1,2,3-Triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazines

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Some new 1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazines were prepared starting from the corresponding 1,2,3-triazolo[4,5-*d*]pyridazines *via* the formation of the 1,2,4-triazole ring, by condensation of an appropriate monocarbon fragment with the 4-hydrazino substituent and the nitrogen atom in the 5 position of the heterocycle. Condensation of 4-phenylhydrazino substituted derivatives with formic acid gave zwitterionic compounds.

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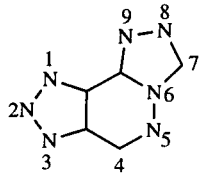
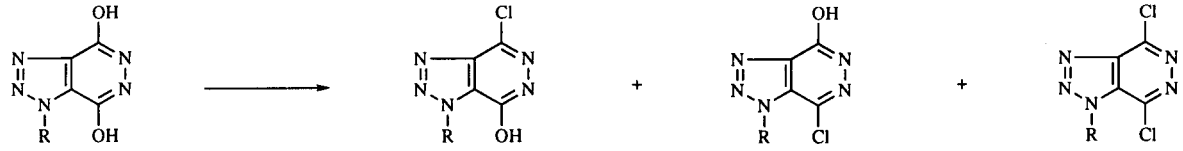
As progress of the program concerning 1,2,3-triazolo-[4,5-*d*]pyridazine derivatives [1-4], this paper takes into consideration new tricyclic nitrogen heterocycles (1,2,3-triazolo-1,2,4-triazolopyridazines), corresponding to the general formula **A**.



A

The only reference goes back to 1970 [5] where the 4-methyl- and the 4-methoxy-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine were prepared in good yield by

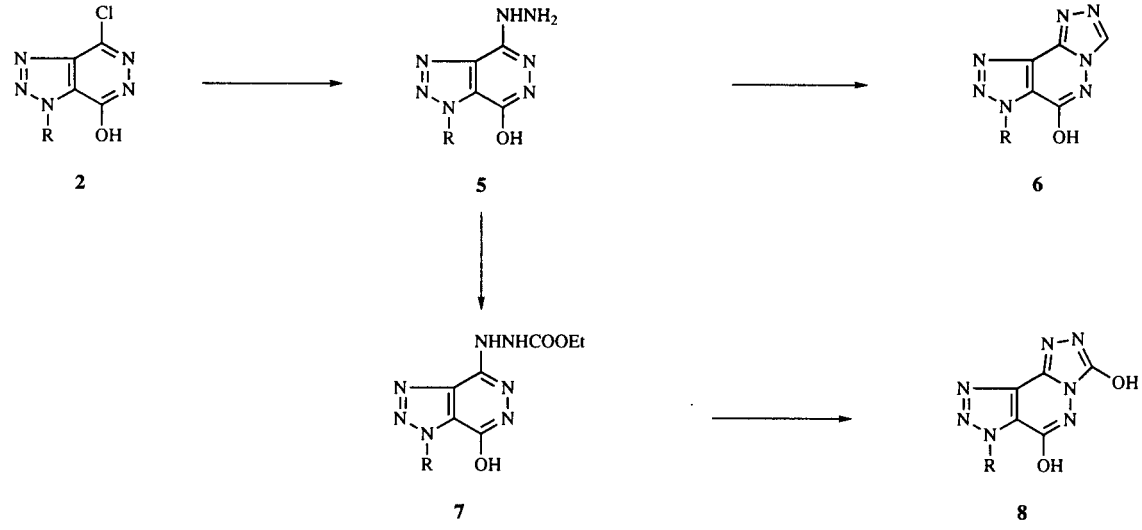
Scheme 1



1 **2** **3** **4**

a: R = $C_6H_5CH_2$; **b**: R = *p*-$CH_3C_6H_4CH_2$; **c**: R = *p*-$CH_3C_6H_4$

Scheme 2



2 **5** **6** **7** **8**

a: R = $C_6H_5CH_2$; **b**: R = *p*-$CH_3C_6H_4CH_2$; **c**: R = *p*-$CH_3C_6H_4$

heating the corresponding 4-hydrazino-7-substituted-1,2,3-triazolo[4,5-*d*]pyridazines with formic acid; similarly the analogous 4,7-dimethyl-1,2,3-triazolo[4,3-*b*]pyridazine was obtained by heating in acetic anhydride.

These new heterocyclic structures appeared interesting for medicinal chemistry because their biological properties were unknown and could be connected to tricyclic nitrogen heterocycles which have considerable biological activity (affinity towards the benzodiazepine receptor [6]; selective affinity towards the A_2-adenosine receptor [7,8,9]).

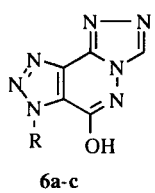
Therefore some new title compounds were prepared according to the previously described synthethic route [5], based upon the formation of the 1,2,4-triazole ring by condensation of an appropriate monocarbon fragment with the 4-hydrazino substituent and with the nitrogen atom in the 5 position of the 1,2,3-triazolo[4,5-*d*]pyridazine ring.

The 1-substituted-4-hydrazino-7-hydroxy-1,2,3-triazolo-[4,5-*d*]pyridazines {1-benzyl- **5a** [2], 1-(4-methylbenzyl)-**5b** and 1-(4-methylphenyl)-**5c**} were obtained in 70-80% yield from the corresponding 4-chloro compounds **2a-c** (Scheme 1), by reaction with 99% hydrazine hydrate in dimethyl sulfoxide at 100° (Scheme 2). The 4-chloro compounds **2a** [3] and **2b** [4] have been described; compound **2c** was obtained from the 4,7-dihydroxy-1-(4-methylphenyl)-1,2,3-triazolo[4,5-*d*]pyridazine **1c** [3] by chlorination with phosphorus oxychloride. The reaction, as previously experimented [2,3], provided the two isomeric monochloro derivatives **2c** and **3c**, together with the dichloro compound **4c** (Scheme 1).

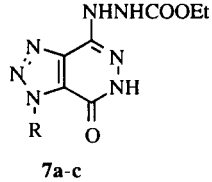
The 4-hydrazinotriazolopyridazines **5a-c** (Scheme 2), by refluxing in formic acid, gave the expected tricyclic derivatives **6a-c** in 50%, 80% and 95% yield respectively; while, by heating with an excess of ethyl chloroformate, the corresponding carboethoxy hydrazino derivatives **7a-c** were obtained in good yields. The latter by refluxing in diphenyl ether (250-260°) underwent intramolecular cyclization with elimination of ethanol; the formed tricyclic derivatives **8a-c** crystallized from the reaction mixture and were isolated by filtration in high yield. It is worth noting that the open intermediate **7a** sublimed at 250°/0.2-0.3 mm Hg and it was unchanged by refluxing either in *N,N*-dimethylformamide (bp 154°) or in cumene (bp 152°) in the presence of a catalytic amount of *p*-tolu-

Table I

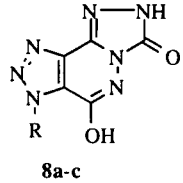
Chemical and Physical Properties of Derivatives **6**, **7**, **8** and **12**



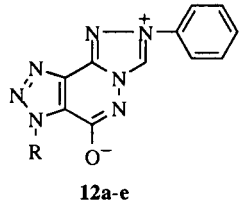
6a-c



7a-c



8a-c



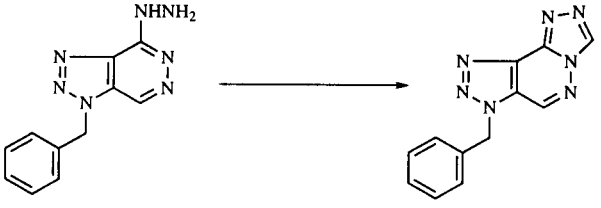
12a-e

Compound	R	Crystallization Solvent	Yield %	Mp °C	Elemental Analysis	Calcd./Found C	H	N
6a	Benzyl	DMF-H_2O	50.5	294-296	$C_{12}H_9N_7O$	53.93 53.63	3.39 3.32	36.69 36.93
6b	*p*-Me-benzyl	DMF-H_2O	81	276-280	$C_{13}H_{11}N_7O$	55.51 55.87	3.94 3.94	34.86 34.57
6c	*p*-Me-phenyl	EtOH	65	>310	$C_{12}H_9N_7O$	53.93 53.60	3.39 3.36	36.69 36.56
7a	Benzyl	DMF-H_2O	58	250 dec	$C_{14}H_{15}N_7O_3$	51.06 51.23	4.59 4.36	29.77 29.44
7b	*p*-Me-benzyl	EtOH	83	250-252	$C_{15}H_{17}N_7O_3$	52.47 52.36	4.99 4.84	28.56 28.27
7c	*p*-Me-phenyl	EtOH	88	256-258	$C_{14}H_{15}N_7O_3$	51.06 51.02	4.59 4.61	29.77 29.93
8a	Benzyl	Diphenyl ether	91	>310	$C_{12}H_9N_7O_2$	50.89 50.76	3.20 3.00	34.62 34.82
8b	*p*-Me-benzyl	Diphenyl ether	88	>300	$C_{13}H_{11}N_7O_2$	52.52 52.81	3.73 3.70	32.98 32.65
8c	*p*-Me-phenyl	Diphenyl ether	84	>300	$C_{12}H_9N_7O_2$	50.89 50.90	3.20 3.17	34.62 34.35
12a	Benzyl	DMF	45	>310	$C_{18}H_{13}N_7O$	62.97 62.69	3.82 3.68	28.56 28.29
12b	*p*-Me-benzyl	DMF	52	>305	$C_{19}H_{15}N_7O$	63.86 63.62	4.23 4.21	27.44 27.29
12c	*p*-Me-phenyl	DMF	49	>310	$C_{18}H_{13}N_7O$	62.97 63.10	3.82 3.92	28.56 28.86
12d	Phenethyl	DMF	38	>310	$C_{19}H_{15}N_7O$	63.86 63.74	4.23 4.32	27.44 27.53
12e	Cyclohexyl	MeOH	35	>310	$C_{17}H_{17}N_7O$	60.88 60.66	5.11 5.07	29.24 29.55

ensulfonic acid; the cyclized compound **8a** reacted with 10% sodium hydroxide solution to give a slightly soluble sodium salt.

Reaction of 1-benzyl-4,7-dichloro-1,2,3-triazolo-[4,5-*d*]pyridazine (**4a**) with excess of 99% hydrazine hydrate mainly provided the 4-monohydrazino derivative **9a** [4] (Scheme 3), by hydrogenolysis of the chloro atom in the **7** position; the same reaction carried out on the analogous dichloro derivatives **4b** and **4c** gave mixtures from which the monohydrazino compounds **9b** and **9c** could not be isolated from the disubstituted compounds and other by-products. Thus only **9a** underwent cyclization with formic acid to give the corresponding *v*-triazolo-*s*-triazolopyridazine **10a**.

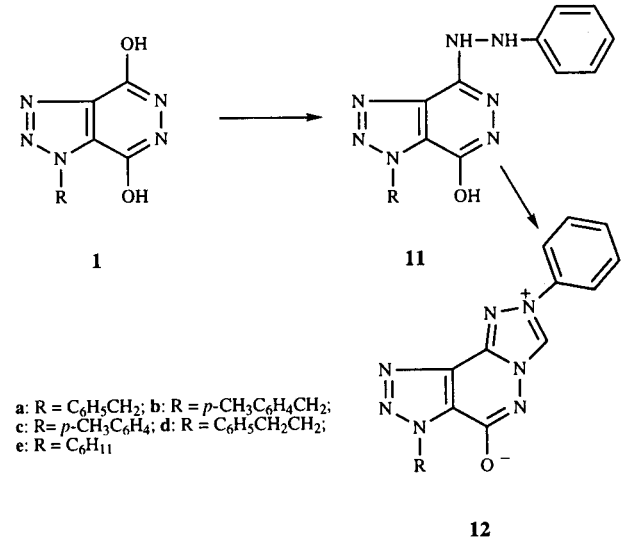
Scheme 3



9a **10a**

Finally the 4-phenylhydrazino derivatives **11a** [4], **11b**, **11c** [4], **11d** [4] and **11e** [4], (Scheme 4), obtained from the suitable 4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**1a** [2], **1b** [4], **1c** [3], **1d** [2] and **1e** [3]) by reaction with phenylhydrazine in hexamethyldisilazane and catalytic amounts of ammonium sulfate [10], were cyclized by refluxing in formic acid to the compounds **12a-e** bearing a zwitterionic structure stabilized by electronic resonance.

Scheme 4



a: R = $C_6H_5CH_2$; **b**: R = *p*-$CH_3C_6H_4CH_2$; **c**: R= *p*-$CH_3C_6H_4$; **d**: R = $C_6H_5CH_2CH_2$; **e**: R = C_6H_{11}

1 **11** **12**

Structures of all the prepared compounds were assigned on the basis of reaction mechanisms and of analytical and spectroscopic data referring to considerations reported in our previous papers [1-4] about the preparation of the 4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]pyridazines, the 4-monochloro compounds and the hydrazino and phenylhydrazino derivatives. Structures of the tricyclic heterocycles (1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazines) were assigned by comparison with the analogous compounds previously prepared [5] and were confirmed by analytical and spectroscopic data.

Some tricyclic compounds, tested by binding procedures on the benzodiazepine receptor and A_1 and A_2 adenosine receptors, did not show biological activity, but it could be interesting to evaluate the biological affinity of this heterocyclic structure properly functionalized.

Table II

Mass Spectra (m/z) of Compounds **6**, **7**, **8** and **12**

6a	267 (M^+), 238, 91 (base), 65, 39, 29
6b	281 (M^+), 252, 155, 105 (base), 77, 28
6c	267 (M^+), 238, 195, 183, 155, 142, 116, 91 (base), 65, 39
7a	329 (M^+), 283, 257, 227, 155, 128, 91 (base), 65, 29
7b	343 (M^+), 297, 209, 169, 105 (base), 77, 29
7c	329 (M^+), 283, 226, 183, 156, 118, 91, 65, 29 (base)
8a	283 (M^+), 254, 212, 197, 181, 153, 128, 91 (base), 65, 51
8b	297 (M^+), 268, 226, 195, 167, 152, 105 (base), 77, 65, 29
8c	283 (M^+), 255, 213, 182, 156 (base), 155, 128, 91, 65, 29
12a	343 (M^+), 331, 270, 242, 213, 153, 129, 91 (base), 77, 65, 29
12b	357 (M^+), 328, 314, 285, 210, 167, 143, 105 (base), 77, 44
12c	343 (M^+), 314, 286, 258, 243, 198, 156, 114, 91 (base), 65, 44
12d	357 (M^+), 328, 301, 254, 182, 145, 104, 91, 77 (base), 65, 51
12e	335 (M^+), 254 (base), 226, 171, 104, 77, 41

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 spectra were recorded with a Varian 60 FT or with a Varian CFT-20 spectrometer in DMSO-d_6 in δ units from TMS as an internal standard. Mass spectra were performed with a Hewlett Packard MS/System 5988. The tlc data were obtained with Riedel de Haen, 37360 DC-Karten F_{254}, 0.2 mm, eluting with ethyl acetate/60-80° petroleum ether 1:2 mixture. Elemental analyses (C,H,N) were performed on a Carlo Erba Elemental Analyzer Model 1106 apparatus.

1-(*p*-Methylphenyl)-4-chloro-7-hydroxy-1,2,3-triazolo[4,5-*d*]-pyridazine (**2c**), 1-(*p*-Methylphenyl)-4-hydroxy-7-chloro-1,2,3-triazolo[4,5-*d*]pyridazine (**3c**) and 1-(*p*-Methylphenyl)-4,7-dichloro-1,2,3-triazolo[4,5-*d*]pyridazine (**4c**).

A suspension of **1c** (2.54 g, 10.5 mmoles) in phosphorus oxychloride (25 ml) was refluxed for 4 hours under anhydrous conditions. The solution obtained was poured into crushed ice and the precipitate was collected by filtration, washed with water and extracted with 10% sodium hydroxide. The insoluble material consisted of the 4,7-dichloro derivative **4c** was filtered off, 1.10 g (38%), mp 168-170° (ethyl acetate), Rf 0.63.

Anal. Calcd. for $C_{11}H_7N_5Cl_2$: C, 47.17, H, 2.52; N, 25.00. Found: C, 47.46; H, 2.37; N, 25.20.

Table III

IR and ^{1}H NMR Data of Compounds **6**, **7**, **8** and **12**

	iIR (μ)	^{1}H NMR (δ)
6a	Combination bands 4.36, 5.34	6.13 (s, 2H, CH_2), 7.40 (s, 5H, C_6H_5), 8.66 (brs, 1H, NH), 9.40 (s, 1H, CH)
6b	Combination bands 4.25, 5.30	2.33 (s, 3H, CH_3), 6.13 (s, 2H, CH_2), 7.33 (s, 4H, C_6H_4), 9.20 (s, 1H, CH)
7a	3.01, 3.09, 3.18 (NHNH), 5.98 (CO)	1.20 (t, 3H, CH_3), 4.05 (q, 2H, CH_2), 6.01 (s, 2H, CH_2), 7.34 (s, 5H, C_6H_5), 8.92 (s, 2H, NH), 12.06 (s, 1H, NH)
7b	3.00, 3.07, 3.16 (NHNH), 5.97 (CO)	1.17 (t, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.01 (q, 2H, CH_2), 7.11 and 7.27 (2d, 4H, C_6H_4)
8a	3.12, 4.08 (NH/OH), 5.89 (CO)	4.38 (brs, 1H, exchangeable), 5.97 (s, 2H, CH_2), 7.32 (s, 5H, C_6H_5), 12.38 (brs, 1H, exchangeable)
8c	3.08, 4.00 (NH/OH), 5.78 (CO)	2.37 (s, 3H, CH_3), 4.70 (brs, 1H, exchangeable), 7.4 and 7.48 (2d, 4H, C_6H_4)
12a		6.18 (s, 2H, CH_2), 7.34 (s, 5H, C_6H_5), 7.50-8.14 (m, 5H, C_6H_5), 11.05 (s, 1H, CH)
12b		2.26 (s, 3H, CH_3), 6.09 (d, 2H, CH_2), 6.98-8.22 (m, 9H, aromatics), 11.03 (s, 1H, CH)
12d		3.30 (t, 2H, CH_2), 5.17 (t, 2H, CH_2), 7.19 (s, 5H, C_6H_5), 7.51-8.17 (m, 5H, C_6H_5), 11.04 (s, 1H, CH)
12e		1.09-2.29 (m, 11H, C_6H_{11}), 7.48-8.17 (m, 5H, C_6H_5), 11.05 (s, 1H, CH)

By acidification (*p*H 1-2) of the alkaline filtrate the mixture of the two monochloro isomers precipitated (1.59 g, 58%). Crystallization from benzene of this mixture provided the 4-monochloro isomer **2c**, 0.240 g (12%), mp 243-246°, Rf 0.42; ir: μ 5.95 (CO).

Anal. Calcd. for $C_{11}H_8N_5OCl$: C, 50.49; H, 3.08; N, 26.76. Found: C, 50.26; H, 2.82; N, 26.39.

The residue obtained by evaporation of the benzene mother liquors (mixture **2c**, **3c**) was separated by flash chromatography. A solution of 0.260 g of the mixture in 15 ml of ethyl acetate was absorbed on 1.4 g of silica gel by evaporation of the solvent under reduced pressure. The residue was placed on the head of a silica gel column (25 x 2.5 cm) and the column was eluted with ethyl acetate/60-80° petroleum ether (1:2). Compound **2c** was first eluted; 0.100 g (39%), after a little fraction of the isomer mixture (0.015 g, 5.8%), the 7-chloro isomer **3c** was obtained, 0.125 g (48%), mp 281-283°, Rf 0.20; ir: μ 5.90 (CO).

Anal. Calcd. for $C_{11}H_8N_5OCl$: C, 50.49; H, 3.08; N, 26.76. Found: C, 50.47; H, 3.19; N, 26.48.

1-(*p*-Methylbenzyl)-4-hydrazino-7-hydroxy-1,2,3-triazolo[4,5-*d*]-pyridazine (**5b**) and 1-(*p*-Methylphenyl)-4-hydrazino-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**5c**).

To a solution of 1.0 mmole of the appropriate 4-chloro derivative **2b** or **2c** in 0.5 ml of dimethyl sulfoxide 99% hydrazine hydrate (1.5 ml, ≈ 30 mmoles) was added and heated at 100° for 6 hours under stirring. Dilution with water of the reaction mixture precipitated the title compounds.

Compound **5b** was obtained in 74% yield, (0.200 g), mp 255-258° (ethanol); ir: μ 3.05-3.25 ($NHNH_2$), 5.95 (CO); ms: m/z 271, 3.87% (M^+), 105, 100% ($CH_3C_6H_4CH_2$).

Anal. Calcd. for $C_{12}H_{13}N_7O$: C, 53.13; H, 4.83; N, 36.14. Found: C, 53.44; H, 4.89; N, 35.86.

Compound **5c** was obtained in 79% yield, (0.203 g), mp 290-293° (dimethylformamide/water); ir: μ 3.05-3.25 ($NHNH_2$), 5.95 (CO), ms: m/z 257, 48.47% (M^+), 91, 100% ($C_6H_5CH_2$).

Anal. Calcd. for $C_{11}H_{11}N_7O$: C, 51.36; H, 4.31; N, 38.11. Found: C, 51.17; H, 4.11; N, 37.79.

3-Benzyl-4-hydroxy-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]-pyridazine (**6a**), 3-(*p*-Methylbenzyl)-4-hydroxy-1,2,3-triazolo-[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine (**6b**) and 3-(*p*-Methylphenyl)-4-hydroxy-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]-pyridazine (**6c**).

A solution of 0.50 mmole of the appropriate hydrazino derivative **5a**, **5b** or **5c** in 5 ml of formic acid was refluxed for 8 hours. The reaction mixture was evaporated *in vacuo* and the residue was treated with water to obtain the title compounds as a solid residue which was collected by filtration and purified by crystallization (Table I).

1-Benzyl-4-(2-ethoxycarbonylhydrazino)-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**7a**), 1-(*p*-Methylbenzyl)-4-(2-ethoxycarbonylhydrazino)-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**7b**), and 1-(*p*-Methylphenyl)-4-(2-ethoxycarbonylhydrazino)-7-hydroxy-1,2,3-triazolo[4,5-*d*]pyridazine (**7c**).

A solution of 0.7 mmole of the suitable hydrazino derivative **5a**, **5b** or **5c** in 2 ml of ethyl chloroformate was refluxed for 30 minutes. The reaction mixture was evaporated *in vacuo* and the residue was treated with water. The separated solid was collected by filtration and purified by crystallization (Table I).

3-Benzyl-4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]-pyridazine (**8a**), 3-(*p*-Methylbenzyl)-4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine (**8b**) and 3-(*p*-Methylphenyl)-4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine (**8c**).

A solution of 0.30 mmole of the appropriate ethoxycarbonylhydrazino derivative **7a**, **7b** or **7c** in 2 ml of diphenyl ether was refluxed for 2 hours. By cooling, the title compounds crystallized and were collected by filtration and washed with 60-80° petroleum ether (Table I).

3-Benzyl-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazine (**10a**).

A solution of the 4-hydrazino derivative **9a** [4] (0.200 g, 0.83 mmole) in 5 ml of formic acid was refluxed for 6 hours. The

reaction mixture was evaporated *in vacuo* and the residue was treated with water and 10% sodium hydroxide; the aqueous layer was decanted off and the residue was crystallized from ethanol to provide **10a**, 0.062 g (30%), mp 198-201°; ms: m/z 251, 8.72% (M^+), 91, 100% ($C_6H_5CH_2$); ^1H nmr: δ 6.13 (s, 2H, CH_2), 7.27 (s, 1H, CH), 7.37 (s, 5H, C_6H_5), 9.45 (s, 1H, CH).

Anal. Calcd. for $C_{12}H_9N_7$: C, 57.37; H, 3.61; N, 39.02. Found: C, 57.22; H, 3.77; N, 38.76.

1-(*p*-Methylbenzyl)-4-phenylhydrazino-7-hydroxy-1,2,3-triazolo-[4,5-*d*]pyridazine (**11b**).

A mixture of 1-(*p*-methylbenzyl)-4,7-dihydroxy-1,2,3-triazolo[4,5-*d*]pyridazine [4] (1.50 g, 5.84 mmoles), hexamethyldisilazane (6 ml, ≈ 29 mmoles), ammonium sulfate (0.250 g, 1.95 mmoles) and phenylhydrazine (4 ml, 40 mmoles) was heated at 140° for 24 hours. The reaction mixture was evaporated *in vacuo* and the residue was washed with boiling benzene and 10% hydrochloric acid. The insoluble material was then purified by crystallization from dimethylformamide/water, 1.22 g (60%), mp 223-226°; ir: μ 3.05-3.10-3.20 (NHNH), 6.00 (CO); ms: m/z 347, 8.32% (M^+), 105, 100% (p-$CH_3C_6H_4CH_2$), ^1H nmr: δ 2.32 (s, 3H, CH_3), 5.99 (s, 2H, CH_2), 6.53-7.48 (m, 9H, aromatics), 7.52 and 8.93 (brs, 2H, exchangeable).

Anal. Calcd. for $C_{18}H_{17}N_7O$: C, 62.24; H, 4.93; N, 28.22. Found: C, 62.18; H, 4.78; N, 28.11.

3-Benzyl-4-hydroxy-8-phenyl-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-8-ium (**12a**), 3-(*p*-Methylbenzyl)-4-hydroxy-8-phenyl-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-8-ium (**12b**), 3-(*p*-Methylphenyl)-4-hydroxy-8-phenyl-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-8-ium (**12c**), 3-Phenethyl-4-hydroxy-8-phenyl-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-8-ium (**12d**) and 3-cyclohexyl-4-hydroxy-8-phenyl-1,2,3-triazolo[4,5-*d*]-1,2,4-triazolo[4,3-*b*]pyridazin-8-ium (**12e**).

A solution of 0.78 mmole of the suitable phenylhydrazino derivative (**11a** [4], **11b**, **11c** [4], **11d** [4] or **11e** [4]) in 6 ml of formic acid was refluxed for 22 hours. The reaction mixture was evaporated *in vacuo* and the residue was treated with water, collected by filtration and purified by crystallization (Table I).

REFERENCES AND NOTES

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[1] G. Biagi, M. Ferretti, I. Giorgi, O. Livi, V. Scartoni and A. Lucacchini, *Farmaco*, **48**, 1159 (1993).

[2] G. Biagi, I. Giorgi, O. Livi, V. Scartoni, P. Tacchi, C. Martini, S. Merlino and M. Pasero, *Farmaco*, **49**, 175 (1994).

[3] G. Biagi, I. Giorgi, O. Livi, V. Scartoni, A. Lucacchini, G. Senatore and P. L. Barili, *Farmaco*, **49**, 357 (1994).

[4] G. Biagi, I. Giorgi, O. Livi, V. Scartoni, S. Velo, C. Martini, G. Senatore and P. L. Barili, *Farmaco*, **50**, 99 (1995).

[5] M. Yanai, T. Kinoshita, S. Takeda, M. Mori, H. Sadaki and H. Watanabe, *Chem. Pharm. Bull.*, **18**, 1685 (1970).

[6] J. E. Francis, D. A. Bennett, J. L. Hyun, S. L. Rovinski, C. L. Amrick, P. S. Loo, D. Murphy, R. F. Neale and D. L. Wilson, *J. Med. Chem*, **34**, 2899 (1991).

[7] M. G. Collins and S. M. O. Hourani, *TiPS*, **14**, 360 (1993).

[8] P. G. Baraldi, L. Zappaterra and E. Ongini, PCT Int. Appl. WO 95 01, 356; *Chem. Abstr.*, **122**, 239712h (1995).

[9] P. G. Baraldi, B. Cacciari, G. Spalluto, A. Borioni, M. Viziano, S. Dionisotti and E. Ongini, *Curr. Med. Chem.*, **2**, 707 (1995).

[10] H. Vorbruggen and K. Krolikiewiez, *Chem. Ber.*, **117**, 1523 (1984).