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1,5-Benzodiazepines XI. 5-(Dialkylamino) or 5-(alkylthio) substituted 8-chloro-6-phenyl-6*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepines with anticonvulsant activity

GC Grossi[1], M Di Braccio[1], G Roma[1]*, M Ghia[2], G Brambilla[2]

[1]*Istituto di Scienze Farmaceutiche, Università di Genova, Viale Benedetto XV, 3, 16132 Genoa;*
[2]*Istituto di Farmacologia, Università di Genova, Viale Benedetto XV, 2, 16132 Genoa, Italy*

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Summary — The cyclocondensation of (dimethylamino)benzodiazepinones **3a,b** with hydrazides yielded triazolobenzodiazepinones **4** which were treated with Lawesson's reagent to give thiolactams **5**. The phase-transfer catalyzed (TEBA) alkylation of compounds **5** with suitable alkyl halides afforded 5-(alkylthio)-6-phenyl-6*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepines **6a–f**. The desired *N,N*-dialkyl-6-phenyl-6*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5-amines **7a–k** were finally obtained from the reaction of the (methylthio)derivatives **6a–d** with proper dialkylamines. Compounds **6b–f** and **7a–e**, **g–k** were screened for anticonvulsant activity after a preliminary evaluation of their gross behavioral effects and acute toxicity. Nine of the 15 triazolobenzodiazepines tested exerted a clear-cut anticonvulsant effect associated with low acute toxicity. In particular, the most active compounds **6e**, **f** and **7h** showed LD_{50}/ED_{50} ratios that were notably higher than that of phenobarbital and ranging from 50% to 20% of that of diazepam, the latter used as reference drugs.

5-(dialkylamino) or 5-(alkylthio) substituted 8-chloro-6-phenyl-6*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepines / toxicity / anticonvulsant activity

Introduction

In recent papers we described the preparation (through 2 different synthetic pathways) of the substituted 4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5-amines **1**, some of which showed statistically significant analgesic and/or anti-inflammatory activities, depending on the structure [1, 2]. No example of [1,2,4]triazolo-[4,3-*a*][1,5]benzodiazepines amino substituted on the diazepine ring was previously reported in the literature.

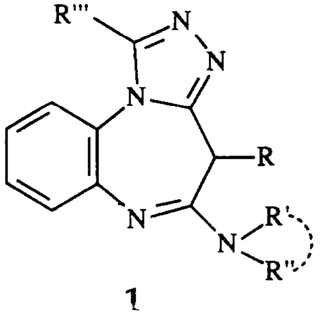

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Fig 1. Structure of compounds **1**.

As a further part of our chemical and pharmacological interest in this field, we considered compounds **7** as an interesting new group of 5-amino substituted [1,2,4]triazolo[4,3-*a*][1,5]benzodiazepines. Indeed, the 6-phenyl and 8-chloro substituents could endow these compounds with central nervous system (CNS) activity, most likely with anticonvulsant activity: for instance, the 8-chloro-6-phenyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5(6*H*)-ones **4b,c** have been reported to exhibit anticonvulsant properties [3, 4]. On the other hand, the C-4, C-5 double bond and the 5-(dialkylamino) substituent confer a peculiar structural feature on compounds **7**.

The above considerations prompted us to synthesize the *N,N*-dialkyl-6-phenyl-6*H*-[1,2,4]triazolo-[4,3-*a*][1,5]benzodiazepin-5-amines **7a–k** (scheme 1) and to check their anticonvulsant activity. The novel analogous 5-(alkylthio) derivatives **6b–f** (scheme 1) were also tested for their anticonvulsant properties.

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*Correspondence and reprints

Chemistry

Compounds **7** were prepared *via* the synthetic route shown in scheme 1.

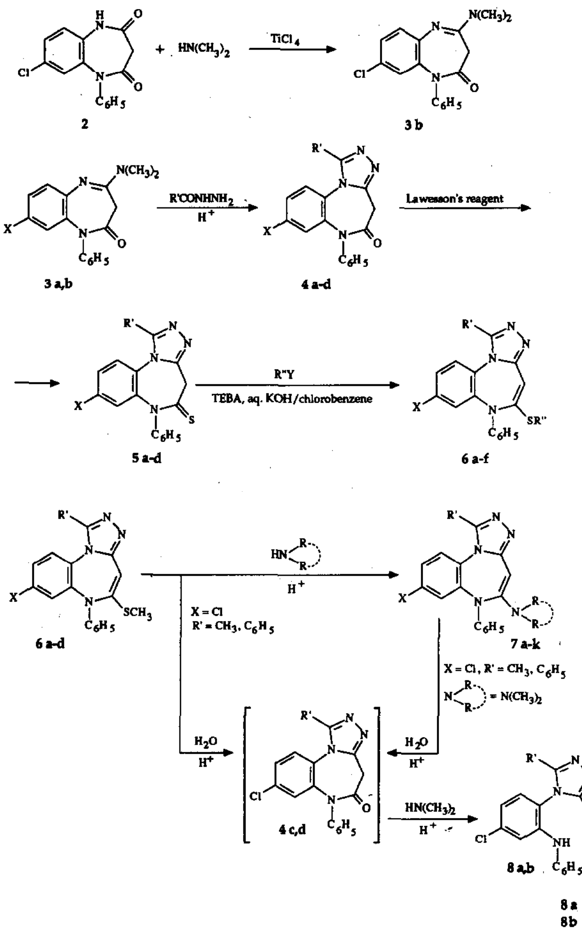
The intermediate triazolobenzodiazepinones **4b,c** [3–7] and **4a,d** were obtained through the cyclocondensation of 4-(dimethylamino)-1,3-dihydro-1-phenyl-2*H*-1,5-benzodiazepin-2-ones **3a,b** with excess hydrazides in the presence of glacial acetic acid (Dowtherm A, 200°C, 2 h). The starting compound **3a** was previously described by us [8], and **3b** [9, 10] has now been prepared by the reaction of the benzodiazepinedione **2** [11] with excess dimethylamine in the presence of titanium tetrachloride and anisole [12].

Treatment of intermediates **4** with Lawesson's reagent (Dowtherm A, 150°C, 30–60 min) yielded the corresponding triazolobenzodiazepinethiones **5** and their phase-transfer catalyzed [benzyltriethylammonium chloride (TEBA)] alkylation [13] with suitable excess alkyl halides (40% aqueous potassium hydroxide/chlorobenzene, room temperature, overnight) afforded 5-(alkylthio)-6-phenyl-6*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepines **6a–f**.

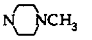
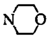
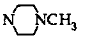
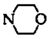
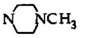
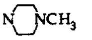
By treating the (methylthio)derivatives **6a–d** with excess dialkylamines, in the presence of *p*-toluenesulphonic acid as catalyst, the desired *N*,*N*-dialkyl-6-phenyl-6*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5-amines **7a–k** were obtained (Dowtherm A, 200°C, 24–40 h; closed vessel, anhydrous toluene, 115–130°C, 48 h, when dimethylamine was used).

When compounds **6c,d** were treated with excess dimethylamine under the above stringent conditions, both the desired (dimethylamino)derivatives **7f,i** and the corresponding ring-opened amides **8a,b** were obtained.

The formation of compounds **8a,b** most likely occurred through the preliminary hydrolysis of (methylthio)derivatives **6c,d** and/or of (dimethyl-



Scheme 1. Synthetic route to compounds **6** and **7**.

Compound	X	R'	R''	
3a	H	---	—	—
4a,5a	H	H	—	—
4b,5b	Cl	H	—	—
4c,5c	Cl	CH_3	—	—
4d,5d	Cl	C_6H_5	—	—
6a	H	H	CH_3	—
6b	Cl	H	CH_3	—
6c	Cl	CH_3	CH_3	—
6d	Cl	C_6H_5	CH_3	—
6e	Cl	H	$(CH_2)_2N(CH_3)_2$	—
6f	Cl	CH_3	$(CH_2)_2N(CH_3)_2$	—
7a	H	H	—	$N(CH_3)_2$
7b	H	H	—	
7c	Cl	H	—	$N(CH_3)_2$
7d	Cl	H	—	
7e	Cl	H	—	
7f	Cl	CH_3	—	$N(CH_3)_2$
7g	Cl	CH_3	—	
7h	Cl	CH_3	—	
7i	Cl	C_6H_5	—	$N(CH_3)_2$
7j	Cl	C_6H_5	—	
7k	Cl	C_6H_5	—	

amino)derivatives **7f,i** to the lactams **4c,d** and the subsequent aminolysis of these intermediates (see scheme 1). The water involved in the hydrolysis step probably derived from the condensation of moisture when the cooled liquid dimethylamine was introduced in the reaction vessel. The experimental conditions herein reported for the reaction of **6c,d** with dimethylamine were chosen after a number of experiments in order to obtain as much as possible both the highest yields of the amino derivatives **7f,i** and the lowest amounts of the undesired ring-opened compounds **8a,b** (see *Experimental protocols*).

Actually the treatment of lactam **4c** with excess dimethylamine under the same conditions used in the reaction of **6c** with dimethylamine afforded a high yield of the ring-opened amide **8a** (see *Experimental protocols*). An analogous aminolytic cleavage of a diazepine lactam ring in the field of [1,2,4]triazolo-[4,3-*d*][1,4]benzodiazepines has been previously reported in the literature [14].

It is interesting to observe that the treatment of (methylthio)derivatives **6a,b** with dimethylamine under the same conditions used for **6d** afforded only (dimethylamino)derivatives **7a,c**, respectively (scheme 1), no trace of amides of type **8** having been isolated from the reaction mixture. This behavior may be attributed to a higher stability of the 1-unsubstituted compounds **6a,b** and/or **7a,c** towards hydrolysis.

The structures attributed to the compounds described in this paper are supported by the results of elemental analyses and by the IR and ^{1}H-NMR spectral data.

It can be observed that in the ^{1}H-NMR spectra of compounds **3b**, **4c,d**, **5a** ($CDCl_3$), and **5b–d** [$(CD_3)_2SO$] the diazepine ring CH_2 signal is an AB quartet, as we previously reported for analogous compounds [2, 8], evidently because no interconversion occurs at the registration temperature (36°C) between the 2 boat conformations of the benzodiazepine ring [14].

Pharmacological results

Compounds **6b–f** and **7a–e**, **g–k** were screened for anticonvulsant activity after a preliminary evaluation of their gross behavioral effects and acute toxicity. All the drugs were administered at log-spaced doses by oral gavage. The results of the pharmacological evaluation are listed in table I.

Nine of the 15 triazolobenzodiazepines tested (**6b,c,e,f** and **7c–e,g,h**) exerted a clear-cut anticonvulsant effect evaluated in mice in terms of protection against pentylenetetrazole-induced lethal convulsions [15]. The ED_{50} values of the active compounds ranged from 12 to 610 mg/kg; the most active compounds were in the order **6e**, **7h** and **6f**, which showed ED_{50}'s of the same order as that of phenobarbital, but higher than the ED_{50} of diazepam. It is worth noting that the LD_{50}/ED_{50} ratio of compound **6e** was ≈ 15-fold higher than that of phenobarbital and one-half of that of diazepam.

Table I. Pharmacological data of compounds **6b–f** and **7a–e, g–k**.

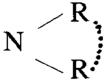
Compound	*Approximate oral LD_{50} in mice (mg/kg)*	*Anticonvulsant activity in mice*[a] *Oral ED_{50} and 95% confidence interval (mg/kg)*
6 b	>1600	610 (410-908)
6 c	>1600	417 (263-660)
6 d	>1600	b
6 e	1600	12 (7-23)
6 f	1350	25 (19-32)
7 a	>1600	b
7 b	860	c
7 c	>1600	78 (60-100)
7 d	>1600	250 (134-465)
7 e	670	66 (60-72)
7 g	>1600	78 (60-100)
7 h	750	13 (6-26)
7 i	>1600	b
7 j	>1600	b
7 k	1600	c
Phenobarbital	168	19 (11-32)
Diazepam	535	2 (1.3-3.0)

[a]Protection against pentylenetetrazole-induced lethal convulsions (see *Experimental protocols*); [b]inactive after oral administration of 1 g/kg; [c]inactive after oral administration of 1/4 LD_{50}.

Concerning the behavioral effects evaluated in mice by the Irwin–Morpurgo screening procedure [15], subtoxic doses of compounds **6e,f** and **7b,e,h,k** produced slight and inconstant signs of CNS depression such as sedation, decrease of spontaneous motor activity, passivity and ptosis. No significant gross behavioral alterations were observed with the highest doses tested of the other compounds. With all the compounds tested, the surviving animals appeared normal 24 h after treatment, and remained so during the 7-d observation period.

Conclusions

Pharmacological results indicate that some of the triazolobenzodiazepines tested possess interesting anticonvulsant activity associated with low acute toxicity, as shown by the high LD_{50}/ED_{50} ratio of compounds **6e**,**f** and **7h**.

Furthermore, the results obtained suggest some structure–activity relationship considerations for the 6*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepine derivatives **6** and **7**. Actually, these results clearly confirm the importance of the 8-chloro substituent (X = Cl) for the CNS activity in this field (see table I; compounds **7a**,**b**), and show the remarkable negative effect of the 1-phenyl substituent (R' = C_6H_5) on the anticonvulsant activity of both compounds **6** and **7** (see compounds **6d**, **7i–k**). Concerning the 5-substituent SR" (compounds **6**) or  $N\begin{smallmatrix}R\\R\end{smallmatrix}$ (compounds **7**), the 2-(dimethylamino)ethyl]thio group for compounds **6** and the 4-methyl-1-piperazinyl for compounds **7** afford the highest anticonvulsant activity (see compounds **6e**,**f** and **7e**,**h**).

Experimental protocols

Chemical synthesis

Melting points were determined using a Fisher–Johns apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 398 spectrophotometer. ^{1}H-NMR spectra were recorded partly on a Hitachi Perkin–Elmer R 600 (60 MHz) spectrometer and partly on a Varian Gemini 200 (200 MHz) spectrometer using $(CH_3)_4Si$ as internal reference (δ = 0). Analyses of all new compounds, indicated by the symbols of the elements, were within ±0.4% of the theoretical values and were performed by the Laboratorio di Microanalisi (Istituto di Scienze Farmaceutiche, Università di Genova).

Thin-layer chromatograms were run on Merck silica gel 60 F_{254} precoated plastic sheets (layer thickness 0.2 mm). Column chromatography was performed using Carlo-Erba silica gel (0.05–0.20 mm) or Carlo-Erba neutral aluminum oxide (Brockmann activity I).

8-Chloro-4-(dimethylamino)-1,3-dihydro-1-phenyl-2H-1,5-benzodiazepin-2-one ***3b***

To an ice bath cooled solution of 0.0218 mol (2.4 ml) of titanium tetrachloride and 4 ml anisole in 80 ml dry toluene, 10 ml dimethylamine (previously cooled to –20°C) were rapidly added. 0.020 mol (5.73 g) of 8-chloro-1-phenyl-1*H*-1,5-benzodiazepine-2,4(3*H*,5*H*)-dione **2** [11] was then added to the suspension obtained, and the resulting mixture refluxed with stirring for 6 h.

After cooling, 6 ml 2-propanol, 4 g diatomaceous earth and 6 ml concentrated ammonium hydroxide were added to the mixture. After stirring, the resulting suspension was filtered and the solid cake was thoroughly washed with toluene. The filtrate and washings were dried (anhydrous sodium sulphate), then thoroughly evaporated under reduced pressure. The dark oil thus obtained was dissolved in a little chloroform and chromatographed on a silica gel column, eluting with the mixture chloroform–ethyl acetate (1:1). The solvents were then removed from the eluate to give an oily residue from which, after addition of a little ethyl ether and after it was left to stand, the nearly pure compound **3b** crystallized (4.40 g, 70%) as a white solid; mp: 141.5–142°C after recrystallization from the same solvent. Anal $C_{17}H_{16}ClN_3O$ (C, H, N). IR ($CHCl_3$), cm^{-1}: 1668 (CO), 1603,1578. ^{1}H-NMR ($CDCl_3$), δ: 3.09 and 3.85 (AB q, *J* = 12 Hz, 2H, 3-CH_2), 3.20 (s, 6H, CH_3), 6.77 (mc, 1H, H-9), 7.01–7.49 (m, 7H, H-6,7 + phenyl H's).

6-Phenyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepin-5(6H)-ones ***4a–d***

General procedure

A mixture of 0.006 mol of compound **3a** [8] (1.68 g) or **3b** (1.88 g), 0.012 mol of formylhydrazine (0.72 g), acetylhydrazine (0.89 g) or benzoylhydrazine (1.63 g), 15 ml Dowtherm A and 1.5 ml glacial acetic acid was heated at 200°C for 2 h while stirring. After cooling, compounds **4a–d** were isolated from the final reaction mixture as described below.

6-Phenyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepin-5(6H)-one ***4a***

The solution obtained from the reaction of **3a** [8] with formylhydrazine was diluted with a little chloroform and chromatographed on a silica gel column.The column was first eluted with chloroform until Dowtherm A and impurities were completely removed, then with chloroform–methanol (9:1). This eluate was evaporated and a little ethyl acetate was added to the thick oily residue. After standing, crude compound **4a** separated out as a white solid. By crystallizing from ethyl acetate, pure **4a** (1.08 g, 65%) was obtained as white needles; mp: 229.5–230°C after recrystallization from dichloromethane–petroleum ether 40–70°C. Anal $C_{16}H_{12}N_4O$ (C, H, N). IR ($CHCl_3$), cm^{-1}: 1690 (CO), 1594, 1531, 1502. ^{1}H-NMR [$(CD_3)_2SO$], δ: 3.97 (s, 2H, 4-CH_2), 6.50–7.97 (m, 9H, H-7,8,9,10 + phenyl H's), 9.19 (s, 1H, H-1).

8-Chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepin-5(6H)-one ***4b***

The solution obtained from the reaction of **3b** with formylhydrazine was diluted with ethyl ether until light turbidity was observed, then was kept standing overnight at room temperature. The white solid that separated out was filtered and crystallized from methanol to yield 1.40 g (75%) of pure compound **4b** as white crystals; mp: 297.5–299°C after recrystallization from the same solvent. Anal $C_{16}H_{11}ClN_4O$ (C, H, N). IR ($CHCl_3$), cm^{-1}: 1690 (CO), 1596, 1528, 1500. ^{1}H-NMR [$(CD_3)_2SO$], δ: 4.05 (s, 2H, 4-CH_2), 6.76–8.04 (m, 8H, H-7,9,10 + phenyl H's), 9.24 (s, 1H, H-1).

8-Chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,5]-benzodiazepin-5(6H)-one ***4c***

Starting from **3b** and acetylhydrazine and following the procedure described above for the preparation of compound **4b**, crude compound **4c** ultimately separated out. After crystallization from ethanol, white crystals of pure **4c** (1.56 g, 80%) were obtained; mp: 297–299°C after recrystallization from the same solvent (lit: mp: 297–298°C [6], 302–305°C [7]). Anal $C_{17}H_{13}ClN_4O$ (C,H,N). IR ($CHCl_3$), cm^{-1}: 1700 (CO), 1596, 1530, 1493. ^{1}H-NMR ($CDCl_3$), δ: 2.66 (s, 3H, 1-CH_3), 3.60 and 4.24 (AB q, *J* = 14.4 Hz, 2H, 4-CH_2), 6.94–7.63 (m, 8H, H-7,9,10 + phenyl H's).

8-Chloro-1,6-diphenyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepin-5(6H)-one ***4d***

The mixture obtained from the reaction of **3b** with benzoylhydrazine was allowed to stand overnight at room temperature.

The white solid that separated out (0.30 g) was recovered by filtration and washed with acetone. It was shown (elemental analysis, IR and ^{1}H-NMR spectra) to be 1,2-dibenzoylhydrazine, white needles, mp: 239–240°C, after crystallization from ethanol (lit [16]: mp: 238°C). The filtrate and washings, after removing acetone under reduced pressure, afforded a liquid residue which was submitted to column chromatography (silica gel), eluting first with a chloroform–benzene mixture (1:1) until Dowtherm A and impurities were completely removed, then with ethyl acetate. This eluate was evaporated and the oily residue was treated with a little ethyl acetate–ethyl ether (1:1). After standing, the nearly pure solid compound **4d** separated out (1.40 g, 60%) as white crystals; mp: 264–265°C after crystallization from ethanol. Anal $C_{22}H_{15}ClN_4O$ (C, H, N). IR ($CHCl_3$), cm^{-1}: 1696 (CO), 1594, 1530, 1490. ^{1}H-NMR ($CDCl_3$), δ: 3.70 and 4.31 (AB q, J = 14.4 Hz, 2H, 4-CH_2), 6.70–7.80 (m, 13H, H-7,9,10 + phenyl H's).

*6-Phenyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine-5(6H)-thiones **5a–d***

General procedure

A mixture of 0.005 mol of the proper compound **4**, 0.005 mol (2.02 g) Lawesson's reagent and 10 ml Dowtherm A was stirred and heated at 150°C for 30 min (60 min in the case of compound **5d**). After cooling, compounds **5a–d** were recovered from the reaction mixture as described below.

*6-Phenyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine-5(6H)-thione **5a***

The turbid yellow solution obtained from the reaction of **4a** (1.38 g) was diluted with a little toluene and chromatographed on a neutral aluminum oxide column, eluting with the same solvent until Dowtherm A was completely removed. Further elution with tetrahydrofuran afforded the nearly pure compound **5a** (1.23 g, 84%), as a pale yellow solid; mp: 225–226°C after crystallization from ethyl acetate. Anal $C_{16}H_{12}N_4S$ (C, H, N, S). IR ($CHCl_3$), cm^{-1}: 1592, 1530, 1500. ^{1}H-NMR ($CDCl_3$), δ: 4.03 and 5.00 (AB q, J = 13.8 Hz, 2H, 4-CH_2), 6.96–7.77 (m, 9H, H-7,8,9,10 + phenyl H's), 8.72 (s, 1H, H-1).

*8-Chloro-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine-5(6H)-thione **5b***

The suspension obtained from the reaction of **4b** (1.55 g) was diluted with a little toluene then filtered, after which the solid collected was washed with ethyl ether. The nearly pure compound **5b** (1.03 g) was thus obtained as yellow crystals; mp: 292–294°C after crystallization from ethyl acetate. Anal $C_{16}H_{11}ClN_4S$ (C, H, N, S). IR (KBr), cm^{-1}: 1593, 1530, 1500. ^{1}H-NMR [$(CD_3)_2SO$], δ: 4.35 and 4.68 (AB q, J = 13.8 Hz, 2H, 4-CH_2), 7.00–8.04 (m, 8H, H-7,9,10 + phenyl H's), 9.24 (s, 1H, H-1).

The filtrate was chromatographed on a neutral aluminum oxide column, eluting with toluene until Dowtherm A was completely removed. By further elution of the column with tetrahydrofuran an additional yield (0.39 g) of **5b** was obtained (total yield: 87%).

*8-Chloro-1-methyl-6-phenyl-4H-[1,2,4]triazolo[4,3-a][1,5]-benzodiazepine-5(6H)-thione **5c***

Starting from compound **4c** (1.62 g) and following the procedure described above for the preparation of **5b**, 1.33 g (78%) of compound **5c** was ultimately obtained (2 amounts of 0.87 g and 0.46 g, respectively). The crystallization from ethanol yielded yellow crystals; mp: 296–298°C dec. Anal $C_{17}H_{13}ClN_4S$ (C,H,N,S). IR (KBr), cm^{-1}: 1593, 1538, 1522, 1499. ^{1}H-NMR [$(CD_3)_2SO$], δ: 2.65 (s, 3H, 1-CH_3), 4.23 and 4.57 (AB q, J = 13.8 Hz, 2H, 4-CH_2), 7.10–8.10 (m, 8H, H-7,9,10 + phenyl H's).

*8-Chloro-1,6-diphenyl-4H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepine-5(6H)-thione **5d***

The suspension of yellow solid obtained from the reaction of compound **4d** (1.93 g) was diluted with ethyl ether and allowed to stand overnight at room temperature. The solid was then collected by filtration and washed with ethyl ether, affording 1.02 g of the nearly pure compound **5d** as yellow crystals; mp: 268–270°C after crystallization from ethanol. Anal $C_{22}H_{15}ClN_4S$ (C, H, N, S). IR ($CHCl_3$), cm^{-1}: 1593, 1530, 1492. ^{1}H-NMR [$(CD_3)_2SO$], δ: 4.37 and 4.67 (AB q, J = 14.4 Hz, 2H, 4-CH_2), 6.80–7.82 (m, 13H, H-7,9,10 + phenyl H's).

The filtrate was then evaporated to remove ethyl ether, and the liquid residue was subjected to column chromatography (neutral aluminum oxide), eluting with toluene until complete removal of Dowtherm A. Further elution with ethyl acetate gave an additional amount (0.50 g) of pure **5d** (total yield 75%).

*5-(Alkylthio)-6-phenyl-6H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepines **6a–f***

General procedure

To a suspension of 0.005 mol of suitable compound **5** (1.46 g **5a**, 1.63 g **5b**, 1.70 g **5c**, 2.01 g **5d**) and 0.0065 mol (1.48 g) benzyltriethylammonium chloride in 30 ml chlorobenzene, 5 ml 40% aqueous potassium hydroxide and 0.020 mol (2.84 g) methyl iodide were added. For the preparation of compounds **6e,f**, 0.005 mol compound **5b** (1.63 g) or **5c** (1.70 g) respectively, 0.020 mol (4.56 g) benzyltriethylammonium chloride, 90 ml chlorobenzene, 15 ml 40% aqueous potassium hydroxide, and 0.060 mol (8.64 g) 2-dimethylaminoethyl chloride hydrochloride were used. The mixture obtained was stirred overnight at room temperature, then diluted with water (100 ml) and chloroform (100 ml) and vigorously shaken in a separatory funnel. The organic layer was collected and the aqueous phase extracted several times with chloroform. The combined organic phases were washed with water (until neutral), dried (anhydrous sodium sulphate), and evaporated to dryness under reduced pressure. From the resulting residue compound **6** was recovered according to the following procedures.

*Compounds **6a–d**.* The nearly solid residue was taken up in a little ethyl acetate–ethyl ether (1:1) to give white crystalline compound **6**, which was recrystallized from the suitable solvent.

*Compounds **6e–f**.* The thick oily residue was treated with a little ethyl ether and the resulting solution was allowed to stand at room temperature until white crystalline compound **6** separated out, which was recrystallized from the suitable solvent.

The data of compounds **6a–f** are reported in table II.

*N,N-Dialkyl-6-phenyl-6H-[1,2,4]triazolo[4,3-a][1,5]benzodiazepin-5-amines **7a–k** and N,N-dimethyl-2-[3-(4,5-disubstituted-1,2,4-triazolyl)]acetamides **8a,b***

General procedure

A mixture of 2.0 g of the proper (methylthio)derivative **6**, 0.50 g of anhydrous *p*-toluenesulphonic acid, 10 ml Dowtherm

Table II. Data of compounds **6a**–**f** and **7a**–**k**.

Compd.	Molecular formula[a]	Yield (%)	mp °C (solv.)[b]	IR[c] (cm^{-1})	^{1}H NMR[d] (δ, ppm)
6a	$C_{17}H_{14}N_4S$	70	209-210 (A)	1611,1592,1490.	2.48(s,3H,CH_3), 6.55-7.90(m,10H,H-4,7,8,9,10 + phenyl H's), 8.75(s,1H,H-1).
6b	$C_{17}H_{13}ClN_4S$	88	241-242 (A)	1611,1590,1492.	2.55(s,3H,CH_3), 6.48-8.08(m,9H,H-4,7,9,10 + phenyl H's), 9.16(s,1H,H-1).
6c	$C_{18}H_{15}ClN_4S$	80	208-209 (A)	1600,1590,1492.	2.47(s,3H,SCH_3), 2.57(s,3H,1-CH_3), 6.52-7.80(m,9H,H-4,7,9,10 + phenyl H's).
6d	$C_{23}H_{17}ClN_4S$	87	276-277 (A)	1600,1590,1493.	2.50(s,3H,CH_3), 6.60-7.73(m,14H,H-4,7,9,10 + phenyl H's).
6e	$C_{20}H_{20}ClN_5S$	57	146-147 (B)	1610,1590,1493.	2.25(s,6H,CH_3), 2.40-3.29(m,4H,CH_2-CH_2), 6.53-7.76(m,9H,H-4,7,9,10 + phenyl H's), 8.52(s,1H,H-1).
6f	$C_{21}H_{22}ClN_5S$	82	134-135 (C)	1603,1593,1496.	2.26[s,6H,$N(CH_3)_2$], 2.42-3.24(m,4H,CH_2-CH_2), 2.54(s,3H,1-CH_3), 6.58--7.77(m,9H,H-4,7,9,10 + phenyl H's).
7a	$C_{18}H_{17}N_5$	61	279-280 (D)	1624,1603,1596, 1493.	3.02(s,6H,CH_3), 5.53(s,1H,H-4), 6.37-7.76(m,9H,H-7,8,9,10 + phenyl H's), 8.43(s,1H,H-1).
7b	$C_{21}H_{22}N_6$	64	264-265 (D)	1621,1606,1596, 1493.	2.05-2.66[m,4H,$CH_3N(\mathit{CH}_2)_2$], 2.31(s,3H,CH_3), 3.15-3.68[m,4H,$N(CH_2)_2$], 5.69(s,1H,H-4), 6.38-7.73(m,9H,H-7,8,9,10 + phenyl H's), 8.45(s,1H,H-1).
7c	$C_{18}H_{16}ClN_5$	56	278-279 (D)	1625,1602,1591, 1494.	3.06(s,6H,CH_3), 5.50(s,1H,H-4), 6.35-7.76(m,8H,H-7,9,10 + phenyl H's), 8.55(s,1H,H-1).
7d	$C_{20}H_{18}ClN_5O$	71	216-217 (A)	1623,1599,1590, 1493.	3.36[mc,4H,$N(CH_2)_2$], 3.75[mc,4H,$O(CH_2)_2$], 5.72(s,1H,H-4), 6.42-7.78(m,8H, H-7,9,10 + phenyl H's), 8.46(s,1H,H-1).
7e	$C_{21}H_{21}ClN_6$	60	207-208 (E)	1622,1599,1589, 1492.	2.13-2.69[m,4H,$CH_3N(\mathit{CH}_2)_2$], 2.32(s,3H,CH_3), 3.19-3.66[m,4H,$N(CH_2)_2$], 5.69(s,1H,H-4), 6.41-7.73(m,8H,H-7,9,10 + phenyl H's), 8.43(s,1H,H-1).
7f	$C_{19}H_{18}ClN_5$	28	238-239 (A)	1618,1600,1590, 1491.	2.51(s,3H,1-CH_3), 3.03[s,6H,$N(CH_3)_2$], 5.45(s,1H,H-4), 6.38-7.74(m,8H,H-7,9,10 + phenyl H's).
7g	$C_{21}H_{20}ClN_5O$	45	266-267 (A)	1627,1603,1593, 1494.	2.52(s,3H,1-CH_3), 3.35[mc,4H,$N(CH_2)_2$], 3.72[mc,4H,$O(CH_2)_2$], 5.62(s,1H,H-4), 6.52-7.69(m,8H,H-7,9,10 + phenyl H's).
7h	$C_{22}H_{23}ClN_6$	52	220-221 (F)	1624,1603,1592, 1493.	2.13-2.72[m,4H,$CH_3N(\mathit{CH}_2)_2$], 2.31(s,3H,N-CH_3), 2.51(s,3H,1-CH_3), 3.16-3.63 [m,4H,$N(CH_2)_2$], 5.60(s,1H,H-4), 6.50-7.75(m,8H,H-7,9,10 + phenyl H's).
7i	$C_{24}H_{20}ClN_5$	40	272-273 (A)	1614,1600 sh,1590 sh, 1490.	3.07(s,6H,CH_3), 5.57(s,1H,H-4), 6.51-7.66(m,13H,H-7,9,10 + phenyl H's).
7j	$C_{26}H_{22}ClN_5O$	80	249-250 (E)	1619,1600,1590 sh, 1493.	3.44[mc,4H,$N(CH_2)_2$], 3.76[mc,4H,$O(CH_2)_2$], 5.75(s,1H,H-4), 6.51-7.70(m,13H, H-7,9,10 + phenyl H's).
7k	$C_{27}H_{25}ClN_6$	59	239-240 (G)	1619,1605 sh,1593 sh, 1490.	2.20-2.72[m,4H,$CH_3N(\mathit{CH}_2)_2$], 2.33(s,3H,CH_3), 3.27-3.71[m,4H,$N(CH_2)_2$], 5.73(s,1H,H-4), 6.58-7.66(m,13H,H-7,9,10 + phenyl H's).

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[a] Compounds **6a–f**: anal C, H, N, S. Compounds **7a–k**: anal C, H, N. [b] Crystallization solvent: A = ethyl acetate, B = cyclohexane, C = petroleum ether 40–70°C, D = acetone, E = ethyl acetate/petroleum ether 40–70°C, F = ethyl acetate/cyclohexane, G = isopropyl ether. [c] In $CHCl_3$ solutions. Abbreviations: sh = shoulder. [d] Solvents: $CDCl_3$ for all compounds except for **6b**, for which $(CD_3)_2SO$ was used.

A and 12 ml dry morpholine or 1-methylpiperazine was heated at 200°C for 24 h (compounds **7b,d,g,h,j,k**) or for 40 h (compound **7e**), while stirring. When dimethylamine was used in the reaction (compounds **7a,c,f,i**), a mixture of 2.0 g of the suitable (methylthio)derivative **6**, 0.50 g anhydrous *p*-toluenesulphonic acid, 40 ml dry toluene and 10 ml dimethylamine (previously cooled to –20°C) was heated for 48 h at 130°C (compounds **7a,c,i**) or at 115°C (compound **7f**) in a closed vessel.

After cooling, the mixture was taken up in chloroform and the resulting solution was washed with water, dried (anhydrous sodium sulphate) and evaporated under reduced pressure to afford a residue from which compound **7** and (when present) compound **8** were recovered according to the following procedures.

Compound 7a. The nearly solid residue was treated with a little acetone and the white crystalline compound **7a** that separated was collected by filtration and recrystallized from the same solvent.

Compounds 7b,d,e,g,h,j,k. The liquid residue obtained was dissolved in a little chloroform and subjected to column chromatography (silica gel). The column was first eluted with benzene until Dowtherm A and some impurities were completely removed, then with benzene–triethylamine (9:1) (compounds **7d,g,j,k**) or chloroform–triethylamine (9:1) (compounds **7b,e,h**). After removal of the solvents, this eluate afforded a thick oil which was treated with a little ethyl ether–petroleum ether 40–70°C (1:1). After standing, the nearly pure compound **7** separated out as white or whitish solid that was crystallized from the suitable solvent.

Compounds 7c,f,i. The solid residue obtained was dissolved in a little chloroform and chromatographed on a silica gel column. By eluting with acetone–ethyl acetate (1:1) (compounds **7c,f**) or ethyl acetate (compound **7i**) the starting compounds **6b** (16%), **6c** (22%) or **6d** (11%) respectively were recovered. By then eluting with chloroform–triethylamine (9:1) (compounds **7c,f**) or benzene–triethylamine (9:1) (compound **7i**) and following a procedure identical to that described above for the recovery of compounds **7b,d,e,g,h,j,k**, compounds **7c,f,i** were obtained.

In the case of compounds **7f,i** column elution was then completed with methanol. From this eluate, after removal of the solvent, acetamides **8a** or **8b** were obtained as described below.

The data of compounds **7a–k** are reported in table II.

Acetamide 8a. The thick oil obtained from the final methanol eluate (preparation of **7f**) was treated with a little ethyl acetate–ethyl ether (1:1). After standing, a whitish solid separated out which was collected by filtration, washed with water and dried. There was thus obtained 0.48 g (23%) of nearly pure compound **8a** which was crystallized from ethyl acetate to give white crystals; mp: 197–197.5°C. Anal $C_{19}H_{20}ClN_5O$ (C, H, N). IR ($CHCl_3$), cm^{-1}: 3285 (NH), 1640 (CO), 1590, 1510 shoulder, 1483. ^{1}H-NMR [$(CD_3)_2SO$], δ: 2.14 (s, 3H, CH_3), 2.80 (s, 3H, N-CH_3), 2.97(s, 3H, N-CH_3), 3.81(s, 2H, CH_2), 6.88–7.62 (m, 8H, aromatic), 7.74 (s, 1H, NH; dis D_2O).

Acetamide 8b. By proceeding in the same manner as for **8a**, from the final methanol eluate (preparation of **7i**) 0.54 g (26%) of nearly pure compound **8b** was ultimately obtained as white crystals; mp: 208–208.5°C after crystallization from ethanol. Anal $C_{24}H_{22}ClN_5O$ (C, H, N). IR ($CHCl_3$), cm^{-1}: 3285 (NH), 1646 (CO), 1592, 1512 shoulder, 1487. ^{1}H-NMR [$(CD_3)_2SO$], δ: 2.82 (s, 3H, N-CH_3), 2.99 (s, 3H, N-CH_3), 3.90 (s, 2H, CH_2), 6.80–7.68 (m, 13H, aromatic), 7.90 (s, 1H, NH; dis D_2O).

*Preparation of acetamide **8a** from compound **4c***

A mixture of 1.0 g of compound **4c**, 0.25 g anhydrous *p*-toluene sulphonic acid, 40 ml dry toluene and 5 ml dimethylamine (previously cooled to –20°C) was heated at 115°C for 48 h in a closed vessel.

After cooling, 100 ml chloroform was added to the mixture and the resulting solution was washed with water, dried (anhydrous sodium sulphate), and evaporated to dryness under reduced pressure. The thick oily residue was then treated with a little ethyl acetate–ethyl ether (1:1). It was left to stand, after which 0.92 g (81%) of nearly pure compound **8a** was obtained.

Pharmacological evaluation

Male albino Swiss mice (18–22 g) were used. The animals were starved for ≈ 12 h before treatment. All the test compounds were administered by oral gavage in a 1% carboxymethylcellulose suspension.

Gross behavioral effects and acute toxicity in mice

Morpurgo's modification [15] of the Irwin's multidimensional screening procedure was used on groups of 4 mice to evaluate drug-induced behavioral alterations. The test compounds were administered at log-spaced doses, and detailed observation of mice was performed 1, 3 and 24 h after treatment. Perphenazine (50 mg/kg ip) and methyl phenidate (50 mg/kg ip) were used for comparison. The approximate LD_{50} was obtained from the mortality observed during a 7-d period.

Anticonvulsant activity

Test compounds were given to groups of 5 mice 1 h before the ip injection of 130 mg/kg pentylenetetrazole [15]. The protection against pentylenetetrazole-induced lethal convulsions was evaluated for a 15-min observation period. For those compounds with a LD_{50} in mice > 1.6 g/kg the first dose employed was 1 g/kg; for the other compounds the initial dose was 1/4 LD_{50}. If such doses had an active effect, successive log-spaced doses were tested and the ED_{50} values and 95% confidence intervals were estimated by the method of Spearman and Karber [17]. Phenobarbital and diazepam were used as reference drugs.

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