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Original article

1,5-Benzodiazepines VIII Novel 4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepine derivatives with analgesic or anti-inflammatory activity

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Summary — The reaction of *N,N*-disubstituted 4-(methylthio)-3*H*-1,5-benzodiazepin-2-amines **8** with formylhydrazine, acetylhydrazine or benzoylhydrazine afforded the expected *N,N*-disubstituted 4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5-amines **9**, along with lower yields of tetracyclic compounds 10. A number of compounds **9** and **10** were tested for their analgesic, anti-inflammatory and anticonvulsant activities, as well as for their acute toxicity and gross behavioral effects. Dipyrone, indomethacin and phenobarbital were used as reference drugs. Some compounds **9** showed statistically significant analgesic or anti-inflammatory properties, depending on the structure.

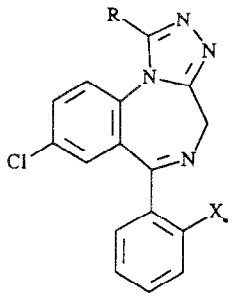
Résumé — 1,5-Benzodiazépines VIII. Nouveaux dérivés de la 4*H*-[1,2,4]triazolo[4,3-*a*][1,5]-benzodiazépine à activité analgésique ou anti-inflammatoire. *La réaction des 4-(méthylthio)-3*H*-1,5-benzodiazépine-2-amines* N,N-*disubstituées* ***8*** *avec la formylhydrazine, l'acétylhydrazine ou la benzoylhydrazine a donné les* 4H-*[1,2,4]triazolo[4,3-*a*][1,5]-benzodiazépine-5-amines* N,N-*disubstituées* ***9*** *attendues, avec de faibles quantités de composés tétracycliques* ***10****. Plusieurs composés* ***9*** *et* ***10*** *ont été examinés quant à leurs activités analgésique, anti-inflammatoire et anti-convulsivante, aussi qu'à leur toxicité aiguë et pour les effets comportementaux. Le dipyrone, l'indométhacine et le phénobarbital ont été utilisés en qualité de produits de référence. Certains, parmi les composés* ***9****, ont manifesté une activité analgésique ou anti-inflammatoire statistiquement intéressante, en rapport avec leur structure.*

***N,N*-disubstituted 4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5-amines / analgesic activity / anti-inflammatory activity**

Introduction

The psychotropic activity of some 4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine derivatives is well known. Estazolam (**1**: R = X = H), alprazolam (**1**: R = CH_3, X = H), and triazolam (**1**: R = CH_3, X = Cl) are presently available for clinical use as hypnotics or tranquilizers.

Analogous tricyclic derivatives were also prepared starting from the 1,5-benzodiazepine system in order to obtain new compounds provided with central nervous system (CNS) activity. For instance, the 4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepine derivatives **2a**, **b** were actually active as anticonvulsants [1,2] and **2c** showed CNS depressant properties [3] in test animals.



1

On the other hand, it is interesting to observe that compounds **3**, a different group of 4*H*-[1,2,4]triazolo[4,3-a][1,5]benzodiazepines lacking the 6-phenyl substituent, showed no CNS activity [4], but, depending on the substituents, exhibited remarkable anal-

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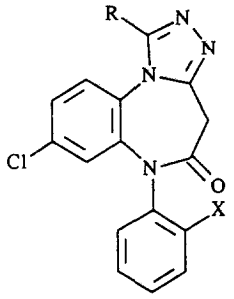
gesic and anti-inflammatory properties, also when Y = R = H [4].



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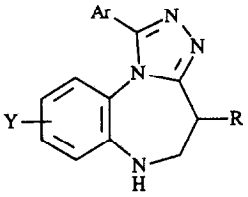
2a : R=H, X=Cl
2b : R=H, X=CF_3
2c : R=CH_3, X=H



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R=H, CH_3
Y=H, 8-Cl, 9-Cl, 8-Cl and 9-Cl, 9-OCH_3
Ar=C_6H_5, or other aromatic or heteroaromatic substituent.

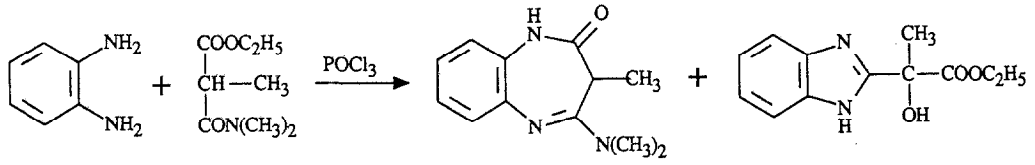
The latter findings prompted us to prepare compounds **9**, a new class of 4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepine derivatives, and to check their analgesic and anti-inflammatory activities. Compounds **9** are unsubstituted both in the position 6 and in the fused benzene ring, but are characterized by the presence of a *N,N*-disubstituted amino group in the position 5.

Chemistry

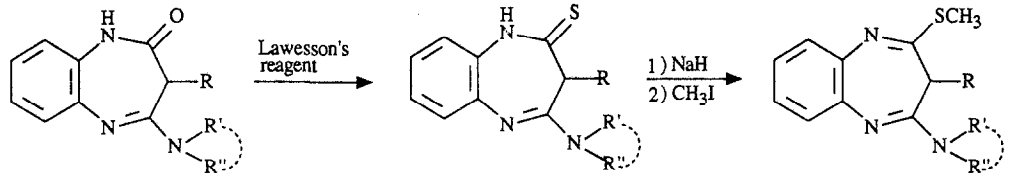
The desired compounds **9** have been synthesized starting from the (methylthio)derivatives **8** (Scheme 3), among which **8c–e** were previously obtained by us [5] and **8a**, **b** have been now similarly prepared (Scheme 2).

Thus, from the reaction of ethyl 2-methyl-*N,N*-dimethylmalonamate **4** with *o*-phenylenediamine in the presence of phosphorus oxychloride (120°C, 5 h) a mixture of (dimethylamino)benzodiazepinone **5a** (low yield) and benzimidazole derivative **6** was obtained [6] (Scheme 1).

Compounds **5a** and **5b** [6] were then treated with Lawesson's reagent (anhydrous toluene, 100°C, 30 min) to afford the corresponding aminobenzodiazepinthiones **7a**, **b**, from which, by reaction with sodium hydride and methyl iodide under mild conditions, the (methylthio)derivatives **8a**, **b** were obtained (Scheme 2).



Scheme 1. 4 5a 6



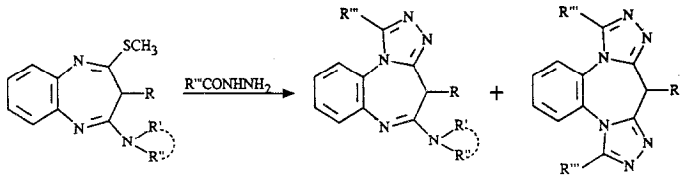
5 7 8

Scheme 2.

5a , 7a , 8a : R = CH_3 , N(R')(R'') = $N(CH_3)_2$

5b , 7b , 8b : R = H , N(R')(R'') = $N(C_2H_5)(C_6H_5)$

Finally, the reaction of the (methylthio)derivatives **8a–e** with suitable hydrazides (Dowtherm A, 200°C, 1-2 h) yielded the expected *N,N*-disubstituted 4*H*-[1,2,4]triazolo[4,3-*a*][1,5]benzodiazepin-5-amines **9a–i**, along with lower amounts of tetracyclic compounds **10a–d** (Scheme 3).



Scheme 3.

Compound	R	$N\begin{matrix}R'\\R''\end{matrix}$	R'''
8a	CH_3	$N(CH_3)_2$	—
8b	H	$N(C_2H_5)(C_6H_5)$	—
8c	H	$N(CH_3)_2$	—
8d	H	$N(C_2H_5)_2$	—
8e	H	N⟨ ⟩	—
9a	CH_3	$N(CH_3)_2$	C_6H_5
9b	H	$N(C_2H_5)(C_6H_5)$	C_6H_5
9c	H	$N(CH_3)_2$	H
9d	H	$N(CH_3)_2$	CH_3
9e	H	$N(CH_3)_2$	C_6H_5
9f	H	$N(C_2H_5)_2$	H
9g	H	$N(C_2H_5)_2$	CH_3
9h	H	$N(C_2H_5)_2$	C_6H_5
9i	H	N⟨ ⟩	C_6H_5
10a	CH_3	—	C_6H_5
10b	H	—	C_6H_5
10c	H	—	H
10d	H	—	CH_3

The formation of tetracyclic derivatives **10** confirms that, as already previously observed [5], under suitable conditions not only the methylthio but also the amino group of compounds **8** can be substituted by aminic reagents, most likely through an addition-elimination mechanism.

At last we can observe that it is possible to reduce the amounts of tetracyclic derivatives **10** by increasing the size and steric hindrance of the amino substituent in the starting compounds **8** (see *Experimental protocols*).

The structures attributed to the compounds described in the present paper are in accordance with the results of elemental analyses and with IR and ^1H NMR spectral data (see table I and *Experimental protocols*).

Two NH stretching bands appear in the IR spectra ($CHCl_3$) of compounds **5a** and **7a**, **b**, arising from the free and associated states of these lactam and thiolactams in solution.

It is interesting to point out that in the ^1H NMR spectra ($CDCl_3$) of triazolobenzodiazepine derivatives **9b–i** the 4-CH_2 signal is an AB quartet [3] or a sharp singlet according to whether the 1-carbon of the compound is substituted or not, respectively. It seems evident that in the first case only one of the two boat conformations of the benzodiazepine ring is present in solution at room temperature and no interconversion occurs [7], most likely due to steric hindrance of the 1-substituent. This behavior does not seem to be affected by the amino substituents at the 5 position, as we can see by comparing the spectra of compounds **9c–e** and **9f–h**, and according to peripheral position of 5-substituent (Dreiding stereomodel).

Also in the ^1H NMR spectrum [$(CD_3)_2SO$] of tetracyclic compound **10d** the 9-CH_2 signal appears as an AB quartet [8], whereas in the spectrum (CF_3COOD) of **10b** this signal is absent due to replacement of the methylene protons with deuterium. It was not possible to register the spectrum of compound **10c** because of its insufficient solubility in all the normally used solvents.

No example of [1,2,4]triazolo[4,3-*a*][1,5]benzodiazepines bearing an amino substituent on the diazepine ring was previously described in the literature. Only recently the *bis*[1,2,4]triazolo[4,3-*a*:3',4'-*d*][1,5]benzodiazepine system, which is present in compounds **10**, was reported for the first time [8].

Pharmacological results

Compounds **9a–i** and **10a**, **b** were screened for their analgesic and anti-inflammatory activities, as well as for their acute toxicity and gross behavioral effects. Some of them were also tested for anticonvulsant action. All the drugs were administered orally; the dose, unless otherwise stated, was equal to 1/4 LD_{50} in mice. The results of pharmacological evaluation are given in table II.

Compounds **9f** and **9g** exhibited a statistically significant analgesic action in the hot-plate test in the mouse, being however less active than the equitoxic dose of dipyrone (780 mg/kg); **9a**, **9d**, **9e** and **9h**

Table I. IR and ^{1}H NMR data of compounds **9a–i** and **10a–d**.

Compd.	IR [a] (cm^{-1})	^{1}H NMR [b] (δ, ppm)
9a	1608,1583 s,1516 w.	1.11(d,3H,4-CH_3), 3.22(s,6H,N-CH_3), 4.99(q,1H,H-4), 6.62-7.72(m,9H,H-7,8,9,10+phenyl H's).
9b	1612,1578 s,1527 w.	1.19(t,3H,CH_3), 3.04 and 4.02(AB q,J=14.4 Hz,2H,4-CH_2), 3.97(q,2H,N-CH_2), 6.73-7.92(m,14H, H-7,8,9,10+phenyl H's).
9c	1613,1588 s,1530.	3.18(s,6H,CH_3), 3.80(s,2H,4-CH_2), 6.91-7.53(m,4H,H-7,8,9,10), 8.54(s,1H,H-1).
9d	1611,1586 s,1537 w.	2.58(s,3H,1-CH_3), 3.02 and 4.42(AB q,J=13.8 Hz,2H,4-CH_2), 3.18(s,6H,N-CH_3), 6.78-7.46(m,4H, H-7,8,9,10).
9e	1611,1584 s,1528 w.	2.91 and 4.49(AB q,J=15 Hz,2H,4-CH_2), 3.22(s,6H,CH_3),6.62-7.73(m,9H,H-7,8,9,10+phenyl H's).
9f	1610,1579 s,1530.	1.23(t,6H,CH_3), 3.55(q,4H,N-CH_2), 3.75(s,2H,4-CH_2), 6.86-7.56(m,4H,H-7,8,9,10), 8.54(s,1H,H-1).
9g	1610,1580 s,1537 w.	1.23(t,6H,CH_3), 2.59(s,3H,1-CH_3), 3.03 and 4.31(AB q,J=14.4 Hz,2H,4-CH_2), 3.54(q,4H,N-CH_2), 6.80-7.46(m,4H,H-7,8,9,10).
9h	1611,1581 s,1531 w.	1.27(t,6H,CH_3), 3.12 and 4.36(AB q,J=14.4 Hz,2H,4-CH_2), 3.58(q,4H,N-CH_2), 6.65-7.75(m,9H, H-7,8,9,10+phenyl H's).
9i	1610,1578 s,1534 w.	1.98(mc,4H,β-CH_2), 3.25 and 4.31(AB q,J=14.4 Hz,2H,4-CH_2), 3.71(mc,4H,α-CH_2), 6.65-7.75(m, 9H,H-7,8,9,10+phenyl H's).
10a	1605 w,1592 w,1579 w,1523 br,1501.	2.00(near d,3H,CH_3),4.42(near q,1H,H-9), 6.77-7.84(m,14H,H-1,2,3,4+phenyl H's).
10b	1606 w,1594 w,1580 w,1540 br,1502.	6.89-7.78(m,H-1,2,3,4+phenyl H's). [c]
10c	3110,1598 w,1587 w,1535,1515,1502.	compound insufficiently soluble
10d	1590 w,1542,1506 br.	2.46(s,6H,CH_3), 4.04 and 4.47(AB q,J=15 Hz,2H,9-CH_2), 7.47-8.03(m,4H,H-1,2,3,4).

[a]In $CHCl_3$ solutions for **9a–i,** in KBr pellets for **10a–d**. Abbreviations: s = strong, w = weak, br = broad. [b]Solvents: $CDCl_3$ for **9a–i**, $(CD_3)_2SO$ for **10a**, **d**, CF_3COOD for **10b**. [c]The 9-CH_2 signal of **10b** is absent due to replacement of methylene protons with deuterium.

Table II. Pharmacological data of compounds **9a–i** and **10a**, **b**.

Compd.	Approximate oral LD_{50} in mice (mg/kg)	Analgesic activity in mice[a]	Anti-inflammatory activity in rats[b] Edema (μl) (mean ± S.D.)	Inhibition (%)
9a	980	20	182±15*	31
9b	>3200	10	282±66	0
9c	950	10	237±67	10
9d	1490	20	275±95	0
9e	510	20	135±51*	49
9f	830	60*	242±34	8
9g	860	50**	212±83	20
9h	430	20	193±36**	27
9i	1020	0	197±53**	25
10a	>2000	0	283±37	0
10b	>3200	0	194±84	26
dipyrone	3120	80*	-	-
indomethacin	25	-	106±42*	60

[a]Hot plate test; % protection produced by oral administration of 1/4 LD_{50} in mice, except for **9b**, **10a**, **10b** given at the dose of 1.0 g/kg; *$P < 0.01$, **$P < 0.02$ Fisher exact test *versus* controls. [b]Carrageenin paw edema test (control value 264 ± 53 μl); effect produced by oral administration of 1/4 LD_{50} in mice, except for **9b**, **10a** and **10b** (1.0 g/kg); *$P < 0.01$, **$P < 0.05$ Student's *t* test *versus* controls.

showed a weak activity, whereas the remaining compounds were minimally active or completely inactive.

Compounds **9a**, **9e**, **9h** and **9i** gave a statistically significant but variably pronounced anti-inflammatory response in the carrageenin-induced edema assay in the rat. The most active was **9e** which afforded a protection of 49%, whereas the equitoxic dose of indomethacin (6 mg/kg) exhibited a protection of 60%. The remaining compounds were weakly active or completely inactive.

All the 5 compounds tested (**9d–h**) were completely devoid of activity in antagonizing pentylenetetrazole-induced lethal clonic convulsions in mice, whereas 100% protection was obtained with 100 mg/kg of phenobarbital.

No significant gross behavioral effects were observed in mice. Changes indicative of CNS depression, such as slight sedation, moderate decrease of spontaneous motor activity or ptosis were inconstantly observed 1 h after treatment with **9a**, **9e** and **9i**; in contrast, **9c** produced at the same time weak symptoms of CNS stimulation, such as hyperactivity, stereotypies and exophthalmus.

Conclusions

Our results indicate that some of the tricyclic compounds **9** possess analgesic or anti-inflammatory properties, associated with low acute toxicity, whereas practically no activity was showed by the tetracyclic compounds **10a**, **b**.

In terms of analgesic activity, favourable results in the hot plate test were obtained with **9f** and **9g**. By comparing these results with those obtained with compounds **9h**, **9c** and **9d**, it appears reasonable to suggest that the presence of the phenyl substituent in position 1 and of a small dialkylamino group in position 5 is unfavourable for analgesic activity in this class of [1,2,4]triazolo[4,3-*a*][1,5]benzodiazepine derivatives.

On the other hand, compounds **9a**, **9e**, **9h** and **9i** were effective in the carrageenin-induced edema assay in the rat. It is interesting to observe that in this case the presence of the phenyl group in position 1 seems to be necessary for anti-inflammatory activity (compare **9e** with **9c** and **9d**) and that an unbulky dialkylamino substituent in position 5 appears to be more favourable.

Experimental protocols

Chemistry

Melting points were determined using a Fisher–Johns (Electrothermal when above 300°C) apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer 398 spectrophotometer. ^{1}H NMR spectra were recorded on a Hitachi Perkin–Elmer R 600 (60 MHz) spectrometer, using $(CH_3)_4Si$ as an internal reference ($\delta = 0$). Analyses of all new compounds, indicated by the symbols of the elements, were within ± 0.4% of the theoretical values and were performed by Laboratorio di Microanalisi, Istituto di Scienze Farmaceutiche, Università di Genova.

Thin layer chromatograms were run on Merck silica gel 60 F_{254} pre-coated 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).

*4-(Dimethylamino)-1,3-dihydro-3-methyl-2*H*-1,5-benzodiazepin-2-one **5a** and ethyl 2-(2-benzimidazolyl)-2-hydroxypropanoate **6***

Phosphorus oxychloride (15.33 g, 0.10 mol) was added dropwise with stirring to an ice bath cooled mixture of *o*-phenylenediamine (10.81 g, 0.10 mol) and ethyl 2-methyl-*N*,*N*-dimethylmalonamate **4** [9] (34.64 g, 0.20 mol). The viscous mixture was then heated for 5 h at 120°C, while stirring. After cooling, the resulting amorphous solid material was treated many times with cold, then with boiling water, while vigorously stirring. The resulting suspension was treated with charcoal, then filtered, and the filter cake was thoroughly washed with boiling water. The acid solution obtained was cooled and made alkaline by the addition of concentrated aqueous ammonia, then exhaustively extracted with chloroform to recover the oil that separated. The combined extracts were washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The resulting oily residue was dissolved in ethyl ether. After standing, the white crystalline compound **5a** (1.96 g, 9% yield) separated out, mp 192-193°C after recrystallization from ethyl acetate. Anal $C_{12}H_{15}N_3O$ (C, H, N). IR ($CHCl_3$), cm^{-1}: 3390 and 3195 broad (NH), 1664 (CO), 1611, 1582. ^{1}H NMR ($CDCl_3$), δ: 1.04 (d, 3H, 3-CH_3), 3.11 (s, 6H, N-CH_3), 4.22 (near q, 1H, H-3), 6.82-7.37 (m, 4H, H-6, 7, 8, 9), 9.72 (broad s, 1H, H-1; disappeared with D_2O).

By allowing the ethyl ether solution to stand at room temperature, the crystallization of compound 6 (4.92 g, 21%) was obtained, which was identified by direct comparison (mp, IR) with an authentic sample [6].

*4-(Dimethylamino)-1,3-dihydro-3-methyl-2*H*-1,5-benzodiazepin-2-thione **7a**, 4-[(*N*-ethyl, N-phenyl)amino]-1,3-dihydro-2*H*-1,5-benzodiazepin-2-thione **7b***

A mixture of 0.01 mol of compound **5a** (2.17 g) or **5b** [10] (2.79 g), 0.0055 mol (2.22 g) of Lawesson's reagent and 20 ml of anhydrous toluene was heated at 100°C for 30 min, while stirring. The solvent was then removed *in vacuo*, the residue treated with a little chloroform, and the resulting solution submitted to column chromatography (neutral aluminum oxide). By eluting with a mixture chloroform-ethyl acetate (1/1) compound **7a** or **7b** was recovered, yellow solid which was then crystallized from ethanol.

7a: 2.13 g (91%), mp 152-153°C after crystallization. Anal $C_{12}H_{15}N_3S$ (C, H, N, S). IR ($CHCl_3$), cm^{-1}: 3355 and 3160 broad, weak (NH), 1610, 1580 strong. ^{1}H NMR ($CDCl_3$), δ: 0.98 (d, 3H, 3-CH_3), 3.17 (s, 6H, N-CH_3), 5.03 (q, 1H, H-3), 6.71-7.28 (m, 4H, H-6, 7, 8, 9), 11.18 (broad s, 1H, H-1; disappeared with D_2O).

7b: 2.75 g (93%), mp 206-207°C after crystallization. Anal $C_{17}H_{17}N_3S$ (C, H, N, S). IR ($CHCl_3$), cm^{-1}: 3360 and 3150 broad, weak (NH), 1612, 1573 strong. ^{1}H NMR ($CDCl_3$), δ: 1.17 (t, 3H, CH_3), 3.32 (s, 2H, CH_2), 3.94 (q, 2H, N-CH_2),

6.72-7.71 (m, 9H, H-6, 7, 8, 9 + phenyl H's), 11.82 (broad s, 1H, H-1; disappeared with D_2O).

3-Methyl-N,N-*dimethyl-4-(methylthio)-3*H-*1,5-benzodiazepin-2-amine* ***8a***, N-*ethyl*-N-*phenyl-4-(methylthio)-3*H-*1,5-benzodiazepin-2-amine* ***8b***

To a solution containing 0.0125 mol of compound **7a** (2.92 g) or **7b** (3.69 g) and 100 ml of anhydrous tetrahydrofuran-anhydrous toluene (1/1), 0.38 g of 80% NaH in white oil (0.0125 mol) was added. After stirring at 50°C for 45 min, 0.0145 mol (2.05 g) of CH_3I was added and the mixture was further stirred at 50°C for 90 min. The solvents were then removed *in vacuo* and the residue was partitioned between ethyl acetate and water. The aqueous phase was extracted several times with ethyl acetate. The combined organic phases were dried (anhydrous sodium sulfate) and the solvent removed to afford nearly pure compound **8a** or **8b** as thick oil.

8a. The oil (2.75 g, 89%) was used for the preparation of **9a** without further purification. IR ($CHCl_3$), cm^{-1}: 1602, 1571. ^1H NMR ($CDCl_3$), δ: 0.77 (d, 3H, 3-CH_3), 2.45 (s, 3H, SCH_3), 3.11 (s, 6H, N-CH_3), 4.24 (q, 1H, H-3), 6.79-7.45 (m, 4H, H-6, 7, 8, 9).

8b. By adding some ethyl ether–petroleum ether 40-70°C (1/1) to the oil, 3.60 g (93%) of solid pure compound **8b** separated out, white crystals melting at 116-117°C after crystallization from petroleum ether 40-70°C. Anal $C_{18}H_{19}N_3S$ (C, H, N, S). IR ($CHCl_3$), cm^{-1}: 1590, 1563. ^1H NMR ($CDCl_3$), δ: 1.16 (t, 3H, ethyl CH_3), 2.42 (s, 3H, SCH_3), 2.83 (s, 2H, CH_2), 3.91 (q, 2H, N-CH_2), 6.81-7.64 (m, 9H, H-6, 7, 8, 9 + phenyl H's).

N,N-*Disubstituted* 4H-*[1,2,4]triazolo[4,3*-a*][1,5]benzodiazepin-5-amines* ***9a–i*** *and* 9H-bis*[1,2,4]triazolo[4,3*-a*:3',4'*-d*][1,5]benzodiazepines* ***10a–d***

General procedure. A mixture of 0.006 mol of suitable compound **8** (1.48 g of **8a**, 1.86 g of **8b**, 1.40 g of **8c**, 1.57 g of **8d**, 1.56 g of **8e**), 0.008 mol of formylhydrazine (0.48 g) or acetylhydrazine (0.59 g) or benzoylhydrazine (1.09 g), and 10 ml of Dowtherm A was heated at 200°C for 2 h while stirring. Only in the reaction with **8a**, 0.006 mol (0.82 g) of benzoylhydrazine was used and the mixture heated at 200°C for 1 h. After cooling, the final suspension was diluted with ethanol (10 ml) and filtered to collect compound **10** as white solid which was then washed with a little ethanol and dried. The filtrate was then evaporated under reduced pressure to remove ethanol and volatile reaction products, then the residue was chromatographed on a silica gel column. The column was first eluted with benzene until Dowtherm A and impurities were completely removed, then with benzene–triethylamine (9/1). This eluate was evaporated and a little ethyl ether was added to the thick oily residue. After standing, white crystalline compound **9** separated out.

4-Methyl-N,N-*dimethyl-1-phenyl-4*H-*[1,2,4]triazolo[4,3*-a*][1,5]benzodiazepin-5-amine* ***9a***. Obtained from benzoylhydrazine and **8a**, 0.65 g (34%), mp 188-189°C after recrystallization from cyclohexane. Anal $C_{19}H_{19}N_5$ (C, H, N).

N-*Ethyl*-N-*phenyl-1-phenyl-4*H-*[1,2,4]triazolo[4,3*-a*][1,5]benzodiazepin-5-amine* ***9b***. Obtained from benzoylhydrazine and **8b**, 1.58 g (69%), mp 190-191°C (from cyclohexane). Anal $C_{24}H_{21}N_5$ (C, H, N).

N,N-*Dimethyl-4*H-*[1,2,4]triazolo[4,3*-a*][1,5]benzodiazepin-5-amine* ***9c***. Obtained from formylhydrazine and **8c** [5], 0.34 g (25%), mp 223-224°C (from ethyl acetate). Anal $C_{12}H_{13}N_5$ (C, H, N).

1-Methyl-N,N-*dimethyl-4*H-*[1,2,4]triazolo[4,3*-a*][1,5]benzodiazepin-5-amine* ***9d***. Obtained from acetylhydrazine and **8c**, 0.80 g (55%), mp 212-213°C (from ethyl acetate). Anal $C_{13}H_{15}N_5$ (C, H, N).

N,N-*Dimethyl-1-phenyl-4H-[1,2,4]triazolo[4,3*-a*][1,5]benzodiazepin-5-amine* ***9e***. Obtained from benzoylhydrazine and **8c**, 0.86 g (47%), mp 179-180°C (from cyclohexane). Anal $C_{18}H_{17}N_5$ (C, H, N).

N,N-*Diethyl-4*H-*[1,2,4]triazolo[4,3*-a*][1,5]benzodiazepin-5-amine* ***9f***. Obtained from formylhydrazine and **8d** [5], 0.58 g (38%), mp 145-146°C (from cyclohexane). Anal $C_{14}H_{17}N_5$ (C, H, N).

N,N-*Diethyl-1-methyl-4*H-*[1,2,4]triazolo[4,3*-a*][1,5]benzodiazepin-5-amine* ***9g***. Obtained from acetylhydrazine and **8d**, 1.12 g (69%), mp 169-170°C (from cyclohexane). Anal $C_{15}H_{19}N_5$ (C, H, N).

N,N-*Diethyl-1-phenyl-4*H-*[1,2,4]triazolo[4,3*-a*][1,5]benzodiazepin-5-amine* ***9h***. Obtained from benzoylhydrazine and **8d**, 1.50 g (75%), mp 138-139°C (from cyclohexane). Anal $C_{20}H_{21}N_5$ (C, H, N).

1-Phenyl-N,N-*tetramethylene-4*H-*[1,2,4]triazolo[4,3*-a*][1,5]benzodiazepin-5-amine* ***9i***. Obtained from benzoylhydrazine and **8e** [5], 1.20 g (61%), mp 226-227°C (from ethyl acetate). Anal $C_{20}H_{19}N_5$ (C, H, N).

*9-Methyl-6,12-diphenyl-9*H-bis*[1,2,4]triazolo[4,3*-a*: 3',4'*-d*][1,5]benzodiazepine* ***10a***. Obtained from benzoylhydrazine and **8a**, 0.31 g (13%), mp 350-352°C dec after crystallization from ethanol. Anal $C_{24}H_{18}N_6$ (C, H, N).

*6,12-Diphenyl-9*H-bis*[1,2,4]triazolo[4,3*-a*: 3',4'*-d*][1,5]benzodiazepine* ***10b***. Obtained from benzoylhydrazine and **8b** (0.27 g, 12%), **8c** (0.50 g, 22%), **8d** (0.26 g, 12%), or **8e** (0.53 g, 23%). Mp 350-351°C dec (from ethanol). Anal $C_{23}H_{16}N_6$ (C, H, N).

9H-Bis*[1,2,4]triazolo[4,3*-a*:3',4'*-d*][1,5]benzodiazepine* ***10c***. Obtained from formylhydrazine and **8c** (0.30 g, 22%), or **8d** (0.10 g, 7%). Mp > 360°C [from chloroform–methanol (1/1)]. Anal $C_{11}H_8N_6$ (C, H, N).

*6,12-Dimethyl-9*H-bis*[1,2,4]triazolo[4,3*-a*: 3',4'*-d*][1,5]benzodiazepine* ***10d***. Obtained from acetylhydrazine and **8c** (0.30 g, 20%), or **8d** (0.17 g, 11%). Mp 352-354°C dec (from ethanol). Anal $C_{13}H_{12}N_6$ (C, H, N).

IR and ^1H NMR data of compounds **9a–i** and **10a–d** are reported in Table I.

Pharmacology

Male albino Swiss mice (18-22 g) and male Sprague–Dawley rats (140-160 g) were used. The animals were starved for about 12 h before treatment. All compounds were administered orally in a 1% carboxymethylcellulose suspension. With the exception of compounds **9b**, **10a** and **10b** tested at 1.0 g/kg, the dose constantly employed in pharmacological assays was 1/4 *po* LD_{50} in mice.

Acute toxicity and gross behavorial effects in mice

The approximate LD_{50} was obtained from the mortality observed during a 7-day period in groups of 5 animals treated with log-spaced doses. Behavioral alteration of groups of 4 mice was studied according to the Morpurgo's modification [11] of the Irwin's multidimensional screening procedure. Detailed observation of mice was performed 1, 3 and 24 h after treatment. Perphenazine (50 mg/kg, ip) and methylphenidate (50 mg/kg ip) were used for comparison.

Analgesic activity

This was determined according to the hot plate method described by Eddy *et al* [12]. Groups of 10 mice were used. They were placed individually on a copper plate (48 ± 0.5°C), and

the time of a reaction to pain, licking of the hind paws or jumping, was recorded before and 30, 45, 60 and 90 min after administration of the test compound. The mice were removed as soon as they reacted or, if they failed to react, after 60 s. An equitoxic dose of dipyrone (780 mg/kg) was used as reference standard.

Anti-inflammatory activity
The carrageenin-induced paw edema test [13] was used on groups of 6 rats. Sixty min after drug administration, 0.05 ml of a 1% carrageenin solution in saline was injected into the plantar surface of the right hind paw of each rat. Paw volume, determined by measuring the amount of water displaced after immersing the paw to the level of the lateral malleolus, was calculated immediately after the carrageenin injection, and again 2 h later; the difference between these 2 values was taken as edema volume. The percent inhibition of the edema of treated rats with respect to controls was calculated and compared with that produced by an equitoxic dose of indomethacin (6 mg/kg).

Anticonvulsant activity
Test compound was given orally to 6 mice 1 h before the ip injection of 130 mg/kg pentylenetetrazole. The protection against pentylenetetrazole-induced lethal convulsions was evaluated for a period of 15 min, and compared with that afforded by phenobarbital (100 mg/kg).

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