1,2,3-Triazolodiazepines. I. Preparation and Benzodiazepine Receptor Binding of 1-Benzyl- and 1-Phenethyl-1,2,3-triazolo-[4,5-*b*][1,4]diazepines

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Several new 1,2,3-triazolo[4,5-*b*][1,4]diazepines were prepared starting from 1-benzyl-**1** and 1-phenethyl-4,5-diamino-1,2,3-triazole **2** (Scheme 1), by condensation reactions with β-diketones (Scheme 2), β-ketoesters (Scheme 3), and diethyl malonates (Scheme 4). In the first case we obtained compounds **3** and **4** with basic properties, while the ester function condensations gave cyclic amide derivatives **7**, **8**, **10**, **12** and **13** with acid properties. Some *N*-methyl derivatives **11**, **14** and **15** were obtained from the cyclic amide compounds. Most of compounds were tested for their ability to displace [^{3}H]flunitrazepam from bovine brain membranes but no compound showed benzodiazepine receptor binding affinity.

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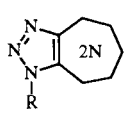
The 1,2,3-triazoles fused with a diazepine ring, corresponding to the general structures **A** and **B**, which bear 4 and 5 nitrogen atoms respectively, have been studied very little up to today.

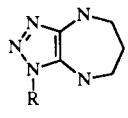
In fact, after the preparation of one 1,2,3-triazolo[4,5-*b*]-[1,4]diazepine compound published in 1972 by Lovelette and Long [1], some 1,2,3-triazolo[4,5-*e*][1,4]diazepines were synthesized in 1986 [2] as potential bronchoconstrictors because they were blood platelet-activating factor agonists. An analogous derivative was prepared in 1989 [3]. The structure and the conformation of the 2-azacoformycin, a 1,2,3-triazolo-[4,5-*d*][1,3]diazepine, 2-nitrogen analog of the antibiotic nucleoside coformycin, were elucidated in 1985 [4]. This aza-analog is much more effective than the parent antibiotic as a potent adenosine-deaminase inhibitor, and its total synthesis was reported in 1986 [5]. At last a recent patent [6] concerning diazolo- and triazolo[1,3]diazepine nucleosides confirms the interest in these structures as antitumor agents.

Therefore stimulated by the present pharmaceutical interest, by the traditional tranquillizing activity associated with the diazepine structures and with a poor knowledge of the subject, we have undertaken the study of 1,2,3-triazolodiazepine compounds beginning from the preparation of 1-substituted-1,2,3-triazolo[4,5-*b*][1,4]-diazepines corresponding to the general formula **C**.



A

B



C

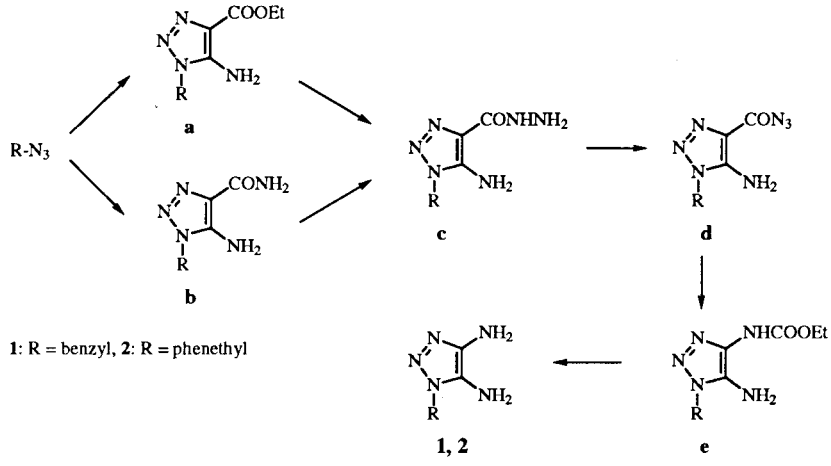
In Scheme 1 is illustrated the synthesis of 1-benzyl-4,5-diamino-1,2,3-triazole **1**, according to Lovelette and Long [1] and of 1-phenethyl-4,5-diamino-1,2,3-triazole **2**, starting from benzylazide [7] and phenethylazide [8] respectively. The 1,3-dipolar cycloaddition reaction of benzylazide or phenethylazide to ethyl cyanoacetate under the usual experimental conditions, provided the expected triazole derivatives **1a** and **2a** in poor yield, as reported in the literature for the benzylazide [9,10]. On the contrary the reaction of the same azide with cyanacetamide gave the corresponding triazole derivatives **1b** [11] and **2b** in good yield. Thus the carboxyhydrazides **1c** and **2c**, easily obtained from the poorly available ester derivatives, were prepared from the respective carboxamides **1b** and **2b** by heating at 140° with hydrazine hydrate in DMSO solution. The carboxyhydrazides **1c** and **2c** in diluted hydrochloric acid, by treatment with an equimolar amount of sodium nitrite, gave the carbonylazides **1c** and **2c** respectively. These compounds, since the Curtius reaction failed, were converted, by refluxing in ethanol, to the corresponding urethanes **1e** [1] and **2e**, which provided the expected 4,5-diaminotriazoles **1** [1] and **2** by alkaline hydrolysis (Scheme 1).

These two diamino compounds were employed in reactions with the appropriate β-dicarbonyl or β-dicarboxyl agents to obtain seven-membered rings fused with the 1,2,3-triazole ring.

The reaction with β-diketones to synthesize 6*H*-5,7-disubstituted-1,2,3-triazolo[4,5-*b*][1,4]diazepines is reported in Scheme 2.

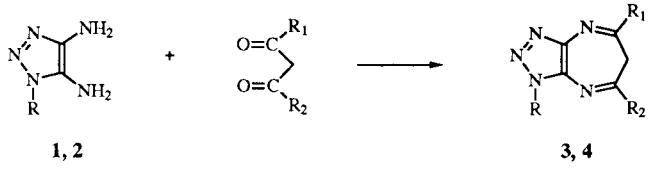
Thus **1** and **2** reacted with dibenzoylmethane in reflux-

Scheme I



ing ethanol in the presence of hydrochloric acid to give respectively the expected derivative **3a**, isolated in good yield, and **4a**, isolated in low yield as the dihydrochloride (Table I). Under the same experimental conditions, the reaction of **1** or **2** with benzoylacetone gave a single compound, isolated in low yield as the monohydrochloride, corresponding to one of the two possible isomer structures **3b** or **3b'** and **4b** or **4b'** respectively (Table I).

Scheme II



The reaction with acetylacetone gave the expected derivatives **3c** and **4c**, which were isolated in moderate yield as the monohydrochloride hydrate (Table I). The structural formulas were assigned considering the analytical and spectroscopic data. The ^{1}H-nmr and ^{13}C-nmr spectra (Table IV) showed the presence of an azomethynic structure when the carbonylic function of the reagent was substituted with a phenyl ring (**3a**, **4a**, **3b**, **4b**) and of a enamine structure when a methyl substituent was present (**3c**, **4c**). This condition did not allow the assignment of the structure to the isomers **3b** or **b'** and **4b** or **b'** by comparison.

The 4,5-diaminotriazoles **1** and **2** reacted with β-ketoesters to give 1,5-disubstituted-1,2,3-triazolo[4,5-*b*]-[1,4]diazepin-7-ones as illustrated in the Scheme 3. Thus **1** reacted with ethyl acetoacetate, as previously reported [1], and the open chain enamine intermediate **5a** was isolated in high yield. This assignment was based on the assumption that the carbonyl function would react preferentially with the more reactive 4-amino group of **1**. The compound **5a** was then cyclized to the diazepine **7a** by heating in ethanolic sodium ethoxide (equivalent amount) under reflux (Table II).

The reaction of **2** with ethyl acetoacetate occurred in the same manner to give the intermediate **6a** and the corresponding cyclized compound **8a** (Table II).

Table I

Chemical and Physical Properties of Derivatives **3** and **4**

Compound	R	R_1	R_2	Yield %	Crystall. Solvent	Mp °C	Elemental Analysis	Calcd./Found C	H	N
3a	benzyl	C_6H_5	C_6H_5	52	EtOH	171-173	$C_{24}H_{19}N_5$	76.39	5.04	18.57
								76.57	5.04	18.69
3b	"	C_6H_5	CH_3	34	EtOH	265 dec	$C_{19}H_{17}N_5$•HCl	64.86	5.12	19.91
3b'	"	CH_3	C_6H_5					64.82	5.02	20.02
3c	"	CH_3	CH_3	22	EtOH-Et_2O	194-196	$C_{14}H_{15}N_5$•HCl•H_2O	54.64	5.89	22.77
								54.80	5.75	23.05
4a	phenethyl	C_6H_5	C_6H_5	13	EtOH-Et_2O	257-260	$C_{25}H_{21}N_5$•2HCl	64.66	4.96	15.09
								65.00	5.23	15.24
4b	"	C_6H_5	CH_3	18.5	EtOH-Et_2O	242-245	$C_{20}H_{19}N_5$•HCl	65.67	5.51	19.14
4b'	"	CH_3	C_6H_5					65.48	5.49	19.22
4c	"	CH_3	CH_3	42.5	EtOH-Et_2O	192-196	$C_{15}H_{17}N_5$•HCl•H_2O	55.99	6.26	21.77
								56.20	6.11	21.54

Table II

Chemical and Physical Properties of Derivatives **5-11**

Compound	R	R_1	Yield %	Crystallization Solvent	Mp °C	Elemental Analysis	Calcd./ Found C H N
5a	$C_6H_5CH_2$	CH_3	81	$CHCl_3$-hexane	123-125	[1]	
5b	"	C_3H_7	82	$CHCl_3$-hexane	111-115	$C_{17}H_{23}N_5O_2$	61.98 7.04 21.28 61.74 6.75 21.52
6a	$C_6H_5(CH_2)_2$	CH_3	84	C_6H_6-petroleum ether	110-113	$C_{16}H_{21}N_5O_2$	60.95 6.71 22.22 61.23 6.92 22.48
6b	"	C_3H_7	65	C_6H_6-petroleum ether	100-102	$C_{18}H_{25}N_5O_2$	62.97 7.34 20.41 63.30 7.16 20.37
7a	$C_6H_5CH_2$	CH_3	84	C_6H_6	230-232 dec	[1]	
7b	"	C_3H_7	90	C_6H_6	210-215 dec	$C_{15}H_{17}N_5O$	63.60 6.07 24.73 63.61 6.03 24.49
8a	$C_6H_5(CH_2)_2$	CH_3	72	dioxane	268-270	$C_{14}H_{15}N_5O$	62.45 5.61 26.02 62.71 5.56 26.08
8b	"	C_3H_7	83	C_6H_6-petroleum ether	222-223	$C_{16}H_{19}N_5O$	64.62 6.44 23.57 64.41 6.14 23.29
9a	$C_6H_5CH_2$		58.5	EtOH	193-195	$C_{18}H_{17}N_5O_2$	64.47 5.11 20.89 64.23 4.89 20.78
9b	$C_6H_5(CH_2)_2$		57.5	EtOH	184-186	$C_{19}H_{19}N_5O_2$	65.32 5.48 20.04 65.38 5.33 20.00
10a	$C_6H_5CH_2$		51	EtOH	200-203	$C_{18}H_{15}N_5O$	68.14 4.73 22.08 67.88 4.85 22.02
10b	$C_6H_5(CH_2)_2$		47	EtOH	260-263	$C_{19}H_{17}N_5O$	68.88 5.14 21.15 69.17 5.13 20.95
11a	$C_6H_5CH_2$		34	EtOH	193-195	$C_{14}H_{15}N_5O$	62.45 5.61 26.02 62.71 5.56 26.08
11b	$C_6H_5(CH_2)_2$		25	EtOH	182-186	$C_{15}H_{17}N_5O$	63.60 6.05 24.73 63.60 5.91 24.41

Similarly with ethyl butyrylacetate **1** and **2** provided the enaminic compounds **5b** and **6b** which were cyclized to the corresponding triazolodiazepines **7b** and **8b** (Table II).

On the contrary with ethyl benzoylacetate **1** and **2** condensed their amino group in the 4 position with the ester function to give the carboxamido intermediates **9a** and **9b**, as suggested by analytical and ^1H nmr spectroscopic data. Therefore these compounds, by acid catalyzed intramolecular cyclization in ethanol, provided the corresponding 1,7-disubstituted-1,2,3-triazolo[4,5-*b*][1,4]-diazepin-5-ones **10a** and **10b** (Table II).

The triazolodiazepines **7a** and **8a** underwent an *N*-methylation with methyl iodide in methanolic sodium hydroxide at room temperature, as well as the analogous benzodiazepine compounds [12], to give the derivatives **11a** and **11b** (Table II).

Finally Scheme 4 shows the preparation, *via* a condensation reaction of **1** and **2** with ethyl malonates, of some 1,2,3-triazolo[4,5-*b*][1,4]diazepine-5,7-diones and their conversion into 4*N*,8*N*-dimethyl derivatives.

Thus heating **1** or **2** with diethyl malonate, diethyl methylmalonate and diethyl phenylmalonate in ethanolic solution in the presence of two equivalents of sodium ethoxide, the triazolodiazepindiones **12a** and **13a** (6-unsubstituted), **12b** and **13b** (6-methyl-substituted), **12c** and **13c** (6-phenyl-substituted) were obtained in moderate yields (Table III). These compounds showed acidic properties which allowed their isolation by acidification of sodium salt solutions. The compounds **12a-c** and **13a-c** were *N*-alkylated under the experimental conditions previously reported [12] to give the corresponding 4*N*,8*N*-dimethyl derivatives **14a-c** and **15a-c** (Table III). The structures of all the prepared compounds agreed with the involved reaction mechanism and were confirmed by analytical and spectroscopic data. The mass, ^1H-nmr and ^{13}C-nmr spectra of some significant compounds are reported in Table IV.

The 1,2,3-triazolo[4,5-*b*][1,4]diazepine derivatives **3a**, **3b** or **3b'**, **4a**, **4b** or **4b'**, **7a**, **8a**, **12a-c**, **13a-c**, **14a-c** and **15a-c**, were tested for their ability to inhibit benzodiazepine receptor binding, measuring the concentration able to displace the [^3H]flunitrazepam from bovine brain membranes. The experimental details of the receptor binding assay were reported in a previous paper [13]. Unfortunately the biological results have shown that none of the compounds possess a significant affinity towards the benzodiazepine receptor.

Table III

Chemical and Physical Properties of Derivatives **12-15**

Compound	R	R_1	Yield %	Crystallization Solvent	Mp °C	Elemental Analysis	Calcd./Found C	H	N
12a	$C_6H_5CH_2$	H	31.5	EtOH	256-259 dec	$C_{12}H_{11}N_5O_2$	56.03	4.31	27.23
							56.17	4.56	27.55
12b	"	CH_3	43.5	EtOH	274-277	$C_{13}H_{13}N_5O_2$	57.56	4.83	25.83
							57.38	4.95	25.51
12c	"	C_6H_5	78	EtOH	282-285	$C_{18}H_{15}N_5O_2$	64.86	4.50	21.02
							64.61	4.51	20.87
13a	$C_6H_5(CH_2)_2$	H	46	EtOH	295-300	$C_{13}H_{13}N_5O_2$	57.56	4.83	25.83
							57.58	4.87	25.80
13b	"	CH_3	57	EtOH	271-275	$C_{14}H_{15}N_5O_2$	58.95	5.30	24.56
							59.09	5.34	24.32
13c	"	C_6H_5	51	EtOH	246-249	$C_{19}H_{17}N_5O_2$	65.71	4.90	20.17
							65.45	5.17	19.89
14a	$C_6H_5CH_2$	H	56	C_6H_6	159-160	$C_{14}H_{15}N_5O_2$	58.94	5.30	24.56
							59.07	4.96	24.74
14b	"	CH_3	77	C_6H_6	177-181	$C_{15}H_{17}N_5O_2$	60.20	5.72	23.41
							60.23	5.50	23.54
14c	"	C_6H_5	34	C_6H_6	182-184	$C_{20}H_{19}N_5O_2$	66.48	5.30	19.39
							66.62	5.22	19.29
15a	$C_6H_5(CH_2)_2$	H	33.5	C_6H_6-petroleum ether	137-139	$C_{15}H_{17}N_5O_2$	60.20	5.72	23.41
							60.42	6.01	23.48
15b	"	CH_3	37.5	C_6H_6-petroleum ether	122-123	$C_{16}H_{19}N_5O_2$	61.34	6.11	22.36
							61.57	5.96	22.20
15c	"	C_6H_5	47	C_6H_6-petroleum ether	127-130	$C_{21}H_{21}N_5O_2$	67.20	5.60	18.66
							67.44	5.75	18.66

Table IV

Spectroscopic Data

^{1}H NMR (δ, ppm)

3a [a] from 8.10 to 8.04 (m, 4H, Ar), from 7.48 to 7.26 (m, 1H, Ar), 5.71 (s, 2H, CH_2), 3.82 (s, 2H, H-6)

3c [b] 7.93 (bs, 1H, NH), from 7.34 to 7.28 (m, 2H, Ar), 7.13 (q, 1H, J 0.8 Hz, H-6), from 7.03 to 6.99 (m, 3H, Ar), 5.77 (s, 2H, CH_2), 2.44 (d, 3H, CH_3), 2.35 (s, 3H, CH_3)

4b [b] 8.38 (q, 1H, J 1.0 Hz, H-6), from 8.33 to 8.26 (m, 2H, Ar), from 7.62 to 7.22 (m, 8H, Ar), 4.92 (m, 2H, CH_2), 3.28 (m, 2H, CH_2), 2.74 (d, 3H, CH_3)

4c [a] 7.75 (bs, 1H, NH), 7.40 (q, 1H, J 1.0 Hz, H-6), from 7.33 to 7.13 (m, 5H, Ar), 5.23 (m, 2H, CH_2), 3.39 (m, 2H, CH_3), 2.68 (d, 3H, CH_3), 2.67 (d, 3H, CH_3)

6a [b] 9.40 (bs, 1H, NH), from 7.27 to 7.19 (m, 5H, Ar), 5.41 (bs, 2H, NH_2), 4.68 (s, 1H, =CH), 4.33 (m, 2H, CH_2), 4.06 (q, 2H, J 7.08, CH_2), 3.07 (m, 2H, CH_2), 1.69 (s, 3H, CH_3), 1.20 (t, 3H, CH_3)

8a [b] 11.19 (bs, 1H, NH), from 7.24 to 7.10 (m, 5H, Ar), 4.53 (t, 2H, J 7.2 Hz, CH_2), 3.09 (t, 2H, CH_2), 2.93 (s, 2H, H-6), 2.22 (s, 3H, CH_3)

9a [b] 10.28 (bs, 1H, NH), 7.94 (bs, 2H, NH_2), from 7.56 to 7.24 (m, 10H, Ar), 5.39 (s, 1H, =CH), 5.30 (bs, 1H, OH)

10b [b] 8.03 (m, 2H, Ar), 7.51 (m, 3H, Ar), from 7.32 to 7.17 (m, 5H, Ar), 4.61 (m, 2H, CH_2), 3.43 (s, 2H, H-6), 3.17 (m, 2H, CH_2)

11b [a] from 7.33 to 7.18 (m, 3H, Ar), 7.03 (m, 2H, Ar), 4.63 (bt, 2H, CH_2), 3.24 (t, 2H, CH_2), 3.17 (s, 3H, CH_3), 2.87 (bs, 2H, H-6), 2.28 (s, 3H, CH_3)

14a [b] from 7.38 to 7.33 (m, 3H, Ar), from 7.26 to 7.21 (m, 2H, Ar), 5.74 and 5.68 (AB system, 2H, CH_2), 3.55 and 3.17 (AB system, 2H, J 12.5 Hz, H-6), 3.38 (s, 3H, CH_3), 3.14 (s, 3H, CH_3)

14b [a] from 7.38 to 7.34 (m, 3H, Ar), from 7.21 to 7.16 (m, 2H, Ar), 5.67 and 5.56 (AB system, 2H, J 16.0 Hz, CH_2), 3.51 (s, 3H, CH_3), 3.01 (q, 1H, J 6.7 Hz, H-6), 1.31 (d, 3H, CH_3)

15a [a] from 7.25 to 7.21 (m, 3H, Ar), 4.83 (ddd, 1H, J 13.9, 5.9, and 6.7 Hz, 1/2 CH_2), 4.45 (ddd, 1H, J 13.9, 6.8, and 8.6 Hz, 1/2 CH_2), 3.44 (s, 3H, CH_3), 3.25 (m, 2H, CH_2), 3.21 (s, 3H, CH_3), 3.21 and 2.56 (AB system, 2H, J 12.6 Hz, H-6)

[a] In deuteriochloroform. [b] In DMSO.

Table 4 (continued)

13 C NMR data (δ, ppm)

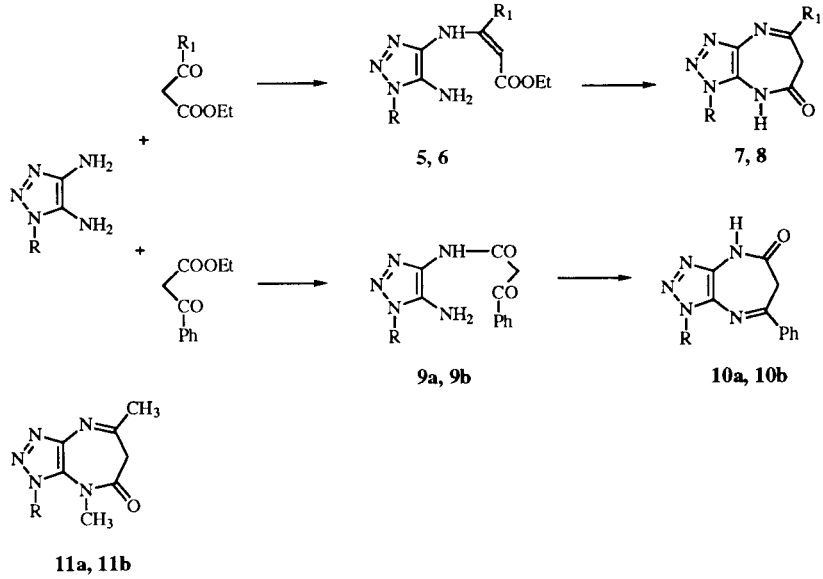
	C-3a	C-5 and C-7	C-6	C-8a	Benzylic or Phenethylic Carbons	Other Carbons
3a [a]	133.9	150.1 147.3	35.9	144.1	50.8, 135.2, from 128.8 to 128.1	136.5, 135.9, 131.7, 131.0
3c	128.8	159.1 140.9	117.9	137.6	52.1, 131.7, 128.2, 128.0, 128.0	23.6, 15.0
4b [a]	129.8	154.5 142.7	114.1	138.7	49.6, 33.3, 136.5, 128.9, 128.8, 127.1	15.5, 134.6, 131.3, 128.2
4c	129.5	160.2 141.6	118.5	138.2	51.5, 33.8, 136.0, 128.9, 128.4, 126.8	24.5, 15.8
6a	125.2	169.1 161.2	85.0	136.6	46.9, 34.1, 137.7, 128.6, 128.0, 126.2	57.8, 18.9, 14.3
8a	123.0	159.9 158.4	42.8	140.5	46.1, 33.3, 135.5, 126.9, 126.4, 124.6	25.9
10b	124.9	161.5 154.4	40.1	142.1	47.7, 34.7, 136.8, 128.4, 127.9, 126.2	137.0, 128.3, 127.1, 130.5
11b	128.0	161.7 163.7	43.9	144.3	50.5, 35.9, 136.5, 128.6, 128.4, 127.1	33.1, 27.9
14a	127.4	162.7 162.0	45.0	138.1	52.0, 134.3, 128.4, 126.7, 127.8	33.5, 31.8
14b	127.1	165.2 164.2	43.8	138.5	52.8, 133.3, 123.0, 126.4, 128.6	34.2, 32.7, 11.0
15a	127.8	163.0 162.1	44.8	138.3	50.4, 35.8, 136.1, 128.8, 128.3, 127.4	34.2, 32.4

[a] Some overlap occurs in the aromatic signals.

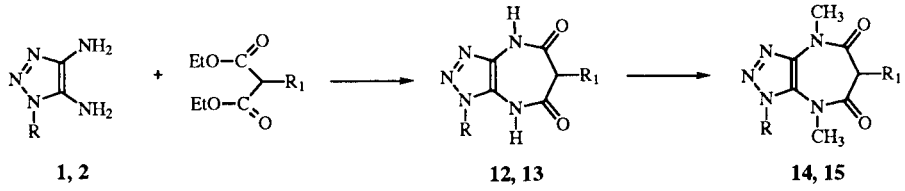
MS m/z (%)

3b	315 (M^+, 5)	196 (43)	169 (67)	129 (67)	91 (97)	67 (100)
4a	391 (M^+, 8)	258 (57)	231 (100)	129 (74)	77 (83)	51 (24)
4c	267 (M^+, 1)	148 (12)	105 (40)	91 (60)	77 (46)	65 (21)
7b	283 (M^+, 1)	254 (3)	184 (3)	118 (3)	91 (100)	65 (17)
10b	331 (M^+, 3)	302 (12)	212 (70)	105 (90)	91 (100)	65 (25)
11b	283 (M^+, 1)	164 (17)	107 (100)	105 (82)	69 (84)	67 (56)
13a	271 (M^+, 1)	152 (5)	105 (13)	91 (33)	69 (34)	42 (100)
14c	361 (M^+, 1)	145 (5)	118 (16)	91 (100)	89 (37)	65 (21)

Scheme III



Scheme IV



EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are uncorrected. The ir spectra in nujol mulls were recorded on a Perkin-Elmer Model 1310 spectrometer. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded with a Bruker AC 200 spectrometer in δ units from TMS as the internal standard. Mass spectra were performed with a Hewlett Packard MS/System 5988. Elemental analyses (C, H, N) were performed on a Carlo Erba Elemental Analyzer Model 1106 apparatus.

1-Phenethyl-4-carbethoxy-5-amino-1*H*-1,2,3-triazole (**2a**).

To a stirred solution of sodium ethoxide, prepared from 0.380 g (16.5 mmoles) of sodium in 25 ml of anhydrous ethanol, a solution of 2.20 g (15 mmoles) of phenethylazide [8] and 1.86 g (16.5 mmoles) of ethyl cyanacetate in 5 ml of ethanol was added dropwise. The reaction mixture was refluxed for 4 hours and the resulting suspension was poured into cold water and extracted with chloroform. The chloroform layer was dried and evaporated *in vacuo* to give a liquid residue from which, the title compound was obtained by washing with 60-80° petroleum ether, 0.65 g (15%), mp 174-175° (ethanol); ir: μ 2.90, 3.05, 3.15 (NH_2), 5.90 (COOEt).

Anal. Calcd. for $C_{13}H_{16}N_4O_2$: C, 60.00; H, 6.20; N, 21.53. Found: C, 59.70; H, 6.21; N, 21.33.

1-Phenethyl-4-carboxamido-5-amino-1*H*-1,2,3-triazole (**2b**).

To a stirred solution of sodium ethoxide, prepared from 4.10 g (0.178 mole) of sodium in 120 ml of anhydrous ethanol, 14.96 g (0.178 mole) of cyanacetamide were added; after 15 minutes of stirring, a solution of 23.81 g (0.162 mole) of phenethylazide [8] in 50 ml of ethanol was added dropwise to the resulting suspension and the mixture was refluxed for 5 hours. After cooling the solid **2b** was collected by filtration and washed with water, 26.81 g (72%); mp 180-182° (ethanol); ir: μ 2.95, 3.05, 3.15 (NH), 6.15 ($CONH_2$).

Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.67; N, 30.30. Found: C, 56.96; H, 6.00; N, 30.10.

1-Phenethyl-4-carboxyhydrazido-5-amino-1*H*-1,2,3-triazole (**2c**).

To a solution of 30.0 g (0.13 mole) of **2b** in 35 ml of DMSO, 125 ml (3.42 moles) of 99% hydrazine hydrate was added and the mixture was heated at 140° for 10 hours. By dilution with water, the title compound precipitated as a white solid which was collected and washed with water; repeated concentrations of the mother liquors and diluition with water provided further amount of the product, 26 g (81%), mp 155-157° (ethanol); ir: μ 2.95, 3.18, 3.25 (NH), 6.00 ($CONHNH_2$).

Anal. Calcd. for $C_{11}H_{14}N_6O$: C, 53.66; H, 5.73; N, 34.13. Found: C, 53.44; H, 5.73; N, 34.12.

1-Phenethyl-4-carbonylazido-5-amino-1*H*-1,2,3-triazole (**2d**).

To a cold suspension of 2.80 g (11.4 mmoles) of **2c** in 37 ml of 3*M* hydrochloric acid, a solution of 0.785 g (11.4 mmoles) of sodium nitrite in 6 ml of water was added dropwise with stirring. After 30 minutes a small amount of urea was added, then the yellow solid **2d** was quickly collected and washed with water, 2.67 g (91%), mp 150° dec (acetone-hexane); ir: μ 4.70 (N_3), 6.00 (CON_3).

Anal. Calcd. for $C_{11}H_{11}N_7O$: C, 51.36; H, 4.28; N, 38.13. Found: C, 51.13; H, 4.36; N, 37.84.

1-Phenethyl-4-ethoxycarbonylamino-5-amino-1*H*-1,2,3-triazole (**2e**).

A solution of 2.40 g (9.3 mmoles) of **2d** in 30 ml of anhydrous ethanol was refluxed for 24 hours. The title compound precipitated by cooling as a white solid which was crystallized from ethanol: 1.60 g (62%), mp 198-201° dec; ir: μ 3.00, 3.05, 3.15 (NH), 5.85, 6.05, 6.20 (NHCOOEt).

Anal. Calcd. for $C_{13}H_{17}N_5O_2$: C, 56.72; H, 6.22; N, 25.45. Found: C, 56.86; H, 6.41; N, 25.60.

1-Phenethyl-4,5-diamino-1,2,3-triazole (**2**).

A solution of 3.01 g (11 mmoles) of **2e** in 6 ml of ethanol and 36 ml of 2*M* sodium hydroxide was gently refluxed for 5 hours. After cooling the solution was extracted with dichloromethane and the organic layer was evaporated to give the title compound as a pale yellow solid, 1.82 g (82%), mp 98-103° (benzene); ir: μ 2.95, 3.05, 3.20 (NH_2).

Anal. Calcd. for $C_{10}H_{13}N_5$: C, 59.11; H, 6.45; N, 34.48. Found: C, 58.99; H, 6.34; N, 34.52.

1-Benzyl-5,7-diphenyl-6*H*-1,2,3-triazolo[4,5-*b*][1,4]diazepine (**3a**).

To a solution of 0.500 g (2.64 mmoles) of 1-benzyl-4,5-diamino-1,2,3-triazole **1** [1] and 2.9 mmoles of dibenzoylmethane in 15 ml of 95% ethanol, 3-5 drops of 12*M* hydrochloric acid was added and the mixture was refluxed for 10 hours. The title compound precipitated by cooling and was collected by filtration (Table I).

1-Benzyl-5-phenyl-7-methyl-6*H*-1,2,3-triazolo[4,5-*b*][1,4]-diazepine (**3b**) or 1-Benzyl-5-methyl-7-phenyl-6*H*-1,2,3-triazolo[4,5-*b*][1,4]diazepine (**3b'**).

Compound **3b** or its isomer **3b'** was prepared as above using the benzoylacetone reagent. The title compound precipitated as the monohydrochloride which appeared as yellow needles (Table I).

1-Phenethyl-5,7-diphenyl-6*H*-1,2,3-triazolo[4,5-*b*][1,4]-diazepine (**4a**).

To a solution of 0.300 g (1.5 mmoles) of 1-phenethyl-4,5-diamino-1,2,3-triazole **2** and 1.63 mmoles of dibenzoylmethane in 10 ml of 70% ethanol, 3 drops of 12*M* hydrochloric acid was added and the mixture was refluxed for 10 hours. After cooling, the solution was concentrated *in vacuo*, extracted with dichloromethane, and the organic layer was evaporated to give a red brown semi-solid residue. Crystallization from ethanol-ether provided **4a**•2HCl as orange needles (Table I).

1-Phenethyl-5-phenyl-7-methyl-6*H*-1,2,3-triazolo[4,5-*b*][1,4]-diazepine (**4b**) or 1-Phenethyl-5-methyl-7-phenyl-6*H*-1,2,3-triazolo[4,5-*b*][1,4]diazepine (**4b'**).

Compound **4b** or its isomer **4b'** was prepared as above using the benzoylacetone reagent. The title compound precipitated as the monohydrochloride which appeared as a yellow solid (Table I).

1-Benzyl- and 1-Phenethyl-5,7-dimethyl-6*H*-1,2,3-triazolo-[4,5-*b*][1,4]diazepines **3c**, **4c**.

To a solution of 1.5 mmoles of the diamino compound **1** [1] or **2** and 1.7 ml (1.65 mmoles) of acetylacetone in 8 ml of 50%

ethanol, 3 drops of 12*M* hydrochloric acid was added and the mixture was refluxed for 5 hours. After concentration and dilution with water, the title compounds precipitated as the monohydrochloride hydrate as yellow needles (Table I).

1-Benzyl- and 1-Phenethyl-4-{3-[3-(substituted)-ethoxyacryloyl]-amino}-5-amino-1,2,3-triazoles **5a** [1], **5b** and **6a**, **6b**.

A mixture of 2 mmoles of the diamino compound **1** or **2** and 16 mmoles of the appropriate β-ketoester (ethyl acetoacetate or ethyl butyrylacetate) was heated at 60° for 90 minutes. For the isolation of **5a**, **5b** and **6a**, the reaction mixture was treated with 2 ml of chloroform and the obtained solution diluted with hexane. The reaction products precipitated as crystalline white solids (Table II). For the isolation of **6b**, the reaction mixture was extracted with hot 60-80° petroleum ether from which the compound crystallized (Table II).

1-Benzyl- and 1-Phenethyl-5-alkyl-6*H*,8*H*-1,2,3-triazolo[4,5-*b*]-[1,4]diazepin-7-ones **7a**, **7b** and **8a**, **8b**.

To a solution of sodium ethoxide (2.0 mg-atoms of sodium in 12 ml of anhydrous ethanol), 1.5 mmoles of the suitable 1,2,3 triazole derivative, **5a**, **5b**, **6a** or **6b** was added and the mixture was refluxed for 5 hours. The solvent was evaporated *in vacuo*, the residue dissolved with water and the solution acidified with hydrochloric acid (pH ≈ 5). The obtained solid was collected by filtration, dried, then refluxed in benzene for 15-20 minutes. The title compounds crystallized by cooling (Table II).

1-Benzyl- and 1-Phenethyl-4-[2-(benzoyl)acetylamino]-5-amino-1,2,3-triazoles **9a** and **9b**.

A solution of 1.60 mmoles of the suitable diaminotriazole **1** or **2** in 2.2 ml (12.8 mmoles) of ethyl benzoylacetate was heated at 90° for 24 hours for compound **9a** or 8 hours for compound **9b**. After cooling the reaction mixture was distilled at 115-120°/0.5 mm Hg to remove the excess ethyl benzoylacetate. The residue, by treatment with ethanol, provided the title compounds which were collected by filtration and washed with ethanol (Table II).

1-Benzyl- and 1-Phenethyl-7-phenyl-4*H*,6*H*-1,2,3-triazolo-[4,5-*b*][1,4]diazepin-5-ones **10a** and **10b**.

A solution of 0.573 mmole of the triazoles **9a** or **9b** in 6 ml of anhydrous ethanol was added of 2-3 drops of 12*M* hydrochloric acid and refluxed for 10 hours. The solvent was evaporated *in vacuo*, the residue was treated with water and collected by filtration to give the title compounds (Table II).

1-Benzyl- and 1-Phenethyl-5,8-dimethyl-6*H*-1,2,3-triazolo-[4,5-*b*][1,4]diazepin-7-ones **11a** and **11b**.

To a solution of sodium hydroxide (0.10 g, 2.5 mmoles) in 6 ml of methanol, 0.78 mmole of the appropriate triazolodiazepinone **7a** or **7b** was added. The mixture was stirred at room temperature until the solution was complete, then 0.78 ml (12.5 mmoles) of iodomethane was added and stirring was continued overnight. The reaction mixture was concentrated *in vacuo*, the residue treated with water and collected to give the title compounds as yellow solids (Table II).

1-Benzyl- and 1-Phenethyl-4*H*,6*H*,8*H*-1,2,3-triazolo[4,5-*b*]-[1,4]diazepin-5,7-diones (**12a** and **13a**).

To a solution of sodium ethoxide prepared from 0.19 g (8.4 mmoles) of sodium in 20 ml of anhydrous ethanol, 4.0 mmoles of the appropriate diaminotriazole **1** or **2** was added and the mixture was stirred at room temperature until the solution was complete. Diethyl malonate (0.64 ml, 4.2 mmoles) was then added and the reaction mixture was refluxed for 24 hours. After cooling, the obtained suspension was concentrated *in vacuo*, the solid residue dissolved in water and, after washing with chloroform, the alkaline solution was acidified to precipitate the title compounds (Table III).

1-Benzyl- and 1-Phenethyl-6-substituted-4*H*,6*H*,8*H*-1,2,3-triazolo[4,5-*b*][1,4]diazepin-5,7-diones (**12b**, **12c** and **13b**, **13c**).

To a solution of sodium ethoxide prepared from 0.12 g (5.2 g-atoms) of sodium in 16 ml of anhydrous ethanol, 2.5 mmoles of the appropriate diaminotriazole **1** or **2** was added and the mixture was stirred at room temperature until the solution was complete. To the reaction mixture was added 2.6 mmoles of the malonate ester (ethyl methylmalonate or ethyl phenylmalonate) and refluxed for 24 hours. The reaction mixture was worked up as described above (Table III).

1-Benzyl- and 1-Phenethyl-4,8-dimethyl-6*H*-1,2,3-triazolo-[4,5-*b*][1,4]diazepin-5,7-diones (**14a** and **15a**).

The title compounds were prepared starting from the appropriate triazolodiazepindione **12a** or **13a** by the procedure reported for compounds **11a** and **11b**. Compound **14a** separated as a solid from the aqueous alkaline solution; compound **15a** was extracted with chloroform, the solvent evaporated *in vacuo* and the soft residue was crystallized from benzene/60-80° petroleum ether (Table III).

1-Benzyl- and 1-Phenethyl-4,6,8-trimethyl-6*H*-1,2,3-triazolo-[4,5-*b*][1,4]diazepin-5,7-diones (**14b** and **15b**).

The title compounds were prepared starting from the appropriate triazolodiazepindione **12b** or **13b** by the procedure reported for compounds **11a** and **11b**. In this case compound **14b** separated as a solid, while compound **15b** was isolated by chloroform extraction and crystallization of the residue (Table III).

1-Benzyl-4,8-dimethyl-6-Phenyl-6*H*-1,2,3-triazolo[4,5-*b*]-[1,4]diazepin-5,7-dione (**14c**).

To a stirred and ice-cooled mixture of the triazolodiazepindione **12c** (0.33 g, 1.0 mmole) and anhydrous potassium carbonate (0.31 g, 2.2 mmoles) in 10 ml of acetonitrile, a solution of dimethyl sulfate (0.38 ml, 4.0 mmoles) in 6 ml of acetone was added dropwise. After 2 hours the ice-bath was removed and stirring was continued for 5 hours at room temperature. The reaction mixture was evaporated *in vacuo*, treated with water and extracted with chloroform. Evaporation of the chloroform extract gave an oil which, by trituration with ethanol, solidified (Table III).

1-Phenethyl-4,8-dimethyl-6-phenyl-6*H*-1,2,3-triazolo[4,5-*b*]-[1,4]diazepine-5,7-dione (**15c**).

To a solution of sodium hydroxide (0.12 g, 3.0 mmoles) in 7 ml of methanol, 0.35 g (1.0 mmole) of the triazolodiazepinone **13c** was added. After stirring 1 hour at room temperature (complete solution), 1.0 ml (16 mmoles) of iodomethane was added and the mixture was allowed to react and worked up as described for the preparation of **11a** and **11b** (Table III).

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