this hypothesis, 2,5-dioxopiperazine should have been formed as a by-product; as a highly hydrophilic compound it could not, however, be isolated by the isolation procedure used. The desired lactam *XVIa* was obtained in a low yield from a more polar fraction

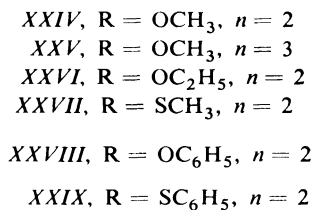
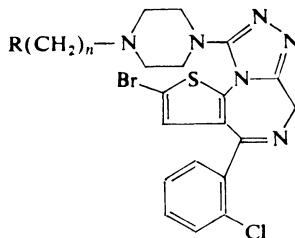
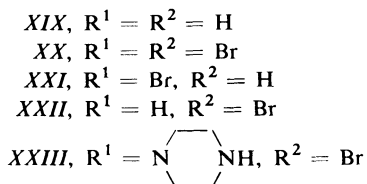
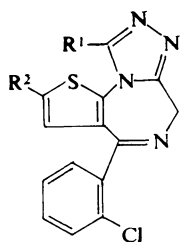
of the chromatography mentioned. Literature⁴⁶ described the cyclization of compound *XV* to the lactam *XVIa* by heating with ethanol and a small amount of acetic acid. We preferred the cyclization with boiling acetic acid without the presence of ethanol (method⁴²) and obtained the wanted compound *XVIa* in a yield of about 50%. Even in this case, the amine *XIII* was isolated in a lesser amount from the mother liquors. The lactam *XVIa* was then transformed by the published methods⁶ to the thiolactam *XVIIa* and further to the hydrazine derivative *XVIIIa*. This compound was cyclized by treatment with triethyl orthoformate in ethanol in the presence of a small amount of sulfuric acid (method⁶) and 4-(2-chlorophenyl)-6*H*-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (*XIX*), which was obtained in a high yield, was brominated (without characterization) with bromine in chloroform in the presence of pyridine in the effort to prepare the 2,9-dibromo derivative *XX*. The analysis, however, showed that the product contains only one bromine atom and it was characterized as the 9-bromo derivative *XXI*. An attempt at its further bromination under similar conditions (excess of bromine in chloroform in the presence of pyridine) did not lead to the desired result; compound *XXI* was recovered quantitatively.



In formulae *XVI*–*XVIII*: *a*, R = H; *b*, R = Br

After this unsuccessful attempt, the bromination was carried out in the stage of the lactam *XVIa* (ref.¹⁸) and the resulting bromo compound *XVib* was transformed by using modifications of known procedures¹⁰ via the thiolactam *XVIIb* to the hydrazine derivative *XVIIIb*. Its cyclization to 2-bromo-4-(2-chlorophenyl)-6*H*-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (*XXII*) (ref.^{10,21}) was carried out by a method not described so far for this case, *i.e.* by a reaction with triethyl orthoformate in ethanol in the presence of a small amount of sulfuric acid (method⁴⁷). Bromination with bromine in chloroform in the presence of pyridine²¹ afforded the 2,9-dibromo derivative *XX*. This compound was subjected to substitution reactions with an excess of 1-(2-methoxyethyl)piperazine⁴, 1-(3-methoxypropyl)piperazine⁴, 1-(2-ethoxyethyl)piperazine⁴ and 1-(2-methylthioethyl)piperazine⁴ at 160 to 165°C, in which only the more reactive atom of bromine in position 9 was substituted. Crystalline bases *XXIV*–*XXVII* were obtained in yields of 60–70%, characterized by spectra and transformed to methanesulfonates for pharmacological testing. The preparation of several different piperazine derivatives of this series has already

been described in patents^{48,49}. Using a method, described in the first of these patents⁴⁸, we prepared as an intermediate the piperazine derivative *XXIII*, which was alkylated with 2-phenoxyethyl bromide⁵⁰ and 2-phenylthioethyl bromide⁵¹ in boiling chloroform in the presence of potassium carbonate. Bases *XXVIII* and *XXIX* were obtained in high yields and used for spectral characterization, as well as for the preparation of methanesulfonates.



In the pharmacological testing of *XXIV–XXIX* (used as methanesulfonates, the doses given were calculated for bases), the substances *I* (ref.^{6–9}) and *V* (ref.⁶) were used as standards. Compound *I* in an oral dose of 1 mg/kg revealed an incomplete protective and anticonvulsant effect (with 30% animals only) in the test of electroshock in mice, in the same dose it had a full protective effect in the test of pentetrazole convulsions in mice (a dose of 0.2 mg/kg orally protects less than 50% animals), in the same dose it did not influence the locomotor activity of mice with statistical significance and in the rotarod test in mice it had only a weak discoordinating activity (ataxia with 10–20% animals). Compound *V* in an oral dose of 1 mg/kg was inactive in the electroshock test in mice, it did not inhibit significantly the locomotor activity of mice and it lacked the discoordinating effect on the rotarod in mice. In the same dose, however, it had a protective effect in 50% animals in the test of pentetrazole convulsions. Both compounds are substantially less active than triazolam².

The acute toxicity in mice on oral administration was estimated. Compounds *XXVIII* and *XXIX* in a dose of 1 g/kg are not toxic (no lethal effects). For compounds *XXIV–XXVI* the LD₅₀ values are between 200 and 400 mg/kg. Compound *XXVII* administered in doses of 0.6–1.0 g/kg causes lethality in mice without a clear dependence of the effect on the dose given. In the test of anticonvulsant

action towards electroshock in mice, compound *XXIV* was the most active one; $PD_{50} = 0.22$ mg/kg orally. It is followed by compound *XXVI* with a PD_{50} value of 0.98 mg/kg orally. The compounds *XXV*, *XXVII*–*XXIX* were inactive in this test in an oral dose of 1 mg/kg. In the rotarod test in mice, compound *XXIV* likewise was the most active one; ED_{50} approximately 1 mg/kg orally (the effect is of a relatively short duration). The same dose of compounds *XXV* and *XXVII* brings about only a brief disturbance of coordination in 30–40% animals; compounds *XXVI*, *XXVIII* and *XXIX* in the same dose are completely inactive. When compared with the analogous piperazine derivatives of the 4*H*-s-triazolo[4,3-*a*]-1,4-benzodiazepine series⁴, the compounds described in this communication are less active. Only compound *XXIV* has an anticonvulsant activity towards electroshock which is approximately comparable with that of the benzo analogue⁴.

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 or at room temperature. The UV spectra (in methanol) were recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol) with a Unicam SP 200G spectrophotometer, the 1H NMR spectra (in C^2HCl_3) with a Tesla BS 487C (80 MHz) spectrometer and the mass spectra with MCH-1320, Varian MAT 44S and Varian MAT 311 spectrometers. The homogeneity of the compounds and composition of the mixtures were checked by chromatography on thin layers of silica gel (Silufol).

Benzoylacetonitrile

A) A refluxing mixture of 650 ml tetrahydrofuran, 32.6 g NaH and 150 g methyl benzoate was stirred and treated over 10 min dropwise with a solution of 45.2 g acetonitrile in 130 ml tetrahydrofuran. The mixture was refluxed for 2.5 h, diluted after cooling with 1 800 ml ether and after standing for 48 h the separated sodium salt of the enol derivative was filtered and washed with ether. It was dissolved in 400 ml water, the solution was acidified with 1 : 1 dilute hydrochloric acid and the product was extracted with a 3 : 1 mixture of ether and benzene. The extract was washed with a saturated solution of $NaHCO_3$, dried with Na_2SO_4 and evaporated. The crude product (91 g, 57%) was crystallized from a mixture of 25 ml light petroleum, 75 ml benzene and 10 ml ethanol; 60.4 g (38%) pure product, m.p. 80–81°C. Lit.²⁹, m.p. 80–81°C.

B) A stirred and refluxing suspension of 18 g NaH in 400 ml ether was treated dropwise with a solution of 4.5 g tert-butyl alcohol in 30 ml ether, then with 61.8 g benzonitrile and finally with 24.6 g acetonitrile. The mixture was stirred and refluxed for 7 h, allowed to stand overnight in a refrigerator, the precipitated sodium salt was filtered, washed with ether, dissolved in 500 ml ethanol, the solution was treated with 200 ml hydrochloric acid and kept for 30 min at room temperature. It was then diluted with 1.5 l water and extracted with ether. The extract was dried ($MgSO_4$) and evaporated; 53 g (65%), m.p. 78–80°C (light petroleum–benzene–ethanol). The product is identical with the substance obtained under *A*.

2-Chlorobenzoylacetonitrile

A suspension of 29.7 g NaH (80% suspension in oil) in 650 ml tetrahydrofuran was stirred and treated over 10 min dropwise with 153.5 g methyl 2-chlorobenzoate³³. The refluxing mixture

was then treated over 20 min with a solution of 37.0 g acetonitrile in 130 ml tetrahydrofuran and the refluxing was continued for 2.5 h. After cooling to 20°C it was diluted with 1.5 l ether and the mixture was kept overnight in a refrigerator. The precipitated salt of the enol derivative was filtered, washed with ether and dissolved in 400 ml water. The solution was acidified with 1 : 1 dilute hydrochloric acid and extracted with dichloromethane. The extract was washed with a saturated NaHCO_3 solution, dried with Na_2SO_4 , treated with 5 g charcoal and filtered through a 5 mm layer of Al_2O_3 . The filtrate was evaporated *in vacuo*, the residue was dissolved in 70 ml benzene, the solution was treated with 50 ml warm hexane and the mixture cooled under shaking. Further 50 ml hexane were added and the mixture kept overnight in a refrigerator. The product was filtered, washed with hexane and dried at room temperature *in vacuo*; 97.5 g (60%), m.p. 57–58°C. Lit.^{24,32}, m.p. 59–60°C, and 56–57°C, respectively.

3-Benzoyl-5-ethyl-2-(phthalimidoacetamido)thiophene (VIIa)

A mixture of 24.7 g *VIa* (ref.¹⁹), 24.1 g phthalimidoacetyl chloride^{35–37} and 110 ml chloroform was refluxed for 5 h. After cooling, about 50 ml chloroform were evaporated *in vacuo* and the residue was poured into 300 ml boiling ethanol. The mixture was cooled for 2 h, the product was filtered, washed with ethanol and dried *in vacuo*; 38.1 g (85%), m.p. 177–178°C. Analytical sample, m.p. 178.5–179.5°C (1 : 3 chloroform–ethanol). UV spectrum: λ_{max} 238 nm ($\log \epsilon$ 4.36), 349 nm (3.96), inflexes at 230 nm (4.41), 250 nm (4.26) and 265 nm (4.20). IR spectrum: 700, 740 (5 and 4 adjacent Ar—H), 1 528, 1 700 (CONH), 1 614 (ArCOAr' in a H bond), 1 715, 1 771 (CONCO), 3 190 cm^{-1} (NH). ^1H NMR spectrum: δ 12.25 (bs, 1 H, NH), 7.25–7.90 (m, 9 H, benzene ArH), 6.65 (bs, 1 H, thiophene 4-H), 4.62 (s, 2 H, COCH_2N), 2.65 (bq, $J = 7.0$ Hz, 2 H, CH_2 of ethyl), 1.18 (t, $J = 7.0$ Hz, 3 H, CH_3 of ethyl). For $\text{C}_{23}\text{H}_{18}\text{N}_2\text{O}_4\text{S}$ (418.5) calculated: 66.01% C, 4.34% H, 6.69% N, 7.66% S; found: 66.08% C, 4.62% H, 6.82% N, 7.90% S.

3-(-2Chlorobenzoyl)-5-ethyl-2-(phthalimidoacetamido)thiophene (VIIb)

A mixture of 22.6 g *VIb* (ref.¹⁹), 19.2 g phthalimidoacetyl chloride^{35–37} and 110 ml chloroform was refluxed for 5 h. Charcoal (5 g) was added and the mixture was allowed to stand overnight at room temperature. After filtration the solution was evaporated *in vacuo*, the residue was dissolved in 50 ml boiling chloroform and the solution poured into 250 ml ethanol which was heated to 60°C. After cooling for 3 h in a refrigerator, the product was filtered, washed with 50 ml cold ethanol and dried *in vacuo*; 33.9 g (88%), m.p. 198–199°C. Analytical sample, m.p. 199.5 to 200.5°C (1 : 3 chloroform–ethanol). UV spectrum: λ_{max} 265 nm ($\log \epsilon$ 4.07), 274 nm (4.09), 348 nm (4.01), inflexes at 230 nm (4.47), 238 nm (4.42). IR spectrum: 759 (4 adjacent Ar—H), 1 534, 1 701 (CONH), 1 601 (ArCOAr' in a H bond), 1 723, 1 779 (CONCO), 3 190 cm^{-1} (NH). ^1H NMR spectrum: δ 12.15 (bs, 1 H, NH), c . 7.75 (m, 4 H, 4 ArH of phthalimido), c . 7.30 (m, 4 H, 4 ArH of chlorobenzoyl), 6.30 (bs, 1 H, thiophene 4-H), 4.65 (s, 2 H, COCH_2N), 2.60 (bq, $J = 7.0$ Hz, 2 H, CH_2 of ethyl), 1.15 (t, $J = 7.0$ Hz, 3 H, CH_3 of ethyl). For $\text{C}_{23}\text{H}_{17}\text{ClN}_2\text{O}_4\text{S}$ (452.9) calculated: 60.99% C, 3.78% H, 7.83% Cl, 6.19% N, 7.08% S; found: 61.29% C, 4.09% H, 8.06% Cl, 6.33% N, 7.35% S.

7-Ethyl-5-phenyl-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-one (Xa)

A) A stirred suspension of 42.8 g *VIIa* in 850 ml methanol was treated over 5 min with 37 ml 18% aqueous N_2H_4 . The mixture was stirred and heated to 60°C for 3 h, then allowed to stand overnight at room temperature and the precipitated phthalylhydrazine (21.6 g, 79%) was filtered off. The filtrate was evaporated *in vacuo*, the residue was stirred with 250 ml 10% aqueous NH_3 ,

the aqueous layer was separated by decantation and the organic material was dissolved in 400 ml chloroform. The solution was washed with water, dried with MgSO_4 , filtered with charcoal and evaporated *in vacuo*. The residue was chromatographed on a column of 650 g neutral Al_2O_3 (activity II). Benzene eluted 8.5 g less polar components which were discarded. Mixture of benzene with 2% ethanol, then 5% ethanol and finally 10% acetone eluted 15.3 g of more polar components from which after treatment with 20 ml acetone there crystallized 3.5 g (13%) *Xa*, m.p. 183–185°C. Analytical sample, m.p. 185.5–186.5°C (cyclohexane–toluene). IR spectrum: 700, 710, 725, 777 (5 adjacent Ar—H), 1495, 1553, 1572, 1592, 3005, 3030, 3040 (Ar), 1686 (CO of lactam), inflexes at 2560 and 3080 cm^{-1} (NH). ^1H NMR spectrum: δ 10.20 (a flat band, 1 H, NH), 7.10–7.70 (m, 5 H, C_6H_5), 6.38 (d, $J = 1.5$ Hz, 1 H, thiophene 4-H), 4.32 (s, 2 H, COCH_2N), 2.62 (bq, $J = 7.0$ Hz, 2 H, CH_2 of ethyl), 1.15 (t, $J = 7.0$ Hz, 3 H, CH_3 of ethyl). For $\text{C}_{15}\text{H}_{14}\cdot\text{N}_2\text{OS}$ (270.4) calculated: 66.64% C, 5.22% H, 10.63% N, 11.86% S; found: 66.90% C, 5.37% H, 10.36% N, 12.20% S. Lit.¹⁹, m.p. 194–195°C.

B) A suspension of 63.9 g *VIIa* in a mixture of 1750 ml ethanol and 300 ml chloroform was slowly treated under stirring with 36.6 ml 18% aqueous N_2H_4 , the mixture was heated to 60°C and stirred for 4 h at this temperature. After standing overnight in a refrigerator, the precipitated phthalylhydrazine (18.3 g, 75%) was filtered off and the filtrate was evaporated *in vacuo*. The residue was shown by TLC to consist mainly of *VIIIa* and *Xa*. It was added to a mixture of 100 ml benzene, 250 ml pyridine and 9.3 g acetic acid and the mixture was refluxed for 7 h with separating the water cleaved by distillation with the benzene vapour (1.8 ml). After cooling the solvents were evaporated *in vacuo*, the residue was diluted with 70 ml toluene which was then evaporated (repeated once more), the residue was treated with 150 ml saturated NaHCO_3 and the product was extracted with chloroform. The extract was dried with Na_2SO_4 , filtered with charcoal and evaporated *in vacuo*. The residue was dissolved in 100 ml toluene and the product precipitated by the addition of light petroleum. It was separated by decantation, dissolved in 80 ml toluene, the solution boiled with charcoal, filtered while hot and the filtrate was allowed to crystallize by standing in a refrigerator; 14.4 g (35%) *Xa*, m.p. 188–189.5°C. Crystallization from toluene gave now the product melting at 194–195.5°C, i.e., the modification described in the literature¹⁹.

3-(2-Chlorobenzoyl)-5-ethyl-2-(isopropylideneaminoacetamido)thiophene (*IXb*)

A suspension of 13.6 g *VIIb* in a mixture of 330 ml ethanol and 60 ml chloroform was stirred and treated over 10 min with 8 ml 18% aqueous N_2H_4 . The mixture was stirred for 3 h at 60°C and then cooled for 2 h in a refrigerator. There crystallized 3.7 g (76%) phthalylhydrazine (m.p. 340–343°C) which was filtered off. The filtrate was evaporated *in vacuo* and the residue was treated with 50 ml acetone. A reaction took place. The mixture was poured into 500 ml water and the precipitated semisolid product was extracted with benzene. Processing of the extract gave 13.3 g crude product which was crystallized from toluene; 7.6 g (70%) *IXb*, m.p. 136 to 138°C. Mass spectrum, m/z : 362 (M^+ corresponding to $\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}_2\text{S}$). UV spectrum: λ_{max} 239 nm ($\log \epsilon$ 3.92), 265 nm (3.71), 350 nm (3.66), infl. 271 nm (3.70). IR spectrum: 737, 759 (4 adjacent Ar—H), 1512, 1671 (CONH), 1620 (ArCOAr' in a H bond), 1691 (C=N), 3035 (Ar), 3165 cm^{-1} (NH). For $\text{C}_{18}\text{H}_{19}\text{ClN}_2\text{O}_2\text{S}$ (362.9) calculated: 59.58% C, 5.28% H, 9.77% Cl, 7.72% N, 8.84% S; found: 60.10% C, 5.19% H, 9.69% Cl, 7.92% N, 8.40% S.

2-(Aminoacetamido)-3-(2-chlorobenzoyl)-5-ethylthiophene (*VIIIb*)

A) *IXb* (2.4 g) was treated with 10 ml ethanol saturated with HCl. The solution formed was diluted with 10 ml water. There crystallized immediately 1.9 g (80%) hydrochloride of *VIIIb*, m.p. 197–200°C. Analytical sample, m.p. 200–203°C (90% ethanol). Mass spectrum, m/z (%): 322 (M^+ corresponding to $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_2\text{S}$, 15%), 305 (14), 289 (80), 265 (67), 250 (100),

230 (22), 214 (13), 138 (93), 111 (66). UV spectrum: $\lambda_{\max}$ 236 nm ($\log \epsilon$ 4.19), 265 nm (4.03), 272 nm (4.02), 248 nm (3.93). IR spectrum: 739, 750 (4 adjacent Ar—H), 897 (solitary thiophene Ar—H), 1 530, 1 650 (CONH), 1 670 (ArCOAr'), 2 570, 2 695, 2 745 (NH^+), 3 023 (Ar), 3 120 cm^{-1} (NH). For $\text{C}_{15}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_2\text{S}$ (359.3) calculated: 50.15% C, 4.49% H, 19.74% Cl, 7.80% N, 8.92% S; found: 50.18% C, 4.34% H, 19.92% Cl, 7.94% N, 9.35% S.

The hydrochloride (2.4 g) was dissolved in 100 ml water and the solution was decomposed with an excess of saturated NaHCO_3 . The base *VIIIb* was isolated by extraction with chloroform, m.p. 147.5–149.5°C (ethanol). UV spectrum: $\lambda_{\max}$ 237 nm ($\log \epsilon$ 4.21), 269 nm (4.04), 273 nm (4.04), 349 nm (3.94). IR spectrum: 773 (4 adjacent Ar—H), 1 234 (C—O of ketone), 1 510, 1 674 (CONH), 1 590 (Ar), 1 621 (ArCOAr' in a H bond), 3 180, 3 310, 3 372 cm^{-1} (NH, NH_2). ^1H NMR spectrum: δ 7.20–7.80 (m, 4 H, ArH of chlorobenzoyl), 6.34 (d, $J = 1.0$ Hz, 1 H, thiophene 4-H), 3.63 (s, 2 H, COCH_2N), 2.68 (q, $J = 7.0$; 1.0 Hz, 2 H, CH_2 of ethyl), 1.70 (bs, 2 H, NH_2), 1.22 (t, $J = 7.0$ Hz, 3 H, CH_3 of ethyl). Lit.¹⁹, m.p. 148–149°C.

B) A mixture of 22.6 g *VIIb*, 580 ml ethanol, 100 ml chloroform and 12 ml 18% aqueous N_2H_4 was stirred for 4 at 60°C. The mixture was allowed to stand overnight in a refrigerator, the precipitated phthalylhydrazine was filtered off and the filtrate was evaporated *in vacuo*. The residue was extracted with 75 ml boiling ethanol, the undissolved rest of phthalylhydrazine was filtered off, the filtrate was cooled and gave by crystallization 12.7 g (83%) *VIIIb*, m.p. 146 to 147°C. Lit.¹⁹, m.p. 148–149°C.

3-(2-Chlorobenzoyl)-2-(phthalimidoacetamido)thiophene (*XIV*)

A solution of 94.3 g *XIII* (ref.¹⁸) in 525 ml chloroform was stirred and treated over 5 min with 88.0 g phthalimidoacetyl chloride^{35–37}, slowly heated to the boiling point and refluxed for 2 h. After standing overnight, 45 g polymeric substance (insoluble in the common solvents) were removed by filtration, the solution was filtered through a column of 60 g Al_2O_3 , evaporated to a volume of about 220 ml and diluted with 160 ml ethanol. After standing for 2 days at room temperature the product was filtered and the mother liquor was processed in the usual way; 72.4 g (43%), m.p. 187–197°C. Analytical sample, m.p. 197–200°C (chloroform–ethanol). UV spectrum: $\lambda_{\max}$ 240 nm ($\log \epsilon$ 4.45), 274 nm (4.00), 340 nm (4.00), infl. 231 nm (4.50). IR spectrum: 753 (4 adjacent Ar—H), 852 (2 adjacent thiophene Ar—H), 1 494, 1 580 (Ar), 1 538, 1 700 (CONH), 1 609 (ArCOAr' in a H bond), 1 715, 1 773 (CONCO), 3 110, 3 205 cm^{-1} (NH). For $\text{C}_{21}\text{H}_{13}\text{ClN}_2\text{O}_4\text{S}$ (424.9) calculated: 59.37% C, 3.08% H, 8.35% Cl, 6.59% N, 7.55% S; found: 59.85% C, 3.09% H, 8.69% Cl, 6.62% N, 7.60% S.

2-(Aminoacetamido)-2-(2-chlorobenzoyl)thiophene (*XV*)

A solution of 105.7 g *XIV* in a mixture of 2.1 l methanol and 330 ml chloroform was stirred and treated at 45°C over 10 min with a solution of 24.8 g 100% $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ in 110 ml water and the mixture was stirred for 1.5 h at 60°C. After standing overnight the precipitated phthalylhydrazine was filtered off and the filtrate was evaporated *in vacuo*. The residue was extracted twice with 750 ml dilute aqueous ammonia, the product was filtered off, dissolved in 250 ml chloroform and the solution filtered through a column of 150 g neutral Al_2O_3 (activity II). The filtrate was evaporated *in vacuo* and the residue crystallized from 210 ml ethanol; 42.2 g (58%), m.p. 159–161°C. Lit.^{10,18}, m.p. 158–160°C.

5-(2-Chlorophenyl)-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-one (*XVIIa*)

A) A mixture of 42.2 g *XV*, 90 ml benzene, 260 ml pyridine and 8.4 ml acetic acid was stirred and refluxed for 5.5 h with continual separation of the water cleaved by azeotropic distillation

(4.9 ml water separated). A part of the solvents (150 ml) was then distilled off under normal pressure and the rest was evaporated *in vacuo*. The residue was dissolved in 200 ml dichloromethane, the solution was washed with 250 ml saturated aqueous NaHCO_3 , dried with K_2CO_3 and evaporated. The residue was chromatographed on a column of 300 g silica gel. Benzene eluted first 13.4 g of the least polar component (m.p. 120–123°C) which was not identified. It was followed (elution with benzene) by 14.8 g (44%) 2-amino-3-(2-chlorobenzoyl)thiophene (*XIII*), m.p. 137–139°C (benzene–hexane). Lit.¹⁸, m.p. 139–141°C. The mixed melting point with an authentic sample¹⁸ was without depression and the TLC behaviour of both samples was identical. The chromatography was continued by elution with benzene containing 10% chloroform. This led to elution of 7.4 g of a further substance (m.p. 247.5–248.5°C) which was not identified. Chloroform eluted then 16.2 g oil which was diluted with 20 ml ethanol and allowed to crystallize; 5.1 g (13%) *XVIa*, m.p. 227–229°C (ethanol). Lit.¹⁸, m.p. 222.5–224.5°C.

B) A solution of 54 g *XV* in 1 050 ml acetic acid was refluxed for 15 min, cooled, evaporated *in vacuo* and the residue was dissolved in 800 ml benzene. By shaking with 500 ml 1.5% hydrochloric acid the product was transferred into the aqueous layer which was washed with benzene, filtered and treated with 750 ml 8.5% NaHCO_3 . The precipitate was filtered, washed with water and dried *in vacuo*; 31.3 g, m.p. 218–227°C. Crystallization from 300 ml ethanol and processing of the mother liquor gave 24.8 g (49%) pure *XVIa*, m.p. 228–230°C. Chromatography of the residue (after the first mother liquor) gave small amounts of *XIII* (m.p. 140–141°C) and of the substance melting at 120–123°C.

9-Bromo-4-(2-chlorophenyl)-6H-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (*XXI*)

A suspension of 2.1 g *XVIIIa* (ref.⁶) in 60 ml ethanol was stirred and treated with 4.7 g triethyl orthoformate and then dropwise with 0.5 ml H_2SO_4 and the stirring at room temperature was continued for 30 min. It was then neutralized with a solution of 3.0 g NaHCO_3 in 30 ml water, ethanol was partly evaporated *in vacuo*, the residue was diluted with 100 ml water and the product was extracted with dichloromethane. The extract was washed with water, dried with MgSO_4 , evaporated to a volume of 30 ml and chromatographed on 20 g silica gel. Elution with dichloromethane removed some less polar components and chloroform containing 2% methanol eluted crude *XIX* which was crystallized from ethanol–ether; 2.3 g (97%), m.p. 196–199°C. It was dissolved in 30 ml chloroform, the solution was treated with 1.89 g pyridine and then under stirring over 30 min with a solution of 3.06 g Br_2 in 30 ml chloroform at room temperature. The mixture was stirred for 3 h at room temperature, washed with 30 ml 2% aqueous ammonia and evaporated *in vacuo*. The residue was chromatographed on 50 g silica gel. Elution with chloroform gave 2.4 g (68%) homogeneous *XXI*, m.p. 205–206°C (ethanol–chloroform). ^1H NMR spectrum: δ 7.35–7.60 (m, 4 H, ArH of chlorophenyl), 7.30 (d, $J = 5.5$ Hz, 1 H, 2-H), 6.79 (d, $J = 5.5$ Hz, 1 H, 3-H), 5.02 (s, 2 H, 6,6- H_2). For $\text{C}_{14}\text{H}_8\text{BrClN}_4\text{S}$ (379.7) calculated: 44.29% C, 2.12% H, 21.05% Br, 9.34% Cl, 14.76% N; found: 44.17% C, 2.13% H, 20.95% Br, 9.30% Cl, 15.02% N.

7-Bromo-5-(2-chlorophenyl)-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-one (*XVIIb*)

A suspension of 33.2 g *XXVIa* in 350 ml chloroform was stirred and treated with 10.4 g pyridine and then at 20–24°C over 75 min with a solution of 21.1 g Br_2 in 250 ml chloroform. The stirring was continued for 2.5 h and the mixture was treated with a solution of 25 g NaHCO_3 in 300 ml water. It was stirred for 15 min, the crystalline product was filtered, washed with water, ethanol and hexane, and dried; 36.6 g (86%), m.p. 246.5–249°C with decomposition. Crystallization from ethanol gave a product melting at 248–250°C with decomposition. Lit.¹⁸, m.p. 248°C.

7-Bromo-5-(2-chlorophenyl)-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-thione (*XVIIb*)

A mixture of 84.8 g *XVIb*, 24.9 g P_2S_5 and 800 ml pyridine was stirred and heated under nitrogen for 2.5 h to 70–75°C. After cooling to 20°C the mixture was poured into a stirred solution of 400 g NaCl in 1.2 l water (cooled to 2°C), stirred for 2 h, the precipitate was filtered, washed with 3 l water, 100 ml ethanol, 50 ml benzene, and finally with 50 ml hexane, and dried *in vacuo*; 75.3 g (85%) crude *XVIIb*, m.p. 212–217°C, which was used in this state for further work. Lit.¹⁰, m.p. 214°C.

7-Bromo-5-(2-chlorophenyl)-2-hydrazino-1,3-dihydrothieno[2,3-*e*]-1,4-diazepin-2-one (*XVIIIb*)

A mixture of 75.3 g crude *XVIIb* and 1 l methanol was treated with 35.5 g 100% $N_2H_4 \cdot H_2O$, the mixture was stirred at room temperature for 3.5 h, allowed to stand overnight, the precipitate was filtered, washed with water, ethanol and hexane, and dried *in vacuo*; 54.5 g (73%) crude *XVIIIb* which does not melt until 300°C. It was used for further work without purification. Lit.¹⁰, m.p. over 300°C.

2-Bromo-4-(2-chlorophenyl)-6*H*-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (*XXII*)

A suspension of 54.5 g *XVIIIb* in 1.5 l ethanol was treated with 76.6 g triethyl orthoformate and then under stirring over 15 min with 16.2 ml H_2SO_4 , added dropwise. The solution formed was stirred for 2 h at room temperature and then neutralized with a solution of 55 g $NaHCO_3$ in 600 ml water. After stirring for 30 min the mixture was allowed to stand overnight, evaporated *in vacuo* to a volume of 900 ml, diluted with 1.2 l water and extracted several times with chloroform. The extract was washed with water, dried with $MgSO_4-Na_2SO_4$, filtered and evaporated *in vacuo*. The residue was dissolved in a mixture of 150 ml chloroform and 150 ml benzene and chromatographed on 280 g silica gel. A 1 : 1 mixture of benzene and chloroform removed least polar compounds; chloroform, and finally chloroform containing 2% methanol eluted 55.5 g (99%) homogeneous *XXI*, m.p. 214–216°C, which was used for further work without purification. Crystallization of a sample from ethanol gave a substance melting at 215.5–217°C. Lit.^{10,21}, m.p. 211–213°C, and 216–218°C, respectively.

2-Bromo-4-(2-chlorophenyl)-9-[4-(2-methoxyethyl)piperazino]-6*H*-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (*XXIV*)

A mixture of 7.7 g *XX* (ref.²¹) and 7.3 g 1-(2-methoxyethyl)piperazine⁴ was stirred and heated for 2 h under nitrogen to 160–165°C. After cooling the mixture was dissolved in 100 ml dichloromethane, the solution was washed with 5% aqueous NH_3 and water, the base was transferred by shaking into 5% hydrochloric acid, the aqueous solution was made alkaline with aqueous NH_3 and the base was extracted with dichloromethane. The extract was washed with water, dried (K_2CO_3) and evaporated *in vacuo*. The residue (11.9 g) was chromatographed on 50 g silica gel. Elution with chloroform and chloroform containing 1% methanol gave in the first fractions 5.55 g (63%) homogeneous *XXIV*, m.p. 204–206°C. Analytical sample, m.p. 205–207°C (ethanol). UV spectrum: λ_{max} 300 nm (log ϵ 3.58), infl. 241 nm (4.30). IR spectrum: 744, 762 (4 adjacent benzene Ar—H), 1125 (R—O—R'), 1531, 1560, 1591 (Ar), 1610 cm^{-1} (C=N in conjugation). ¹H NMR spectrum: δ 7.35 (m, 4 H, ArH of chlorophenyl), 6.60 (s, 1 H, 3-H), 4.85 (s, 2 H, 6,6-H₂), 3.55 (t, $J = 6.0$ Hz, 2 H, OCH₂), 3.38 (s, 3 H, OCH₃), 3.25 (m, 4 H, CH₂N¹CH₂ of piperazine), 2.70 (m, 6 H, remaining 3 NCH₂). For $C_{21}H_{22}BrClN_6OS$ (521.9) calculated: 48.33% C, 4.25% H, 15.31% Br, 6.79% Cl, 16.10% N, 6.14% S; found: 48.51% C, 4.27% H, 14.73% Br, 6.59% Cl, 15.80% N, 6.31% S.

Methanesulfonate, m.p. 238–240°C (ethanol). Mass spectrum, m/z : 520.0421 (M^+ corresponding to $C_{21}H_{22}BrClN_6OS$, calculated: 520.0449). For $C_{22}H_{26}BrClN_6O_4S_2$ (618.0) calculated: 42.76% C, 4.24% H, 12.93% Br, 5.74% Cl, 13.60% N, 10.38% S; found: 42.85% C, 4.24% H, 12.89% Br, 5.72% Cl, 13.30% N, 10.34% S.

2-Bromo-4-(2-chlorophenyl)-9-[4-(3-methoxypropyl)piperazino]-6*H*-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (XXV)

A mixture of 8.9 g XX (ref.²¹) and 9.2 g 1-(3-methoxypropyl)piperazine⁴ was processed similarly like in the preceding case. The crude product (11.9 g) was dissolved in 50 ml chloroform and the solution was decolorized and made free of the starting materials by filtration through a column of 50 g silica gel. The column was washed with 250 ml chloroform and 750 ml chloroform containing 2% methanol. The combined filtrates were evaporated *in vacuo* and the residue was crystallized from 120 ml ethanol; 6.1 g (59%) XXV, m.p. 213–215°C. Analytical sample, m.p. 214–216°C (ethanol). UV spectrum: inflexes at 240 nm ($\log \epsilon$ 4.30), and 300 nm (3.56). IR spectrum: 733, 741, 757 (4 adjacent Ar—H), 1 125, 1 140 (R—O—R'), 1 472, 1 528, 1 590, 3 050, 3 069 (Ar), 1 610 (N=C—Ar), 2 725, 2 810 cm^{-1} (ROCH₃, CH₂—N). ¹H NMR spectrum: δ c. 7.35 (m, 4 H, ArH of chlorophenyl), 6.58 (s, 1 H, 3-H), 4.82 (s, 2 H, 6,6-H₂), 3.40 (t, J = 6.0 Hz, 2 H, OCH₂), 3.31 (s, 3 H, OCH₃), 3.20 (bm, 4 H, CH₂N¹CH₂ of piperazine), 2.60 (bm, 4 H, CH₂N⁴CH₂ of piperazine), 2.50 (t, J = 6.0 Hz, 2 H, CH₂N in the chain), 1.75 (m, 2 H, CH₂ in the middle of the propane chain). For $C_{22}H_{24}BrClN_6OS$ (535.9) calculated: 49.31% C, 4.51% H, 14.91% Br, 6.62% Cl, 15.68% N, 5.98% S; found: 49.57% C, 4.62% H, 14.98% Br, 6.69% Cl, 16.03% N, 6.12% S.

Methanesulfonate, m.p. 227–229°C (ethanol–ether). For $C_{23}H_{28}BrClN_6O_4S_2$ (632.0) calculated: 43.71% C, 4.47% H, 12.64% Br, 5.61% Cl, 13.30% N, 10.15% S; found: 43.77% C, 4.55% H, 12.72% Br, 5.64% Cl, 13.40% N, 10.30% S.

Methanesulfonate monohydrate, m.p. 210–215°C (98% ethanol). For $C_{23}H_{28}BrClN_6O_4S_2 + H_2O$ (650.1) calculated: 42.50% C, 4.65% H, 12.29% Br, 5.45% Cl, 12.93% N, 9.87% S; found: 42.38% C, 4.52% H, 12.38% Br, 4.49% Cl, 12.81% N, 9.85% S.

2-Bromo-4-(2-chlorophenyl)-9-[4-(2-ethoxyethyl)piperazino]-6*H*-thieno[3,2-*f*]-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (XXVI)

A mixture of 6.9 g XX (ref.²¹) and 7.1 g 1-(2-ethoxyethyl)piperazine⁴ was processed similarly like in the preceding case; 5.3 g (66%), m.p. 183–187°C. Analytical sample, m.p. 188–190°C (ethanol). Mass spectrum, m/z : 534 (M^+ corresponding to $C_{22}H_{24}BrClN_6OS$, 1%). UV spectrum: λ_{max} 242 nm ($\log \epsilon$ 4.33), 300 nm (3.57). IR spectrum: 745, 760 (4 adjacent Ar—H), 1 115, 1 138 (R—O—R'), 1 480, 1 530, 1 550, 1 596, 3 070 (Ar), 1 615 cm^{-1} (N=C—Ar). ¹H NMR spectrum: δ 7.40 (m, 4 H, ArH of chlorophenyl), 6.63 (s, 1 H, 3-H), 4.88 (s, 2 H, 6,6-H₂), 3.61 (t, J = 6.0 Hz, 2 H, OCH₂ of aminoethoxy), 3.52 (q, J = 7.0 Hz, 2 H, OCH₂ in ethoxyl), 3.25 (bs, 4 H, CH₂N¹CH₂ of piperazine), 2.70 (bm, 6 H, remaining 3 CH₂N), 1.24 (t, J = 7.0 Hz, 3 H, CH₃ in ethoxyl). For $C_{22}H_{24}BrClN_6OS$ (535.9) calculated: 49.31% C, 4.51% H, 14.91% Br, 6.62% Cl, 15.68% N, 5.98% S; found: 49.40% C, 4.65% H, 14.99% Br, 6.65% Cl, 16.03% N, 6.00% S.

Dimethanesulfonate, m.p. 213–216°C (ethanol). For $C_{24}H_{32}BrClN_6O_7S_3$ (728.1) calculated: 39.59% C, 4.43% H, 10.98% Br, 4.87% Cl, 11.54% N, 13.21% S; found: 39.12% C, 4.46% H, 10.99% Br, 4.88% Cl, 11.52% N, 13.20% S.

2-Bromo-4-(2-chlorophenyl)-9-[4-(2-methylthioethyl)piperazino]-6*H*-thieno[3,2-*f*]-
-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (XXVII)

A mixture of 6.9 g XX (ref.²¹) and 7.2 g 1-(2-methylthioethyl)piperazine⁴ was processed like in the preceding cases. The crude basic product (9.8 g) was chromatographed on a column of 50 g silica gel. Fractions obtained by elution with chloroform and chloroform containing 1% methanol were combined (6.4 g) and crystallized from a mixture of 120 ml ethanol and 30 ml chloroform; 5.6 g (69%), m.p. 240–242°C. Analytical sample, m.p. 245–248°C (ethanol–chloroform). UV spectrum: $\lambda_{\max}$ 300 nm (log ϵ 3.58), infl. 240 nm (4.29). IR spectrum: 746, 767 (4 adjacent Ar–H), 1530, 1550, 1590 (Ar), 1620 cm^{-1} (N=C–Ar). ¹H NMR spectrum: δ 7.10 (m, 4 H, ArH of chlorophenyl), 6.38 (s, 1 H, 3-H), 4.60 (s, 2 H, 6,6-H₂), 3.00 (m, 4 H, CH₂·N¹CH₂ of piperazine), 2.40 (bs, 8 H, remaining 3 CH₂N and CH₂S), 1.90 (s, 3 H, SCH₃). For C₂₁H₂₂BrClN₆S₂ (538.0) calculated: 46.89% C, 4.12% H, 14.86% Br, 6.59% Cl, 15.62% N, 11.92% S; found: 46.96% C, 4.24% H, 15.10% Br, 6.75% Cl, 15.13% N, 11.91% S.

Methanesulfonate, solvate with ethanol, m.p. 248–250°C (ethanol–ether). For C₂₂H₂₆·BrClN₆O₃S₃ + C₂H₆O (680.1) calculated: 42.38% C, 4.74% H, 11.75% Br, 5.21% Cl, 12.36% N, 14.14% S; found: 42.20% C, 4.54% H, 12.17% Br, 5.40% Cl, 12.51% N, 14.17% S.

2-Bromo-4-(2-chlorophenyl)-9-[4-(2-phenoxyethyl)piperazino]-6*H*-thieno[3,2-*f*]-
-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (XXVIII)

A mixture of 3.4 g XXIII (ref.⁴⁸), 2.6 g 2-phenoxyethyl bromide⁵⁰, 2.5 g K₂CO₃ and 10 ml chloroform was stirred and refluxed under nitrogen for 15 h. After standing overnight it was poured into 100 ml water and extracted with chloroform. The extract was washed with water, dried with K₂CO₃ and evaporated. The residue was chromatographed on a column of 150 g silica gel. Elution with benzene and chloroform removed the less polar components and chloroform containing 1–3% methanol eluted 3.5 g (83%) homogeneous XXVIII, m.p. 204–206°C. Analytical sample, m.p. 206–208°C (ethanol–chloroform). For C₂₆H₂₄BrClN₆OS (584.0) calculated: 53.48% C, 4.14% H, 6.07% Cl, 14.39% N, 5.49% S; found: 52.75% C, 4.23% H, 6.50% Cl, 13.74% N, 5.58% S.

Methanesulfonate monohydrate, m.p. 213.5–215.5°C (ethanol–ether). Mass spectrum, m/z : 582 (M⁺ corresponding to C₂₆H₂₄BrClN₆OS). For C₂₇H₂₈BrClN₆O₃S₂ + H₂O (698.1) calculated: 46.46% C, 4.33% H, 11.45% Br, 5.08% Cl, 12.04% N, 9.19% S; found: 46.18% C, 4.10% H, 11.65% Br, 5.18% Cl, 11.58% N, 9.47% S.

2-Bromo-4-(2-chlorophenyl)-9-[4-(2-phenylthioethyl)piperazino]-6*H*-thieno[3,2-*f*]-
-1,2,4-triazolo[4,3-*a*]-1,4-diazepine (XXIX)

A mixture of 3.5 g XXIII (ref.⁴⁸), 2.9 g 2-phenylthioethyl bromide⁵¹, 2.6 g K₂CO₃ and 10 ml chloroform was processed similarly like in the preceding case. The crude product (5.1 g) was chromatographed on 150 g silica gel. After removal of the less polar components by elution with a mixture of benzene and chloroform and by chloroform, the product was eluted with chloroform containing 1.5% methanol; 3.5 g (77%), m.p. 201.5–204°C (ethanol–dichloromethane). Analytical sample, m.p. 202–203.5°C (ethanol–dichloromethane). UV spectrum: $\lambda_{\max}$ 250 nm (log ϵ 4.42), infl. 297.5 nm (3.61). IR spectrum: 690, 741, 765 (5 and 4 adjacent Ar–H), 1542, 1589, 3010, 3050, 3075 (Ar), 1610 cm^{-1} (C=N). ¹H NMR spectrum: δ 7.10–7.50 (m, 9 H, ArH), 6.61 (s, 1 H, 3-H), 4.88 (s, 2 H, 6,6-H₂), 3.20 (m, CH₂N¹CH₂ of piperazine and CH₂S), 2.70 (m, 6 H, remaining 3 CH₂N). For C₂₆H₂₄BrClN₆S₂ (600.0) calculated: 52.04% C, 4.03% H, 13.32% Br, 5.91% Cl, 14.01% N, 10.69% S; found: 52.02% C, 4.08% H, 13.40% Br, 5.95% Cl, 13.85% N, 10.75% S.

Methanesulfonate, m.p. 258–261°C (ethanol-ether). For $C_{27}H_{28}BrClN_6O_3S_3$ (696.1) calculated: 46.59% C, 4.05% H, 11.48% Br, 5.09% Cl, 12.07% N, 13.82% S; found: 46.89% C, 4.18% H, 11.60% Br, 5.18% Cl, 11.74% N, 13.61% S.

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