The Synthesis and Transformations of 9*H*-Imidazo[1,2-*b*]pyrazolo[4,3-*d*]-pyridazine and 9*H*-Pyrazolo[4,3-*d*]-*s*-Triazolo[4,3-*b*]pyridazine Derivatives

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Dedicated to Professor Norman H. Cromwell

The nucleophilic and electrophilic substitutions of 6-substituted 9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo-[4,3-*d*]pyridazines **2**, nucleophilic substitutions of 6-substituted 9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo-[4,3-*b*]pyridazines **7** and some other transformations to give compounds **3** and **8**, respectively, were studied. It was shown that both heterocyclic systems are stable under the conditions employed in these transformations.

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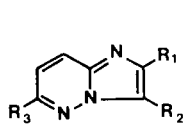
1,3-Dipolar cycloadditions of diazoalkanes are important methods for the synthesis of various five-membered heterocycles [1]. Since there are only sporadic examples of cycloadditions of diazoalkanes to six-membered heteroaromatic systems, mostly polysubstituted, described in the literature [2], a systematic study of cycloadditions of diazoalkanes to azolo- and azinopyridazines with a bridgehead nitrogen atom, and to other fully aromatic 10 π-electron systems has been undertaken in our laboratory. It was shown in preliminary studies, that 2-diazopropane undergoes a regiospecific 1,3-dipolar cycloaddition to imidazo-[1,2-*b*]pyridazines [3], *s*-triazolo[4,3-*b*]pyridazines, *s*-triazolo[1,5,*b*]pyridazines and tetrazolo[1,5-*b*]pyridazines [4], pyrimido[1,2-*b*]pyridazin-4-ones [5], bis-*s*-triazolo[4,3-*b*:-3',4'-*f*]pyridazines [2] and bis-*s*-triazolo[1,5-*b*:3',4'-*f*]pyridazines [6] to give derivatives of new heterocyclic systems. The structures of these new systems have been determined either by photochemical elimination of nitrogen from the pyrazole part of the molecules to produce 8-substituted azolopyridazines and 9-substituted azinopyridazines [4,5,-7,8] or by X-ray analysis for 6-chloro-9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine [9] showing that cycloadditions of diazoalkanes to the partially localized and polarized double bond C_7–C_8 in azolopyridazines or C_8–C_9 in azinopyridazines proceeds in opposite manner in comparison to that observed in α,β-unsaturated carbonyl compounds [1].

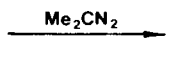
Since pyrazoloazolopyridazines are new heterocyclic systems, it seems worthwhile to study their chemical behaviour. In this communication we report on the preparation of some derivatives and some transformations of 9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazines and 9*H*-pyrazolo-[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazines in order to study the stability of these tricyclic systems, especially the pyrazole part, under the conditions for nucleophilic and electrophilic substitution.

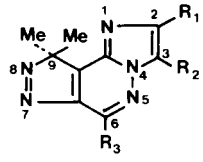
Imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazines **2**, prepared from imidazo[1,2-*b*]pyridazines **1** and 2-diazopropane undergo nucleophilic substitution at position 6. For example, treatment of the compounds **2a,b,d** with sodium methoxide in methanol produced the corresponding 6-methoxy derivatives **3a,b,c**. The compound **3a** is identical with the compound obtained by cycloaddition of 2-diazopropane to **1f** [3]. With hydrazine hydrate the compounds **2a,b,c,d** gave the 6-hydrazino derivatives **3d,e,f,g**, which were converted with aldehydes and ketones into isopropylidene and benzylidene hydrazones **3h,i,j,k,l**, while in the reaction of **3d,e,g** with nitrous acid the corresponding 6-azido compounds **3m,n,o** were formed. On the other hand, in the reaction of **3f** with nitrous acid in 1:1 molar ratio only the hydrazido group was transformed to give acyl azide **3p**, while with nitrous acid in 1:2 molar ratio also the hydrazino group at position 6 reacted to give the bis-azide **3q**. The structure determination of **3p** is based on the comparison of the ir spectra of the starting hydrazino-nydrazide **3f** and monoazide **3p**. Namely, the starting compound **3f** shows the carbonyl band at ν = 1600 cm^{-1}, while the carbonyl band of the monoazide **3p** appears at ν = 1710 cm^{-1}. This is in agreement only with the structure **3p** and not with **3t**. Reduction of the azide **3n** with hydrogen sulphide in ethanol produced 6-amino derivative **3r**, while by catalytic hydrogenation of **2d** over Pd/C under mild conditions only dehalogenation of chlorine at position 6 took place yielding **3s** in the form of hydrochloride salt.

Bromination of the compounds **2a,b,d** unsubstituted at position 3 with bromine in acetic acid took place at position 3 to give 3-bromo derivatives **4a,b,c** when the reaction products were neutralized with sodium hydrogen carbonate and recrystallized from ethanol. On the other hand, when crude reaction product, obtained from **2b**, was crystallized from acetic acid the hydrobromide-bromine complex **4d** was isolated. Quaternization of **2a** with methyl iodide in methanol was taking place at nitrogen at position

Scheme 1





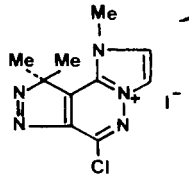


1	R_1	R_2	R_3
a	H	H	Cl
b	Me	H	Cl
c	Me	COOEt	Cl
d	Ph	H	Cl
e	H	Br	Cl
f	H	H	OMe

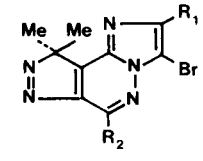
2	R_1	R_2	R_3
a	H	H	Cl
b	Me	H	Cl
c	Me	COOEt	Cl
d	Ph	H	Cl
e	H	Br	Cl
f	H	H	OMe

3	R_1	R_2	R_3
a	H	H	OMe
b	Me	H	OMe
c	Ph	H	OMe
d	H	H	$NHNH_2$
e	Me	H	$NHNH_2$
f	Me	$CONHNH_2$	$NHNH_2$
g	Ph	H	$NHNH_2$
h	H	H	$NHN{=}CMe_2$
i	Me	H	$NHN{=}CMe_2$
j	Ph	H	$NHN{=}CMe$
k	H	H	$NHN{=}CHPh$
l	Ph	H	$NHN{=}CHPh$
m	H	H	N_3
n	Me	H	N_3
o	Ph	H	N_3
p	Me	CON_3	$NHNH_2$
q	Me	CON_3	N_3
r	Me	H	NH_2
s	Ph	H	H (x HCl)
t	Me	$CONHNH_2$	N_3

MeI

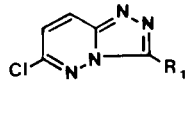


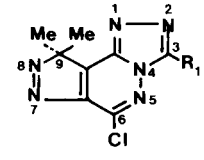
5



4	R_1	R_2
a	H	Cl
b	Me	Cl
c	Ph	Cl
d	Me	Cl (x HBr, Br_2)

Scheme 2





6	R_1
a	H
b	Ph

7	R_1
a	H
b	Ph

8	R_1	R_2
a	H	$NHNH_2$
b	Ph	$NHNH_2$
c	H	N_3
d	Ph	N_3
e	H	NH_2
f	Ph	NH_2
g	H	$NHCH_2CH(OEt)_2$
h	Ph	$NHCH_2CH(OEt)_2$
i	H	$NHCH_2CHMe$ | OH
j	Ph	$NHCH_2CHMe$ | OH
k	H	$NHCH_2CHMe$ | Cl
l	Ph	$NHCH_2CHMe$ | Cl
m	H	H
n	H	Br
o	Ph	Br

1 to give the corresponding methiodide **5** (Scheme 1).

Nucleophilic substitutuon of chlorine at position 6 in 6-chloro-9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]-pyridazines **7a,b**, obtained by dipolar cycloaddition of 2-diazopropane to *s*-triazolo[4,3-*b*]pyridazines **6a,b** [4] with hydrazine hydrate has been studied previously in connection with the preparation of bis-*s*-triazolo[4,3-*b*:3',4'-*f*]pyridazine derivatives [2]. These studies were further extended. 6-Hydrazino compounds **8a,b** were treated with nitrous acid to give 6-azido derivatives **8c,d**. They were reduced with hydrogen sulphide in ethanol to give 6-amino derivatives **8e,f**, identical with the compounds obtained from **7a,b** by substitution of chlorine with liquid ammonia. In further experiments the chlorine at position 6 in compounds **7a,b** was substituted with substituted amines, such as 2,2-diethoxyethylamine and 2-hydroxypropylamine to give the compounds **8g,h** and **8i,j**, respectively. Hydroxy compounds **8i,j** were converted with phosphorus oxychloride into chloro derivatives **8k,l**. These substituted amino compounds were prepared as intermediates for further cyclization into tetracyclic imidazo-pyrazolo-*s*-triazolopyridazine derivatives. However, attempts to form the imidazole ring by cyclization in polyphosphoric acid resulted in the formation of tarry material. Catalytic dehalogenation of **7a** over Pd/C gave at position 6 unsubstituted product **8m**, and oxidation of the hydrazino compounds **8a,b** with bromine in acetic acid yielded 6-bromo derivatives **8n,o** (Scheme 2).

The structure determination of all new compounds are based on microanalytical data for C,H and N, and on nmr spectral data, since the chemical shifts of two methyl groups, which appear as a singlet at δ = 1.63-1.88 ppm, remain throughout these transformations unchanged.

On the basis of these experiments it is possible to conclude, that 9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine and 9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine systems are stable under the conditions described here and, in general, they behave very similarly as the bicyclic systems imidazo[1,2-*b*]pyridazine and *s*-triazolo[4,3-*b*]pyridazine [10].

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage. All nmr spectra were obtained on a JEOL JNM C60-HL spectrometer, and microanalyses for C,H, and N on a Perkin-Elmer Analyser 240 C.

The following compounds were prepared according to the procedures described in the literature: 6-chloro-2-methylimidazo[1,2-*b*]pyridazine (**1b**) [11], 6-chloro-3-ethoxycarbonyl-2-methylimidazo[1,2-*b*]pyridazine (**1c**) [11], 3-bromo-6-chloroimidazo[1,2-*b*]pyridazine (**1e**) [12], 6-methoxy-2-methylimidazo[1,2-*b*]pyridazine (**1f**) [13], 6-chloro-9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**2a**) [3], 6-chloro-9,9-dimethyl-2-phenyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**2d**) [3], 6-methoxy-9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**2f**) [3], 6-hydrazino-9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8a**) [2], 9,9-dimethyl-6-hydrazino-3-phenyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]-pyridazine (**8b**) [2], 6-chloro-9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo-[4,3-*b*]pyridazine (**7a**) [4], 6-chloro-9,9-dimethyl-3-phenyl-9*H*-pyrazolo-[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**7b**) [2].

According to the procedure described in lit [3] for the preparation of **2a,d** the following compounds were prepared:

6-Chloro-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**2b**).

This compound was prepared from **1b** in 89% yield, mp 193-194° (from cyclohexane); nmr (deuteriochloroform): δ 1.75 (s, 9,9-diMe), 2.55 (s, 2-Me), 7.80 (s, H_3).

Anal. Calcd. for $C_{10}H_{10}ClN_5$: C, 50.96; H, 4.24; N, 29.72. Found: C, 50.70; H, 4.32; N, 29.64.

6-Chloro-3-ethoxycarbonyl-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo-[4,3-*d*]pyridazine (**2c**).

This compound was prepared from **1c** in 54% yield, mp 184-187° (from ethanol); nmr (deuteriochloroform): δ 1.45 (t, CH_2Me), 1.80 (s, 9,9-diMe), 2.75 (s, 2-Me), 4.45 (q, CH_2Me), J_{CH_2Me} = 6.5 Hz.

Anal. Calcd. for $C_{13}H_{14}ClN_5O_2$: C, 50.74; H, 4.58; N, 22.76. Found: C, 51.01; H, 4.62; N, 22.61.

3-Bromo-6-chloro-9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**2e**).

This compound was prepared from **1e** in 50% yield, mp 179-180° (from ethanol); ms: M^+ = 299; nmr (DMSO-d_6): δ 8.18 (s, H_2), 1.70 (s, 9,9-diMe).

Anal. Calcd. for $C_9H_7BrClN_5$: C, 35.97; H, 2.35; N, 23.30. Found: C, 36.01; H, 2.35; N, 23.19.

The compound is identical with compound **4a** obtained by bromination of **2a** described below.

6-Methoxy-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**2f**).

This compound was prepared from **1f** in 39% yield, mp 208° (from water); nmr (deuteriochloroform): δ 1.75 (s, 9,9-diMe), 2.48 (d, 2-Me), 4.15 (s, OMe), 7.58 (s, H_3), $J_{2\text{-}Me,H_3}$ = 0.8 Hz.

Anal. Calcd. for $C_{11}H_{13}N_5O$: C, 57.13; H, 5.66; N, 30.28. Found: C, 57.42; H, 5.72; N, 30.55.

6-Methoxy-9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**3a**).

To a solution of sodium methoxide, prepared from sodium (35 mg) in methanol (5 ml) **2a** (221 mg) was added and the mixture was heated under reflux for one hour. The precipitate was, after cooling, collected by filtration to give **3a** in 80% yield, mp 203-205° (from methanol), lit [3] mp 203-205°.

The following compounds were prepared according to this procedure:

6-Methoxy-9,9-dimethyl-2-phenyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**3c**).

This compound was obtained from **2d** in 96% yield, mp 170-172° (from methanol); nmr (deuteriochloroform): δ 1.80 (s, 9,9-diMe), 7.20-7.40 (m) and 7.75-8.00 (m) (2-Ph), 4.13 (s, 6-OMe), 8.13 (s, H_3).

Anal. Calcd. for $C_{16}H_{15}N_5O$: C, 65.51; H, 5.15; N, 23.88. Found: C, 65.26; H, 5.23; N, 23.53.

6-Hydrazino-9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**3d**).

To a solution of **2a** (221 mg, 0.001 mole) in methanol (6 ml) hydrazine hydrate (80%, 1 ml) was added and the mixture was heated under reflux for 30 minutes. The crystals were, after cooling, collected by filtration to give **3d** in 85% yield, mp 265-266° (from methanol); nmr (DMSO-d_6): δ 1.63 (s, 9,9-diMe); 7.60 (d, H_2); 8.05 (d, H_3); 8.95 (br s) and 4.33 (br s) (NH, NH_2).

Anal. Calcd. for $C_9H_{11}N_7$: C, 49.76; H, 5.10; N, 45.14. Found: C, 49.81; H, 5.11; N, 44.91.

The following compounds were prepared according to this procedure:

6-Hydrazino-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**3e**).

This compound was prepared from **2b** in 50% yield, mp 231-233° (from ethanol); nmr (DMSO-d_6): 1.75 (s, 9,9-diMe), 2.75 (d, 2-Me), 7.54 (q, H_3), 4.00 (br s) and 7.15 (br s) (NH, NH_2), $J_{2\text{-Me},H_3}$ = 0.9 Hz.

Anal. Calcd. for $C_{10}H_{13}N_7$: C, 51.93; H, 5.67; N, 42.40. Found: C, 52.03; H, 5.98; N, 42.57.

3-Carbazoyl-6-hydrazino-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**3f**).

A suspension of **2c** (154 mg, 0.0005 mole) in hydrazine hydrate (80%, 3 ml) was heated under reflux for 40 minutes. The precipitate was, after cooling collected by filtration to give **3f** in 53% yield mp 223-227° (from water); nmr DMSO-d_6): 1.65 (s, 9,9-diMe), 2.58 (s, 2-Me), 4.5-5.2 (br s) and 10.05-10.30 (br s) (NH, NH_2).

Anal. Calcd. for $C_{11}H_{15}N_9O$: C, 42.99; H, 5.57; N, 41.02. Found: C, 43.07; H, 5.42; N, 41.23.

6-Hydrazino-9,9-dimethyl-2-phenyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]-pyridazine (**3g**).

This compound was prepared from **2d** in 62% yield, mp 153-154° (from ethanol); nmr (DMSO-d_6): δ 1.65 (s, 9,9-diMe), 7.10-7.40 (m) and 7.70-7.95 (m) (2-Ph), 4.20 (br s) and 7.15 (br s) ($NHNH_2$), 8.30 (s, H_3).

Anal. Calcd. for $C_{15}H_{15}N_7$: C, 61.42; H, 5.15; N, 33.43. Found: C, 61.13; H, 5.16; N, 33.17.

6-Hydrazino-9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine Acetone Hydrazone (**3h**).

A mixture of **3d** (217 gm, 0.001 mole) and acetone (10 ml) was heated under reflux for one hour. The solvent was evaporated *in vacuo* and the solid residue was recrystallized from a mixture of cyclohexane and toluene to give **3h** in 61% yield, mp 154-155°; nmr (deuteriochloroform): 1.78 (s, 9,9-diMe), 2.13 (s) and 2.23 (s) (-N CMe_2), 7.68 (d, H_2), 8.02 (d, H_3), 8.65 (br s, NH), J_{H_2,H_3} = 1.0 Hz.

Anal. Calcd. for $C_{12}H_{15}N_7$: C, 56.01; H, 5.88; N, 38.11. Found: C, 56.13; H, 5.91; N, 37.84.

The following compounds were prepared according to this procedure:

6-Hydrazino-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine Acetone Hydrazone (**3i**).

This compound was prepared from **3e** in 21% yield, mp 153-156° (from cyclohexane); nmr (deuteriochloroform): δ = 1.75 (s, 9,9-diMe), 2.10 (s) and 2.20 (s) (N-CMe_2), 2.45 (s, 2-Me), 8.45 (br s, NH).

Anal. Calcd. for $C_{13}H_{17}N_7$: C, 57.54; H, 6.32; N, 36.14. Found: C, 57.48; H, 6.53; N, 36.27.

6-Hydrazino-9,9-dimethyl-2-phenyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]-pyridazine Acetone Hydrazone (**3j**).

This compound was prepared from **3g** in 55% yield, mp 226-228° (from a mixture of toluene and cyclohexane); nmr (DMSO-d_6): δ 1.70 (s, 9,9-diMe), 2.06 (s, N-CMe_2), 7.25-7.45 (m) and 7.80-8.00 (m) (2-Ph), 8.68 (s, H_3).

Anal. Calcd. for $C_{18}H_{19}N_7$: C, 64.48; H, 5.74; N, 29.41. Found: C, 65.03; H, 5.81; N, 29.61.

6-Hydrazino-9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine Benzaldehyde Hydrazone (**3k**).

To a suspension of **3d** (217 mg, 0.001 mole) in ethanol (5 ml) benzaldehyde (10 g mg, 0.001 mole) and glacial acetic acid (0.2 ml) were added. The mixture was heated under reflux for 30 minutes. Ethanol was evaporated *in vacuo* and cyclohexane (5 ml) was added to the oily residue. The crystals, formed upon standing in the refrigerator for 12 hours, were collected by filtration to give **3k** in 80% yield, mp 229° (from a mixture of cyclohexane and toluene, 4:1); nmr (DMSO-d_6): δ 1.70 (s, 9,9-diMe), 7.30-7.55 (m) and 7.60-7.90 (m) (Ph), 7.71 (d, H_2), 8.23 (d, H_3), 8.50 (s, CH-N), 10.85 (br s, NH), J_{H_2,H_3} = 1.2 Hz.

Anal. Calcd. for $C_{16}H_{15}N_7$: C, 62.93; H, 4.95; N, 32.11. Found: C, 62.78; H, 4.96; N, 31.88.

The following compounds were prepared according to this procedure:

6-Hydrazino-9,9-dimethyl-2-phenyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]-pyridazine Benzaldehyde Hydrazone (**3l**).

This compound was prepared from **3g** in 72% yield, mp 199-200° (from a mixture of toluene and DMF, 4:1); nmr (DMSO-d_6): δ 1.70 (s, 9,9-diMe), 6.85-7.10 (m) and 7.25-7.45 (m) (2-Ph, CH-*Ph*), 9.00 (s, H_3), 9.37 (s, CH-N).

Anal. Calcd. for $C_{22}H_{19}N_7$: C, 69.27; H, 5.02; N, 25.71. Found: C, 69.03; H, 5.17; N, 25.98.

6-Azido-9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**3m**).

Method A. To a solution of **3d** (109 mg, 0.0005 mole) in a mixture of water (7.4 ml) and hydrochloric acid (36%, 0.6 ml) a saturated solution of sodium nitrite (1 ml) was added dropwise at 0°. The crystals were collected by filtration to give **3m** in 63% yield, mp 215-217° (from ethanol); nmr (DMSO-d_6): δ 1.68 (s, 9,9-diMe), 7.97 (d, H_2), 8.50 (d, H_3), J_{H_2,H_3} = 1.0 Hz.

Anal. Calcd. for $C_9H_8N_8$: C, 47.36; H, 3.53; N, 49.10. Found: C, 47.35; H, 3.38; N, 48.89.

Method B. To a solution of **2a** (11 mg, 0.0005 mole) in ethanol (5 ml) a solution of sodium azide (50 mg) in water (0.5 ml) was added and the mixture was heated under reflux for 40 hours. The solid was, after cooling, collected by filtration to give **3m** in 7% yield (from ethanol), mp 215-217°. The ir spectrum was identical with that obtained with compound described under Method A.

The following compounds were prepared according to Method A.

6-Azido-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo]4,3-*d*]pyridazine (**3n**).

This compound was prepared from **3e** in 45% yield, mp 202-205° (from ethanol); nmr (deuteriochloroform): δ = 1.75 (s, 9,9-diMe), 2.55 (s, 2-Me), 8.48 (s, H_3).

Anal. Calcd. for $C_{10}H_{10}N_8$: C, 49.58; H, 4.16; N, 46.26. Found: C, 49.34; H, 4.19; N, 46.40.

6-Azido-9,9-dimethyl-2-phenyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**3o**).

This compound was prepared from **3g** in 57% yield, mp 189-192° (from a mixture of methanol and DMF): nmr (DMSO-d_6): δ 1.71 (s, 9,9-diMe), 7.25-7.50 (m) and 7.85-8.10 (m) (2-Ph), 8.98 (s, H_3).

Anal. Calcd. for $C_{15}H_{12}N_8$: C, 59.29; H, 3.97; N, 36.83. Found: C, 58.97; H, 4.02; N, 36.72.

3-Azidocarbonyl-6-hydrazino-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo-[4,3-*d*]pyridazine (**3p**).

To a solution of **3f** (289 mg, 0.001 mole) in a mixture of water (2 ml) and hydrochloric acid (36%, 1.5 ml) a solution of sodium nitrite (75 mg, 0.0011 mole) in water (1 ml) was added dropwise at 0°. The mixture was, after standing at 0° for one hour, neutralized with solid sodium hydrogen carbonate and the precipitate was collected by filtration to give **3p** in 25% yield, mp 192-194° (from methanol); nmr (deuteriochloroform): δ 1.75 (s, 9,9-diMe), 2.75 (s, 2-Me), 3.95 (br s) and 3.40 (br s) (NH, NH_2).

Anal. Calcd. for $C_{11}H_{12}N_{10}O$: C, 44.00; H, 4.03; N, 46.64. Found: C, 44.26; H, 3.86; N, 46.31.

6-Azido-3-azidocarbonyl-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]-pyridazine (**3q**).

To a solution of **3f** (289 mg, 0.001 mole) in a mixture of water (3 ml) and hydrochloric acid (36%, 3 ml) a solution of sodium nitrite (207 mg, 0.003 mole) in water (2 ml) was added at 0°. The mixture was, after standing at 0° for one hour, neutralized with solid sodim hydrogen carbonate. The precipitate was collected by filtration and washed with cold water to give **3q** in 41% yield, mp 180-184°; nmr (deuteriochloroform): δ 1.75 (s, 9,9-diMe), 2.75 (s, 2-Me).

Anal. Calcd. for $C_{11}H_9N_{11}O$: C, 40.12; H, 3.67; N, 49.79. Found: C, 40.45; H, 3.37; N, 49.43.

6-Amino-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[3,4-*d*]pyridazine (**3r**).

A stream of hydrogen sulphide was bubbled through a boiling solution of **3n** (121 mg, 0.0005 mole) in ethanol (15 ml) for 15 minutes. The precipitated sulphur was, after standing in the refrigerator for 12 hours, filtered off, and the filtrate was evaporated *in vacuo*. The dry residue was recrystallized from a mixture of chloroform and cyclohexane (1:1) to give **3r** in 54% yield, mp 213-216°; nmr (deuteriochloroform): δ 1.75 (s, 9,9-diMe), 2.45 (s, 2-Me), 5.35 (br s, NH_2), 7.55 (s, H_3).

Anal. Calcd. for $C_{10}H_{12}N_6$: C, 55.54; H, 5.59; N, 38.87. Found: C, 55.71; H, 5.83; N, 38.58.

9,9-Dimethyl-2-phenyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine Hydrochloride (**3s**).

To a solution of **2d** (230 mg, 0.001 mole) in ethanol (30 ml) Pd/C (10%, 23 mg) was added and the mixture was hydrogenated in a Parr autoclave at 3 atomospheres. The catalyst was filtered off, the filtrate was evaporated to dryness and the solid residue was recrystallized from a mixture of toluene and ethanol (5:1) to give **3s** in 88% yield, mp 185-187°; nmr (DMSO-d_6): δ 1.74 (s, 9,9-diMe), 7.30-7.60 (m) and 7.95-8.20 (m) (2-Ph), 9.05 (s), and 9.07 (s) (H_3, H_6).

Anal. Calcd. for $C_{15}H_{14}ClN_5$: C, 60.12; H, 4.70; N, 23.37. Found: C, 60.33; H, 4.90; N, 23.09.

3-Bromo-6-chloro-9,9-dimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**4a**).

To a solution of **2a**, (110 mg) in acetic acid (2 ml) a solution of bromine (0.5 ml) in acetic acid (1 ml) was added dropwise. The reaction mixture was left at room temperature for 15 minutes. The precipitate was collected by filtration to give **4a** in 73% yield, mp 179-180° (from ethanol). The compound is identical with **2e** obtained by cycloaddition of 2-diazopropane to **1e**.

The following compounds were prepared according to this procedure:

3-Bromo-6-chloro-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine (**4b**).

This compound was prepared from **2b** in 45% yield, mp 230° (from ethanol); nmr (deuteriochloroform): δ 1.75 (s, 9,9-diMe), 2.55 (s, 2-Me).

Anal. Calcd. for $C_{10}H_9BrClN_5$: C, 38.18; H, 2.89; N, 22.26. Found: C, 38.11; H, 2.67; N, 22.35.

3-Bromo-6-chloro-9,9-dimethyl-2-phenyl-9*H*-imidazo[1,2-*b*]pyrazolo-[3,4-*d*]pyridazine (**4c**).

This compound was prepared from **2d** in 55% yield, mp 300° (from a mixture of methanol and toluene, 1:2); nmr (DMSO-d_6): δ 1.70 (s, 9,9-diMe), 7.25-7.50 (m) and 7.90-8.20 (m) (2-Ph).

Anal. Calcd. for $C_{15}H_{11}BrClN_5$: C, 47.83; H, 2.94; N, 18.59. Found: C, 48.13; H, 3.00; N, 18.31.

3-Bromo-6-chloro-2,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazine Hydrobromide-Bromine Complex (**4d**).

This compound was obtained by recrystallization of the crude prduct, obtained above, from acetic acid, yield 28%; nmr (DMSO-d_6): δ 1.65 (s, 9,9-diMe), 2.45 (s, 2-Me).

Anal. Calcd. for $C_{10}H_{10}Br_4ClN_5$: C, 21.63; H, 1.82; N, 12.61. Found: C, 21.73; H, 1.79; N, 12.84.

6-Chloro-1,9,9-trimethyl-9*H*-imidazo[1,2-*b*]pyrazolo[4,3-*d*]pyridazinium Iodide (**5**).

A mixture of **2a** (221.5 mg, 0.001 mole) and methyl iodide (0.6 ml) in methanol (5 ml) was heated in a sealed tube at 80° for eight hours. The product was, after cooling, collected by filtration to give **5** in 71% yield, mp 300° (from methanol); nmr (DMSO-d_6): δ = 1.82 (s, 9,9-diMe), 3.15 (s, 1-Me), 8.00 (d, H_2), 8.52 (d, H_3), J_{H_2,H_3} = 1.0 Hz.

Anal. Calcd. for $C_{10}H_{11}ClN_5$: C, 33.03; H, 3.05; N, 19.26. Found: C, 32.94; H, 3.13; N, 19.14.

6-Azido-9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8c**).

To a solution of **8a** (218 mg, 0.001 mole) in a mixture of water (5 ml) and hydrochloric acid (36%, 1 ml) a solution of sodium nitrite (75 mg) in water (2 ml) was added dropwise at 0° during vigorous stirring. Stirring was continued for another 10 minutes at 0° and 10 minutes at room temperature, followed by extraction with chloroform (3 times, 10 ml each time). The combined extracts were dried over anhydrous sodium sulphate, the solvent was evaporated *in vacuo* and the solid residue was recrystallized from a mixture of petroleum ether and ethanol to give **8c** in 75% yield, mp 157-160°; ms: 229 (M^+); nmr (DMSO-d_6): δ 1.70 (s, 9,9-diMe), 9.75 (s, H_3).

Anal. Calcd. for $C_8H_7N_9$: C, 41.92; H, 3.08; N, 55.00. Found: C, 41.73; H, 2.95; N, 54.79.

Analogously the following compounds were prepared:

6-Azido-9,9-dimethyl-3-phenyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8d**).

This compound was prepared from **8b** in 70% yield, mp 216-219° (from a mixture of cyclohexane and chloroform); nmr (deuteriochloroform): δ 1.85 (s, 9,9-diMe), 7.45-7.65 (m) and 8.30-8.55 (m) (3-Ph).

Anal. Calcd. for $C_{14}H_{11}N_9$: C, 55.08; H, 3.63; N, 41.29. Found: C, 54.91; H, 3.60; N, 41.01.

6-Amino-9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8e**).

MethodA. A mixture of **7a** (1.11 g, 0.005 mole) and liquid ammonia (20 ml) was heated in an autoclave at 50° for four hours. After cooling, the liquid ammonia was evaporated, water (3 ml) was added to the solid residue in order to dissolve ammonium chloride. Solid material was collected by filtration to give **8e** in 80% yield, mp 259-262° (from toluene); nmr (DMSO-d_6): δ 1.70 (s, 9,9-diMe), 7.50 (br s, NH_2), 9.23 (s, H_3).

Anal. Calcd. for $C_8H_9N_7$: C, 47.28; H, 4.46; N, 48.25. Found: C, 47.70; H, 4.51; N, 47.95.

Method B. A stream of hydrogen sulphide was bubbled through a boiling solution of **8c** (458 mg, 0.002 mole) in ethanol (30 ml) for two hours. Sulphur was, after cooling, filtered off, the filtrate was evaporated *in vacuo* and the solid residue was recrystallized from toluene to give **8e** in 85% yield.

6-Amino-9,9-dimethyl-3-phenyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8f**).

This compound was obtained from **7b** in 65% yield, mp 255-257° (from a mixture of ethanol and water, 1:2); nmr (DMSO-d_6): δ 1.73 (s, 9,9-diMe), 7.30 (br s, NH_2), 7.50-7.85 (m) and 8.40-8.65 (m) (3-Ph).

Anal. Calcd. for $C_{14}H_{13}N_7$: C, 60.20; H, 4.69; N, 35.10. Found: C, 59.98; H, 4.82; N, 35.03.

6-(2,2-Diethoxyethylamino)-9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo-[4,3-*b*]pyridazine (**8g**).

A mixture of **7a** (223 mg, 0.001 mole) and 2,2-diethoxyethylamine (158 mg, 0.0012 mole) in ethanol (15 ml) was heated under reflux for four hours. The solvent was evaporated *in vacuo* and the solid residue recrystallized from cyclohexane to give **8g** in 75% yield, mp 116-117°; nmr (DMSO-d_6): δ 1.15 (t, $MeCH_2$), 1.72 (s, 9,9-diMe), 3.60 (q, $MeCH_2$), 3.60 (d, CH_2CH), 4.90 (t, CH_2CH), 8.05 (br t, NH), 9.35 (s, H_3), J_{MeCH_2} = 7.0 Hz, J_{CH_2CH} = 5.5 Hz, J_{CH_2NH} = 5.5 Hz.

Anal. Calcd. for $C_{14}H_{21}N_7O_2$: C, 52.65; H, 6.63; N, 30.70. Found: C, 52.35; H, 6.82; N, 30.36.

6-(2,2-Diethoxyethylamino)-3-phenyl-9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8h**).

A mixture of **7b** (299 mg, 0.001 mole) and 2,2-diethoxypropylamine (158 mg, 0.0012 mole) in ethanol (20 ml) was heated under reflux for 8 hours. The solvent was evaporated *in vacuo*, petroleum ether (5 ml) was added to the oily residue and the mixture was left in refrigerator for several days. The crystals were collected by filtration to give **8h** in 80% yield, mp 81-83° (from cyclohexane); nmr (deuteriochloroform): δ 1.28 (t, $MeCH_2$), 1.85 (s, 9,9-diMe), 3.30-3.90 (m, CH_2CH, $MeCH_2$), 4.82 (t, CH_2CH), 7.40-7.60 (m) and 8.40-8.60 (m) (3-Ph).

Anal. Calcd. for $C_{20}H_{25}N_7O_2$: C, 60.74; H, 6.37; N, 24.79. Found: C,

60.61; H, 6.32; N, 24.49.

6-(2-Hydroxypropylamino)-9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo-[4,3-*b*]pyridazine (**8i**).

A mixture of **7a** (223 mg, 0.001 mole) and 2-hydroxypropylamine (150 mg) in ethanol (5 ml) was heated under reflux for five hours. The precipitate was, after cooling, collected by filtration to give **8i** in 80% yield, mp 244-247° (from water): nmr (DMSO-d_6): δ 1.17 (d, *Me*CH), 1.70 (s, 9,9-diMe), 3.35 (t, C*H*$_2$CH), 4.05 (m, CH$_2$C*H*), 4.84 (d, OH), 7.95 (br t, NH), 9.30 (s, H_3, J_{MeCH} = 6.0 Hz, J_{CHOH} = 4.5 Hz, J_{CH_2NH} = 6.0 Hz.

Anal. Calcd. for $C_{11}H_{15}N_7O$: C, 48.88; H, 5.59; N, 36.27. Found: C, 49.13; H, 5.66; N, 36.40.

6-(2-Hydroxypropylamino)-9,9-dimethyl-3-phenyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8j**).

A mixture of **7b** (299 mg, 0.001 mole) and 2-hydroxypropylamine (150 mg) in ethanol (5 ml) was heated under reflux until all the starting material was dissolved (approximately 8 hours). The crystals formed upon cooling were collected by filtration to give **8j** in 65% yield, mp 238-240° (from 2-propanol); nmr (DMSO-d_6): δ 1.20 (d, MeCH), 1.73 (s, 9,9-diMe), 3.25-4.40 (m, CHCH$_2$, OH), 7.40-7.65 (m) and 8.25-8.55 (m) (3-Ph), J_{MeCH} = 6.0 Hz.

Anal. Calcd. for $C_{17}H_{19}N_7O$: C, 60.52; H, 5.68; N, 29.06. Found: C, 60.44; H, 5.79; N, 28.86.

6-(2-Chloropropylamino)-9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo-[4,3-*b*]pyridazine (**8k**).

A mixture of **8i** (261 mg, 001 mole) and phosphoryl chloride (4 ml) was heated under reflux for 30 minutes. Phosphoryl chloride was evaporated *in vacuo*, the residue was dissolved in ice-cold water (10 ml), neutralized with solid sodium hydrogen carbonate, followed by extraction with chloroform (3 times, 10 ml each time). The combined extracts were dried over anhydrous sodium sulphate, the solvent was evaporated *in vacuo* and the solid residue recrystallized from ethanol to give **8k** in 70% yield, mp 249-251°; nmr (deuteriochloroform): δ 1.65 (d, *Me*CH), 1.82 (s, 9,9-diMe), 3.83 (t, C*H*$_2$CH), 4.40 (m, CH$_2$C*H*), 6.45 (br s, NH), 8.83 (s, H_3), J_{MeCH} = 6.0 Hz.

Anal. Calcd. for $C_{11}H_{14}ClN_7$: C, 47.23; H, 5.04; N, 35.05. Found: C, 47.15; H, 5.15; N, 34.78.

6-(Chloropropylamino)-9,9-dimethyl-3-phenyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8l**).

A mixture of **8j** (337 mg, 0.001 mole) and phosphoryl chloride (10 ml) was heated under reflux for 30 minutes. The volatile components were evaporated *in vacuo*, ice-cold water (15 ml) was added to the residue, followed by neutralization with the solid sodium hydrogen carbonate. The precipitate was collected by filtration to give **8l** in 35% yield, mp 206-209°; nmr (DMSO-d_6): δ 1.60 (d, *Me*CH), 1.75 (s, 9,9-diMe), 3.73 (dd, C*H*$_2$CH), 4.85 (m, CH$_2$C*H*), 7.40-7.60 (m) and 8.30-8.50 (m) (3-Ph), 8.75 (br t, NH), J_{CH_2CH} = 6.0 Hz, J_{CH_2NH} = 6.0 Hz.

Anal. Calcd. for $C_{17}H_{18}ClN_7$: C, 57.38; H, 5.10; N, 27.55. Found: C, 57.13; H, 5.11; N, 27.41.

9,9-Dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8m**).

To a solution of **7a** (445 mg, 0.002 mole) in methanol (20 ml) Pd/C (10%, 50 mg) was added and the mixture was hydrogenated at normal pressure for five hours. The catalyst was filtered off and the filtrate was evaporated *in vacuo*. Water (10 ml) was added to the dry residue and the mixture was extracted with chloroform (3 times, 10 ml each time). The combined extracts were dried over anhydrous sodium sulphate, chloroform was evaporated *in vacuo* and the solid residue recrystallized from ethanol to give **8m** in 56% yield, mp 212-214°; nmr (deuteriochloroform): δ 1.85 (s, 9,9-diMe), 9.25 (s) and 9.30 (s) (H_3,H_6).

Anal. Calcd. for $C_8H_8N_6$: C, 51.06; H, 4.28; N, 44.66. Found: 50.82; H, 4.33; N, 44.61.

6-Bromo-9,9-dimethyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8n**).

To a stirred suspension of **8a** (218 mg, 0.001 mole) in glacial acetic acid (2 ml) a solution of bromine (320 mg, 0.002 mole) in glacial acetic acid (2 ml) was added dropwise at room temperature. The volatile components were, after two hours, evaporated *in vacuo* to give **8n** in 80% yield, mp 228-230° (from ethanol): nmr (deuteriochloroform): δ 1.70 (s, 9,9-diMe), 9.15 (s, H_3).

Anal. Calcd. for $C_8H_7BrN_6$: C, 35.98; H, 2.64; N, 31.46. Found: C, 35.84; H, 2.50; N, 31.20.

In the same manner the following compound was prepared:

6-Bromo-9,9-dimethyl-3-phenyl-9*H*-pyrazolo[4,3-*d*]-*s*-triazolo[4,3-*b*]pyridazine (**8o**).

This compound was prepared from **8b** in 45% yield, mp 268-271° (from ethanol); nmr (deuteriochloroform): δ 1.88 (s, 9,9-diMe), 7.40-7.60 (m) and 8.20-8.50 (m) (3-Ph).

Anal. Calcd. for $C_{14}H_{11}BrN_6$: C, 49.00; H, 3.23; N, 24.49. Found: C, 48.91; H, 3.39; N, 24.48.

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