Pyridazine Derivatives, VII[*)].

Synthesis and Hypotensive Activity of 3-Hydrazinocycloalkyl[1,2-c]pyridazines and their Derivatives

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The preparation of a series of 3-hydrazinocycloalkyl[1,2-c]-pyridazines **7** and some derivatives as hydrazones **8, 9**, triazoles **10** and pyrroles **11** are described together with their hypotensive activity in normotensive rats.

Pyridazin-Derivate, 7. Mitt.: Synthese und blutdrucksenkende Wirkung von 3-Hydrazinocycloalkyl[1,2-c]pyridazinen und ihrer Derivate

Die Darstellung einer Serie von 3-Hydrazinocycloalkyl[1,2- c]pyridazinen **7** und ihrer Derivate (Hydrazone **8, 9**, Triazole **10** und Pyrrole **11**) wird beschrieben. Weiter wird die hypotensive Wirkung dieser Verbindungen auf Normaldruckratten untersucht.

As a continuation of previous work[1-5] on the synthesis and antihypertensive potential of new structural analogues of the well known antihypertensive agent Hydralazine (I) (Apresoline[R], 1-hydrazinophthalazine)[6], we report now the synthesis and preliminary results on the hypotensive activity of several 3-hydrazino-cycloalkyl[1,2-c]pyridazines **7a-d** and of some derivatives. These derivatives, which were prepared for further study of structure-activity relationships, are: a) hydrazones with acetone **8a-d** and butanone **9a-d** and b) cycloalkyl[1',2'-e]-1,2,4-triazolo[4,3-b] pyridazines **10a-d**. The discovery that N-1H-pyrrol-1-yl-3-pyridazinamines (II)[7] possess considerable antihypertensive activity also led us to incorporate the terminal NH_2 group of compounds **7** in a pyrrole ring (compounds **11a-d**).

The target compounds were prepared in two stages:

1) the preparation of the cycloalkyl[1,2-c]-3(2H) pyridazinones **4**

2) subsequent introduction of the hydrazine group (Scheme I).

For the preparation of **4** two procedures were followed:

a) via an enamine, by alkylation of 1-cyclohexenylpyrrolidine with ethyl bromoacetate to give **1**, formation of the pyridazine ring by refluxing with hydrazine hydrate to afford the 4,5-dihydro-cycloalkyl[1,2-c]-3(2H)pyridazinone **2** in 56% yield, and subsequent aromatization to **4** in 54% yield with bromine in glacial acetic acid. Aromatization with sodium m-nitrobenzene sulphonate gave similar yields (45-50%).

Table I.- Morpholinium salts of 2-morpholino-2-(2-oxo-cycloalkyl)acetic acids

Compd	n	R^1	yield(%)	Mp °C	Crystallized from	Molecular Formula	Analysis (Calcd/Found) C	H	N
3a	2	H	79	128-31	2-propanol/thyl-acetate	$C_{16}H_{28}N_2O_5$	58.5	8.53	8.5
						(328.4)	58.7	8.47	8.2
3b	2	CH_3(6)	66	141-3	"	$C_{17}H_{30}N_2O_5$	59.6	8.77	8.2
						(342.4)	60.0	8.45	7.8
3c	1	H	50	128-32	"	$C_{15}H_{26}N_2O_5$	57.3	8.28	8.9
						(314.4)	57.5	7.59	9.1
3d	3	H	56	147-9	"	$C_{17}H_{30}N_2O_5$	59.6	8.77	8.2
						(342.4)	59.3	8.47	8.7

*)For part VI, see ref. 5

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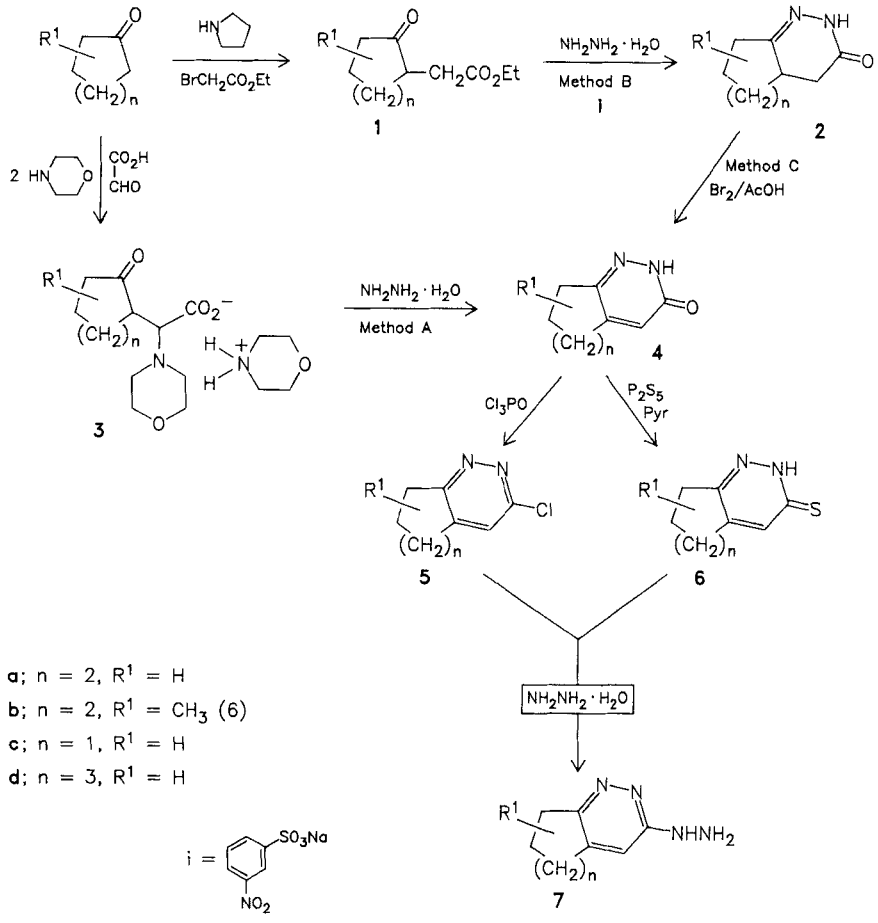
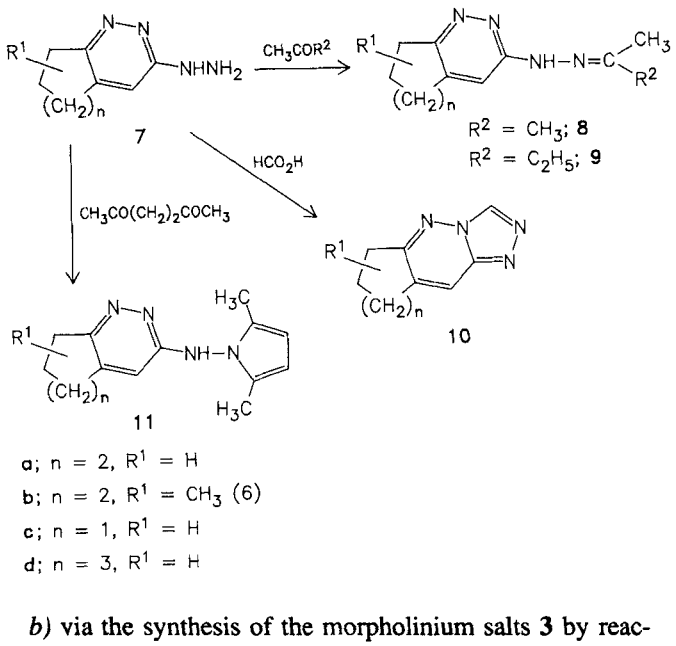
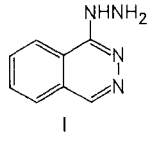


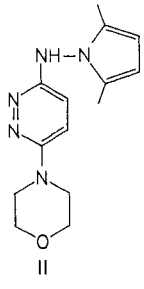
a; n = 2, R^1 = H
b; n = 2, R^1 = CH_3 (6)
c; n = 1, R^1 = H
d; n = 3, R^1 = H



a; n = 2, R^1 = H
b; n = 2, R^1 = CH_3 (6)
c; n = 1, R^1 = H
d; n = 3, R^1 = H



I



II

b) via the synthesis of the morpholinium salts **3** by reaction of cycloalkanones with glyoxylic acid and morpholine, followed by refluxing **3** with hydrazine hydrate to give **4** in very good yields (80%).

The morpholinium salts were prepared, following the procedure described by *Schreiber* et al.[8] for the cyclohexanone, as white crystalline compounds; their structures were confirmed by elemental analysis, IR, and NMR spectroscopy. – IR: 2600-2200 cm^{-1} (NH_4^+), 1700 cm^{-1} (CO) and 1646 cm^{-1} (COO^-). – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 3.96 - 3.67 (m.c., 13 H, $(CH_2)_4O$, $(CH_2)_2N^+$, $CH\text{-}CO_2^-$); 3.03 - 2.84 (m, 4H, $(CH_2)_2N$); 2.74-2.52 (m, 3H, CH_2-CO, CH-CO); 2.04 - 1.62 (m, 6H, CH_2-CH_2-CH_2).

The 3-step procedure (*a*) was used in the synthesis of several 3-hydrazino-cycloalkyl[1,2-c]pyridazines by *Schenker* et al.[9] who did not report any yields. We followed this way only initially for **4a**, later on **4a** was also prepared by the 2-step procedure applied for **4b-d**.

The derivatives **8-11** were prepared according to Scheme II

We thank *Rosario García-Ramos* for his interest and helpful discussions.

Experimental Part

Melting points: Gallemkamp melting point apparatus, uncorrected. – IR spectra: Perkin-Elmer Mod. 297 spectrophotometer; main bands are given in cm^{-1}. – ^{1}H-NMR spectra: Varian LFT-20, 80 Hz, Brucker WM 250, 250 Hz, $CDCl_3$; shifts in ppm, TMS as internal reference. - Elemental analyses: Perkin-Elmer Mod. 240 elemental analyser, Microanalysis Service, University of Santiago de Compostela.

4,4a-Dihydro-cyclohexyl[1,2-c]-3(2H)pyridazinone (**2a**)

This compound was prepared by the reaction of ethyl 2- oxocylohexyl acetate and hydrazine hydrate as described by *Horning* and *Amstutz*[10]. Yield 57%, m.p. 113-116 °C (hexane) (lit.[10] 114-115 °C). - IR (KBr): 3200-2950 (-NH); 1620 (C=N, C=C) cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.58 (s, 1H, NH); 2.73 (m, 1H, C<u>H</u>- CH_2-C=O); 2.58 - 2.41 (m.c., 2H, C<u>H</u>$_2$-C=O); 2.16 - 1.79 (m.c., 4H, -C<u>H</u>$_2$-CH_2-CH_2-C<u>H</u>$_2$-); 1.46 - 1.25 (m.c., 4H, -CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$- CH_2). – $C_8H_{12}N_2O$ (152.2) calculated C 63.2 H 7.85 N 18.4 Found C 63.4 H 8.04 N 18.7.

Morpholinium salt of 2-morpholino-2-(2-oxo-cyclohexyl)-acetic acid (**3a**)

18.2 (0.2 mol) of morpholine were stirred dropwise at <30 °C into a solution of 9.2 g (0.1 mol) of glyoxylic acid in the minimum amount of ethanol. - 9.8 g (0.1 mol) of cyclohexanone were slowly stirred into the salt solution so obtained, and the mixture was left to stand after a few hours, a white crystalline mass was filtered out, carefully washed with isopropyl alcohol/ethyl acetate 1:1 and dried to obtain 24.5 g **3a** (80%), m.p. 128-131 °C. – IR (KBr): 1700 (-CO); 1620 (COO^-); 2200-2600 (NH_2^+) cm^{-1}. Analysis for $C_{16}H_{28}N_2O_5$ (328.4). Calculated C 58.53 H 8.53 N 8.53 Found C 58.72 H 8.47 N 8.23.

Cyclohexyl[1,2-c]-3(2H)pyridazinone (**4a**)

Method A

1.95 g (0.038 mol) of hydrazine hydrate in 60 mL of ethanol were added to a solution of 12.57 g (0.038 mol) of **3a** in ethanol. After 4 h refluxing, the ethanol was evaporated and the residue recrystallized form ethanol/water to give 4.3 g of **4a**. Yield 74.7% M.p. 192-194 (Lit.[8,10] 192-194 °C). – IR (KBr): 3200-2900 (-NH); 1600 (CO); 1600-1480 (C=N, C=C aromatic) cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 9.05 (s, 1H, NH); 6.64 (s, 1H, CH-CO); 2.69 (m, 4H, -C<u>H</u>$_2$- CH_2-CH_2-C<u>H</u>$_2$-); 1.75 (m, 4H, -CH_2- C<u>H</u>$_2$-C<u>H</u>$_2$-CH_2-). – $C_8H_{10}N_2O$ (150.2). Calculated C 61.8 H 5.88 N 20.6 Found C 61.8 H 6.06 N 21.1.

Method B

A suspension of 0.16 g (0.0011 mol) of **2a** 0.24 g (0.0011 mol) of the sodium salt of m-nitrobenzene sulphonic acid, 0.18 g of NaOH and 4 mL of water was boiled for 40 min with stirring to give a brown solution which was acidified with 3N HCl and extracted with chloroform. The org. phase was dried with Na_2SO_4 and the solvent was evaporated at reduced pressure to give a yellow solid that on recrystallization from ethanol/ether afforded 0.07 g of **4a**. Yield 47%. M.p. 193-194.5 °C.

Method C

Aromatization of **2a** with Br_2/AcOH essentially as described by *Horning* and *Amstutz*[10]. Yield 54%. M.p. 192-195 °C (EtOH).

3-Chlorocyclohexyl[1,2-c]pyridazine (**5a**)

1 g (0.0066 mol) of **4a** was warmed in 4.46 mL of $POCl_3$ at 90-100 °C until completely dissolved. The solution was cooled to room temp. The solid precipitate was collected, treated with 25% NH_3 and the resulting mixture extracted with $CHCl_3$. The org. phase was dried with Na_2SO_4 and the solvent evaporated at reduced pressure to give 0.22 g of **5a** as a yellow liquid that was used in the next stage without further purification. Yield 20%. – IR (NaCl): 3100-2850 (NH); 1600 (C=C aromatic); 750-640 (C-Cl) cm^{-1}. No carbonyl bands present.

Cyclohexyl[1,2-c]-3(2H)pyridazinethione (**6a**)

A suspension of 1 g (0.0066 mol) of **4a**, 0.58 g (0.0026 mol) of P_2S_5 and 6 mL of anhydrous pyridine was boiled for 3 h. The pyridine was evaporated and the residue washed with 10% Na_2CO_3 to give a solid that on recrystallization from ethanol afforded 0.69 g of green needles of **6a**. Yield 63%. M.p. 185-189 °C. - IR (KBr): 3150 (NH); 1610-1550 (C=C, C=N, aromatic) 1460-1400 (C=S) cm^{-1}. – $C_8H_{10}N_2S$ (166.3) Calculated C 57.8 H 6.02 N 16.9 Found C 57.5 H 5.97 N 16.5.

3-Hydrazinocyclohexyl[1,2-c]pyridazine (**7a**)

First method

1.5 g (0.009 mol) of **6a** and 18.25 mL (0.37 mol) of 98% hydrazine hydrate were refluxed for 2 h and then cooled to obtain a solid that on recrystallization from ethanol afforded 1.27 g of **7a**. Yield 85.8%. M.p. 137-139 °C. - IR (KBr): 3200 (NH) 1640-1600 (C=N, C=C aromatic) cm^{-1}. – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 6.71 (s, 1H, pyridazine); 3.14 (br.s, 3H, NH-NH_2); 2.99 (m, 2H, -CH_2-C=N); 2.72 (m, 2H, CH_2-C=CH); 1.71-1.93 (m, 4H, -CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-CH_2-). – $C_8H_{12}N_4$ (164.2) Calculated C 58.5, H 7.3 N 34.1 Found C 58.6 H 7.16 N 34.0.

Second Method

A suspension of 0.22 g (0.0013 mol) of **5a** in 2.7 mL (0.057 mol) of hydrazine hydrate was boiled for 2 h and then cooled to obtain a yellow crystalline solid that on recrystallization from ethanol afforded 0.15 g of yellow needles of **7a**. Yield 71.4%. M.p. 136-140 °C.

3-[N^1-(isopropylidene)]hydrazinocyclohexyl[1,2-c]pyridazine (**8a**)

A solution of **7a** (0.2 g, 0.00098 mol) in acetone (3 mL) was refluxed for 10 min. On cooling, **8a** crystallized as brown needles. Yield 80%. M.p. 140-142 °C. - ^{1}NMR ($CDCl_3$): δ (ppm) = 7.18 (s, 1H, pyridazine); 3.00 (t, 2H, J=6.5 Hz, -CH_2-C=N); 2.77 (t, 2H, J=6 Hz, -CH_2-C=CH-); 2.05 (s, 3H, -CH_3); 1.93 (s, 3H, -CH_3); 1.76-1.90 (m, 4H, -CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-CH_2-). – $C_{11}H_{16}N_4$ (204.3). Calculated C 64.7 H 7.84 N 27.4 Found C 64.9 H 8.01 N 27.2.

3-[N^1-(isobutylidene)]hydrazinocycloheptyl[1,2-c]pyridazine (**9d**)

9d was obtained by the same procedure as **8a** from 0.2 g (0.00091 mol) of **7d** and 3 mL of butanone. Yield 75%. M.p. 128- 130 °C. – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.08 (br.s., 1H, NH-N=); 7.23 (s, 1H, pyridazine); 3.09 (m, 2H, - CH_2-C=N-); 2.74 (m, 2H, -CH_2-C=CH-); 2.34 (q, 2H, J = 7.4 Hz, -C<u>H</u>$_2$-CH_3); 1.91 (s, 3H, -CH_3); 1.68- 1.85 (m, 6H, -CH_2-C<u>H</u>$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$-CH_2-); 1.14 (t, 3H, J = 7.4 Hz, -CH_2-C<u>H</u>$_3$). – $C_{13}H_{20}N_4$ (232.3). Calculated C 67.2 H 8.62 N 24.1 Found C 66.9 H 8.42 N 24.3.

Cycloheptyl[1,2-e]-1,2,4-triazolo[4,3-b]pyridazine (**10d**)

A mixture of **7d** (0.5 g, 0.0027 mol) in 1.33 mL of formic acid was refluxed for 5 h. Excess reagent was removed under reduced pressure and the residue was treated with water. The resulting precipitate was recrystallized from ethyl acetate to give 0.30 g of **10d**, 71.4%. M.p. 131-133 °C. – ^{1}H-NMR ($CDCl_3$): δ (ppm) = 8.94 (s, 1H, triazole); 7.76 (s, 1H, pyridazine); 3.02 (m, 2H, -CH_2-C=N); 2.87 (m, 2H, C<u>H</u>$_2$-C=CH); 1.84 (m, 6H, -CH_2-C<u>H</u>$_2$- C<u>H</u>$_2$-C<u>H</u>$_2$-CH_2-). – $C_{10}H_{12}N_4$ (188.2). Calculated C 63.8 H 6.38 N 29.8 Found C 63.7 H 6.20 N 29.6.

Table II.- Cycloalkyl[1,2-c]-3(2H)pyridazinones

Compd	n	R^1	yield(%)	Mp °C	Crystallized from	Molecular Formula	Analysis (Calcd/Found) C	H	N
4a	2	H	75	192-4	EtOH/H_2O	$C_8H_{10}N_2O$ (150.2)	61.7 / 61.7	5.88 / 6.06	20.6 / 21.1
4b	2	CH_3(6)	60	196-200	"	$C_9H_{12}N_2O$ (164.2)	65.9 / 66.2	7.31 / 7.56	17.1 / 17.4
4c	1	H	60	197-9	"	$C_7H_8N_2O$ (136.1)	61.8 / 61.2	5.88 / 6.00	20.6 / 21.1
4d	3	H	67	198-9	"	$C_9H_{12}N_2O$ (164.2)	65.9 / 65.4	7.31 / 6.82	17.1 / 17.1

Table III.- Cycloalkyl[1,2-c]-3(2H)pyridazinthione

Compd	n	R^1	yield(%)	Mp °C	Crystallized from	Molecular Formula	Analysis (Calcd/Found) C	H	N
6a	2	H	63	185-9	EtOH	$C_8H_{10}N_2S$ (166.2)	57.8 / 57.5	6.02 / 5.97	16.9 / 16.5
6b	2	CH_3(6)	61	217-20	EtOH	$C_9H_{12}N_2S$ (180.3)	60.0 / 59.6	6.66 / 6.26	15.5 / 15.3
6c	1	H	62	206-10	EtOH	$C_7H_8N_2S$ (152.2)	55.3 / 55.0	5.26 / 5.16	18.4 / 18.6
6d	3	H	94	143-4	EtOH	$C_9H_{12}N_2S$ (180.3)	60.0 / 60.3	6.66 / 7.01	15.6 / 15.9

Table IV.- 3-Hydrazino-cycloalkyl[1,2-c]pyridazines

Compd	n	R^1	yield(%)	Mp °C	Crystallized from	Molecular Formula	Analysis (Calcd/Found) C	H	N
7a	2	H	86	137-9	EtOH	$C_8H_{12}N_4$ (164.2)	58.5 / 58.6	7.31 / 7.16	34.1 / 34.0
7b	2	CH_3(6)	52	139-41	EtOH	$C_9H_{14}N_4$ (178.2)	60.7 / 60.4	7.86 / 7.49	31.5 / 31.2
7c	1	H	45	143-7	EtOH	$C_7H_{10}N_4$ (158.2)	56.0 / 55.9	6.66 / 6.69	37.3 / 37.0
7d	3	H	88	131-3	EtOH	$C_9H_{14}N_4$ (178.2)	60.7 / 60.4	7.86 / 7.39	31.5 / 31.6

N-(2,5-dimethyl-1H-pyrrol-1-yl)cyclohexyl[1,2-c]-3-pyridazinamine (**11a**)

Acetonylacetone (0.41 g, 0.0036 mol) was slowly added to a stirred suspension of **7a** (0.5 g, 0.003 mol) in acetic acid (2.9 mL). The mixture was heated at 65 °C for 3 h and evaporated to dryness. The residual oil was supensed in water, and pH was adjusted to 8 with $NaHCO_3$. The insoluble material was filtered out and crystallized from ethyl acetate to give 0.58 g of **11a**, 79.4%. M.p. 167-169 °C. - ^{1}H-NMR ($CDCl_3$): δ (ppm) = 7.43 (s, 1H, pyridazine); 5.83 (s, 2H, pyrrol); 3.03 (m, 2H, -CH_2-C=N-); 2.63 (m, 2H, CH_2-C=CH-); 2.09 (s, 6H, 2 x CH_3); 1.81 (m, 4H, - CH_2-CH_2-CH_2-CH_2-). - $C_{14}H_{18}N_4$ (242.3). Calculated C 69.4 H 7.43 N 23.1 Found C 69.2 H 7.22 N 23.0.

Pharmacology

Material and methods

Hypotensive activity was determined indirectly by measuring systolic arterial pressure (SAP) in the caudal artery of unanaesthetized rats. Lots of 6 male normotensive Sprague-Dawley rats weighing 300 +/- 25 g were starved for 24 h before basal SAP and heart rates were determined, and doses of 5, 7.5, or 10 mg/kg of the compound under test were administered per os after which SAP and heart rate continued to be monitored.

SAP was determined using a Narco Bio-Systems PE300 programmed electro-sphygmomanometer connected to a Narco Bio-Systems pneumatic pulse transducer and a Scientific Instrument Centre Mod. 2125 physiopolygraph. Heart rate was obtained from the recorded SAP wave (The rats were warmed for 15 min. prior measurements).

Results

Hypotensive activity and effects on heart rate were quantified as percentage change with respect to basal values[5].

Table V.- 3-[N[1]-(isoalkylidene)]hydrazino-cycloalkyl[1,2-c]paridazines

Compd	n	R^1	R^2	yield(%)	Mp °C	Crystallized from	Molecular Formula	Analysis (Calcd/Found) C	H	N
8a	2	H	CH_3	80	140-2	acetone	$C_{11}H_{16}N_4$	64.7	7.84	27.4
							(204.3)	64.9	8.01	27.2
8b	2	CH_3(6)	CH_3	78	155-7	acetone	$C_{12}H_{18}N_4$	66.0	8.25	25.7
							(218.3)	65.9	8.17	25.5
8c	1	H	CH_3	75	148-9	acetone	$C_{10}H_{14}N_4$	63.2	7.37	29.5
							(190.2)	63.4	7.17	29.2
8d	3	H	CH_3	83	145-7	acetone	$C_{12}H_{18}N_4$	66.1	8.25	25.7
							(218.3)	66.2	8.02	25.5
9a	2	H	C_2H_5	75	79-81	butanone	$C_{12}H_{18}N_4$	66.0	8.25	25.7
							(218.3)	65.8	8.13	25.9
9b	2	CH_3(6)	C_2H_5	72	117-9	butanone	$C_{13}H_{20}N_4$	67.2	8.62	24.1
							(232.3)	67.0	8.16	24.3
bf 9c	1	H	C_2H_5	70	80-3	butanone	$C_{11}H_{16}N_4$	64.7	7.84	27.4
							(204.3)	64.2	8.03	27.2
9d	3	H	C_2H_5	77	128-30	butanone	$C_{13}H_{20}N_4$	67.2	8.62	24.1
							(232.3)	66.9	8.42	24.3

Table VI.- Cycloalkyl[1',2'-e]-1,2,4-triazolo[4,3-b]pyridazines

Compd	n	R^1	yield(%)	Mp °C	Crystallized from	Molecular Formula	Analysis (Calcd/Found) C	H	N
10a	2	H	79	89-92	ethyl acetate	$C_9H_{10}N_4$	62.1	5.74	32.2
						.(174.2)	62.4	5.83	31.8
10b	2	CH_3(6)	43	96-8	ethyl acetate	$C_{10}H_{12}N_4$	63.82	6.38	29.78
						(188.2)	63.50	5.90	30.12
10c	1	H	47	128-30	ethyl acetate	$C_8H_8N_4$	60.0	5.00	35.0
						(160.2)	59.7	5.20	34.7
10d	3	H	71	131-3	ethyl acetate	$C_{10}H_{12}N_4$	63.8	6.38	29.8
						(188.2)	63.7	6.19	29.6

Table VII.- N-(2,5-dimethyl-1H-pyrrol-1-yl)cycloalkyl[1,2-c]-3-pyridazinamines

Compd	n	R^1	yield(%)	Mp °C	Crystallized from	Molecular Formula	Analysis (Calcd/Found) C	H	N
11a	2	H	79	167-9	ethyl acetate	$C_{14}H_{18}N_4$	69.4	7.43	23.1
						(242.3)	69.2	7.22	23.0
11b	2	CH_3(6)	58	193-5	ethyl acetate	$C_{15}H_{20}N_4$	70.3	7.81	21.9
						(256.3)	70.1	7.52	22.1
11c	1	H	95	188-91	ethyl acetate	$C_{13}H_{16}N_4$	68.4	7.01	24.6
						(228.3)	68.1	7.27	24.3
11d	3	H	75	202-3	ethyl acetate	$C_{15}H_{20}N_4$	70.3	7.81	21.9
						(256.3)	69.9	7.60	21.5

Maximum effects on both SAP and heart rate were recorded 1 h after administration and all results presented in what follows refer to this time. DE_{30} (the dosage necessary to produce a 30% fall in SAP or a 30% rise in heart rate) was calculated from the equations of straight lines fitted to the response -log dosage data.

Table VIII lists the percentage decrease in SAP (DSAP), the percentage increase in heart rate (IHR), and the corresponding DE_{30} for hydralazine and for all the other new compounds that exhibited activity; for all of them such activity was unquestionable and dose-dependent. In general, compounds with unsubstituted hydrazine groups were more active in DSAP than the corresponding substituted compounds, the exceptions being the pair **7b**, **8b**, the effects of which on both SAP and heart rate were similar, and **7d** which increased heart rate slightly less than its derivatives.

Table VIII

Compound	Dose (mg/Kg)	DSA P[1] (mean ± S.E.)	ED_{30} (mg/Kg)	IHR[2] (mean ± S.E.)	ED_{30} (mg/Kg)
	5	29.63 ± 1.80		26.18 ± 4.49	
HYDRALAZINE	7.5	35.60 ± 1.94	5.16	30.17 ± 1.09	7.46
	10	40.74 ± 1.95		32.69 ± 3.12	
	5	25.11 ± 1.14		31.33 ± 5.46	
7a	7.5	32.13 ± 0.95	6.62	35.00 ± 1.13	4.27
	10	37.26 ± 2.35		37.32 ± 1.69	
	5	20.96 ± 1.14		29.24 ± 1.13	
8a	7.5	26.98 ± 0.54	9.34	32.69 ± 1.23	5.47
	10	30.91 ± 1.15		35.28 ± 1.35	
	5	21.63 ± 1.21		22.68 ± 1.46	
7b	7.5	25.01 ± 1.42	10.66	26.44 ± 3.05	10.03
	10	29.80 ± 2.25		30.22 ± 4.04	
	5	21.07 ± 1.65		24.09 ± 0.90	
8b	7.5	28.59 ± 1.30	9.25	28.88 ± 2.17	8.57
	10	30.21 ± 0.69		31.47 ± 2.67	
	5	27.63 ± 1.80		26.18 ± 4.49	
7c	7.5	35.60 ± 1.94	5.16	30.17 ± 1.09	7.46
	10	40.74 ± 1.95		32.69 ± 3.12	
	5	22.52 ± 1.10		23.47 ± 1.26	
8c	7.5	30.32 ± 1.65	7.49	25.71 ± 0.92	11.82
	10	35.10 ± 1.64		29.08 ± 1.73	
	5	32.49 ± 3.00		22.45 ± 1.97	
7d	7.5	39.26 ± 1.75	4.33	22.74 ± 0.40	8.34
	10	44.26 ± 1.08		33.16 ± 1.99	
	5	30.01 ± 1.90		29.03 ± 1.62	
8d	7.5	36.83 ± 1.94	5.01	32.66 ± 1.25	5.58
	10	41.94 ± 1.61		36.76 ± 1.44	
	5	26.68 ± 1.40		22.74 ± 1.17	
9d	7.5	33.49 ± 1.22	6.07	30.86 ± 2.29	6.46
	10	38.96 ± 1.06		34.67 ± 1.52	

[1]DSAP: % of decrease in systolic arterial pressure
[2]IHR: % of increase in heart rate.

All the triazole and pyrrol derivatives were inactive at the doses tested.

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