# $^{1}H$ and $^{13}C$ NMR Study of 1-Hydrazino-2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones and -1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones and Their Ring-Chain Tautomerism

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Treatment of 1-hydroxy-2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones and -1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones with hydrazides produces corresponding acylhydrazino derivatives. In this work, ten new hydrazino derivatives were synthesized, and their properties were studied by $^{1}H$ and $^{13}C$ NMR spectroscopy. These compounds exhibited several types of structural variation, including ring-chain tautomerism, *cis*-*trans* isomerism with respect to the substituents in the pyrazole ring, and (*E*)/(*Z*) rotamerism with respect to the nitrogen–carbon hydrazide bond with partial double-bond character. In [$D_6$]DMSO, 2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-dione derivatives were found mainly as linear tautomers, whereas 2,3-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione derivatives favored cyclic tautomers. For the latter compounds, a six-component equilibrium was found, consisting of a linear and of *cis* and *trans* cyclic tautomers, all of which had two rotamers, (*E*) and (*Z*).



## Introduction

Cyclic hydrazides of dicarboxylic acids (such as maleic and phthalic acids) are known[1] to react with unsaturated aldehydes to form condensed-ring hydroxypyrazolidines **I**. These products are potentially capable of ring-chain tautomerism **A** ⇄ **B**, which is characteristic of their analogues 3-hydroxypyrazolidines.[2−4] Thus, the crotonaldehyde derivatives exist as equilibrium mixtures of *cis*- and *trans*-**B** diastereomers,[1] which should interconvert via the linear intermediate **A**.

Furthermore, nitrogen-containing nucleophiles can substitute the hemiaminal hydroxy group in these compounds to form previously unknown hydrazino derivatives, similarly to 3-hydroxypyrazolidines.[5,6] The objective of this work was to synthesize such derivatives and to investigate the possibility of multicomponent equilibria in these systems. Apart from structural investigations, the potential biological activity of these compounds is also of interest, as certain 3-hydroxypyrazolidines have been shown to possess anti-inflammatory activity,[7] but their condensed-ring analogues have not been studied in this respect.

By treatment of 1-hydroxy-2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones **Ia** and **Ib**, and of 1-hydroxy-3-methyl-2,3-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-dione **Ic** with hydrazides **IIa**−**d** (Scheme 1), we obtained the previously unknown 2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones **IIIa**−**d** and **IVa**−**c** and 2,3-dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones **Va**−**c** (Scheme 2) in 30−90% yields and studied their solution- and gas-phase structures by NMR spectroscopy and mass spectrometry.

The compounds were divided into smaller sets, based on the increasing complexity of the multicomponent equilibria they exhibited in solution. Many stereochemical phenomena were found to be relatively slow, enabling the observation of distinct signals from the different isomers in the NMR spectra. The first set contains the pyridazine derivatives **III**, unsubstituted in position 3. Apart from the expected ring-chain tautomerism in this set, the existence of (*E*) and (*Z*) rotamers with respect to the carbon−nitrogen hydrazide bond with partial double-bond character was also observed. This hindered rotation of hydrazine derivatives has been discussed earlier in the literature.[8−13] Another set comprised 3-methyl-substituted analogues **IV**, in which the *cis*/*trans* isomerism can exist in the ring. Phthalazine derivatives **V** form the last set of compounds. Because

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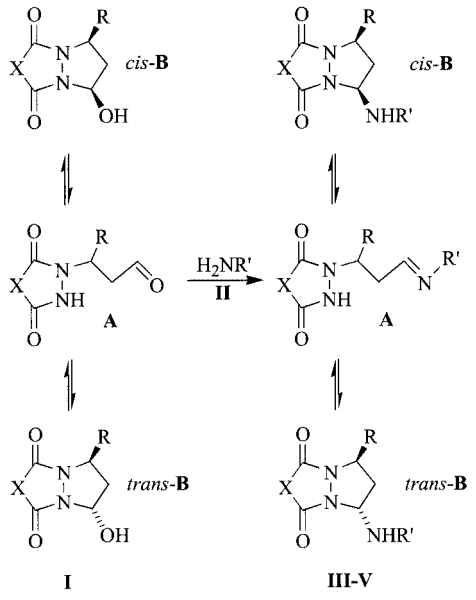
of the higher substitution and conjugation in the ring system, the cyclic forms were expected to be more favored in these compounds. In this set, six different forms altogether were present in observable amounts in [$D_6$]DMSO solution.




**Ia:** X = –CH=CH–, R = H; **Ib:** X = –CH=CH–, R = $CH_3$;
**Ic:** X = *o*-$C_6H_4$<, R = $CH_3$.
**IIa:** R' = HNCOH; **IIb:** R' = $HNCOCH_3$;
**IIc:** R' = $HNCOCH_2CN$; **IId:** R' = $HNCOC_6H_5$.

Scheme 1. Synthetic route and starting materials for compounds **III**–**V** studied in this work

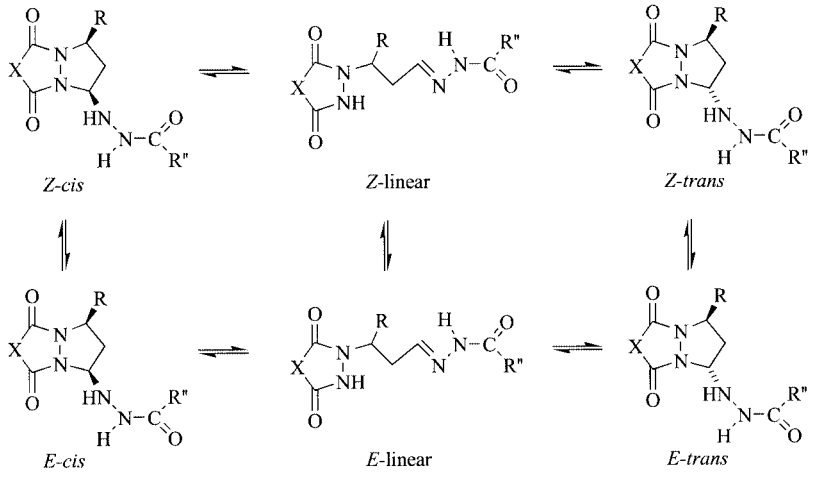
## Results and Discussion

### NMR Structural Assignment

Chemical shift assignments were based mainly on DEPT 135°, phase-sensitive DQF-COSY, and f1-decoupled CH-shift correlation spectra. Long-range correlation spectra (long-range DQF-COSY and HMBC or COLOC) were also recorded when more information was needed for assignments. Proton and carbon chemical shifts are presented in Tables 1–3 and numbering of the compounds in Scheme 3. In all tables, [$D_6$]DMSO was used as a solvent and the temperature was 30 °C. For comparison, some measurements were also made in $CDCl_3$, if the solubility of the compounds allowed this. Stereochemical conclusions were based on chemical shift values, $^1$H,$^1$H coupling constants, and NOE difference spectra.

### 1-Hydrazino-2,3-dihydro-1*H*-pyrazolo[1,2-*a*]pyridazine-5,8-diones IIIa–d

Both ring-chain tautomerism and (*E*)/(*Z*) rotamerism were observed in these compounds. $^1$H and $^{13}$C chemical shifts, selected $^1$H,$^1$H coupling constants, and also the relative amounts of the isomers for compounds **IIIa**–**d** are listed in Table 1. The very poor solubility in $CDCl_3$ (also in MeOD and in [$D_6$]acetone) inhibited measurements in these solvents, so all spectra were measured in [$D_6$]DMSO at 30 °C. Chemical shifts of the pyridazine-5,8-dione moiety are not listed in Table 1, because these shifts were very similar for all compounds; for both linear forms: δ = 6.86–6.88 and 7.03–7.05 ppm (6-H, 7-H); δ = 152.5–152.7 and 157.8–157.9 ppm (C-5, C-8); δ = 126.9–127.1 and 132.7–132.8 ppm (C-6, C-7). For the cyclic form: δ = 6.84–6.93 ppm (6-H, 7-H); 153.2–154.4 ppm (C-5, C-8); δ = 135.2–135.4 ppm (C-6, C-7).




X = –CH=CH–, R = H: **IIIa:** R'' = H; **IIIb:** R'' = $CH_3$; **IIIc:** R'' = $CH_2CN$; **IIId:** R'' = $C_6H_5$.
X = –CH=CH–, R = $CH_3$: **IVa:** R'' = H; **IVb:** R'' = $CH_3$; **IVc:** R'' = $C_6H_5$.
X = *o*-$C_6H_4$<, R = $CH_3$: **Va:** R'' = H; **Vb:** R'' = $CH_2CN$; **Vc:** R'' = $C_6H_5$.

Scheme 2. Compounds **III**–**V** and their different isomeric structures

Table 1. Relative amounts of the isomers, $^1$H and $^{13}$C chemical shifts and selected $^1$H,$^1$H coupling constants for compounds **IIIa**−**d**, recorded at 30 °C in [D$_6$]DMSO (referenced internally to the solvent signals using values δ = 2.49 ppm for $^1$H and δ = 39.50 ppm for $^{13}$C); chemical shifts are in ppm and coupling constants in Hz; in linear isomers, protons in positions 2 and 3 are equal: $2x = 2y = 2$ and $3x = 3y = 3$

| DMSO (%) | **IIIa** (*Z*-linear) 17 | **IIIa** (*E*-linear) 83 | **IIIb** (*Z*-linear) 38 | **IIIb** (*E*-linear) 62 | **IIIc** (*Z*-linear) 28 | **IIIc** (*E*-linear) 72 | **IIId** (*Z*-linear) 90 | **IIId** (cyclic) 10 |
|---|---|---|---|---|---|---|---|---|
| 1-H | 7.48 | 7.33 | 7.40 | 7.27 | 7.45 | 7.33 | 7.75 | 5.69 |
| 2*x*-H | 2.56 | 2.56 | 2.57 | 2.56 | 2.61 | 2.58 | 2.67 | 2.34 |
| 2*y*-H | − | − | − | − | − | − | − | 2.45 |
| 3*x*-H | 4.04 | 4.03 | 4.03 | 4.03 | 4.04 | 4.04 | 4.09 | 3.90 |
| 3*y*-H | − | − | − | − | − | − | − | 4.13 |
| 9-H or 1′-H | 11.1 | 11.1 | 11.09 | 11.09 | 11.09 | 11.09 | 11.13 | 6.09 |
| 2′-H | 11.08 | 11.33 | 10.98 | 10.81 | 11.36 | 11.40 | 11.51 | 10.02 |
| R′′-H | 7.87 | 8.44 | 1.81 | 1.97 | 3.65 | 3.94 | 7.83 | *n.r.*[a] |
| | − | − | − | − | − | − | 7.47 | *n.r.* |
| | − | − | − | − | − | − | 7.55 | *n.r.* |
| C-1 | 149.10 | 146.17 | 146.64 | 143.49 | 149.42 | 146.05 | 149.07 | 73.04 |
| C-2 | 31.20 | 30.92 | 31.13 | 30.72 | 31.20 | 30.76 | 31.29 | 25.39 |
| C-3 | 47.15 | 47.15 | 47.26 | 47.04 | 47.12 | 46.80 | 47.24 | 45.82 |
| C-3′ | 156.62 | 164.40 | 165.10 | 171.28 | 158.42 | 164.08 | 162.83 | 166.60 |
| C-R′′ | − | − | 21.35 | 20.09 | 24.57 | 24.03 | 133.42 | 133.02 |
| | − | − | − | − | 115.74 | 115.92 | 127.50 | 127.22 |
| | − | − | − | − | − | − | 128.35 | 128.29 |
| | − | − | − | − | − | − | 131.56 | 131.37 |
| *J*(1,2*x*) | 5.4 | 5.4 | 5.3 | 5.2 | 5.4 | 4.9 | 5.1 | <1 |
| *J*(1,2*y*) | − | − | − | − | − | − | − | 6.8 |
| *J*(2*x*,2*y*) | − | − | − | − | − | − | − | −13.0 |
| *J*(2*x*,3*x*) | 6.8 | 7.1 | 6.9 | 6.9 | 6.7 | 6.9 | 6.9 | 7.5 |
| *J*(2*x*,3*y*) | − | − | − | − | − | − | − | <1 |
| *J*(2*y*,3*x*) | − | − | − | − | − | − | − | *n.r.* |
| *J*(2*y*,3*y*) | − | − | − | − | − | − | − | *n.r.* |
| *J*(3*x*,3*y*) | − | − | − | − | − | − | − | −11.0 |
| *J*(1,1′) | − | − | − | − | − | − | − | 3.6 |
| *J*(1′,2′) | − | − | − | − | − | − | − | 5.4 |
| *J*(2′,3′) | 0 | 10.3 | − | − | − | − | − | − |

[a] *n.r.*: not resolved.

As can be seen from Table 1, compounds **III** strongly favor linear forms. Only for **IIId** was the amount of cyclic form high enough to allow spectral assignments to be made. In other compounds, traces of a cyclic form were seen, but in very small quantities (1−2%).

The (*E*) and (*Z*) isomers could easily be identified from the chemical shifts of the carbonyl carbon atom. In the (*E*) forms the shift was approx. 6−7 ppm larger than in the (*Z*) forms. A similar effect has been observed earlier for smaller hydrazides and amides.[8,11] A clear difference in chemical shifts is observed in the sp$^2$-hybridized *C*=N carbon atom: the shift in the (*Z*) forms is approx. 3 ppm larger than in the (*E*) forms, which is also in agreement with the literature.[11] In compound **IIIa**, the (*E*) form was also identified from the large (approx. 10 Hz) vicinal coupling constant between the aldehyde proton and the *H*N−C=O proton, which is in harmony with previous investigations.[9] In compound **IIId**, the identification of the (*Z*) form was confirmed by the NOE observed in the phenyl protons when the *H*N−C=O proton was irradiated.

The relative amounts of (*E*) and (*Z*) isomers exhibited a logical trend depending on the substituent on the carbonyl carbon atom. Compound **IIIa** strongly favored the (*E*) form. In compounds **IIIb** and **IIIc** the (*E*) form was still favored, but the amount of (*Z*) form had increased. It was thus the size of the substituent that was controlling the equilibrium through the steric effects. Compound **IIId** was almost entirely in the linear (*Z*) form [some traces of the (*E*) form were seen in the spectra], a natural consequence of steric hindrance by the large phenyl group. For the same reason, the cyclic tautomer also adopted the (*Z*) form. The (*Z*) forms of the cyclic tautomers could be identified from the chemical shift of the carbonyl carbon atom as compared to those of compounds **Va**−**c** (vide infra).

It was interesting to compare the (*E*)/(*Z*) ratios with those observed for *N*-(1-methylethylidene)formo-, -aceto- and -benzohydrazides.[11] The percentage amounts of (*Z*) rotamers for the latter compounds in [D$_6$]DMSO were 24, 40, and 100, respectively,[11] in surprisingly good agreement with the values for **IIIa**, **IIIb**, and **IIId**, respectively (Table 1). The large heterocyclic moiety thus had a fairly small influence on the amounts of the rotamers and it may be expected that the ratios would be approximately the same for many formo-, aceto- and benzohydrazides.

No (*E*)/(*Z*) isomerism in respect to the C=N double bond in the linear tautomers of these or other compounds

Table 2. Relative amounts of the isomers, $^1$H and $^{13}$C chemical shifts, and selected $^1$H,$^1$H coupling constants for compounds **IVa**−**c** recorded at 30 °C in [D$_6$]DMSO (referenced internally to the solvent signals by using values δ = 2.49 ppm for $^1$H and δ = 39.50 ppm for $^{13}$C); chemical shifts are in ppm and coupling constants in Hz

| DMSO (%) | **IVa** (*Z*-linear) 20 | **IVa** (*E*-linear) 80 | **IVb** (*Z*-linear) 35 | **IVb** (*E*-linear) 59 | **IVb** (*cis*) 3 | **IVb** (*trans*) 3 | **IVc** (*Z*-linear) 80 | **IVc** (*cis*) 10 | **IVc** (*trans*) 10 |
|---|---|---|---|---|---|---|---|---|---|
| 1-H | 7.35 | 7.21 | 7.27 | 7.16 | 5.57 | 5.52 | 7.61 | 5.70 | 5.66 |
| 2*x*-H | 2.47 | 2.47 | 2.48 | 2.47 | 1.93 | 2.09 | 2.58 | 2.11 | 2.17 |
| 2*y*-H | 2.57 | 2.57 | 2.61 | 2.61 | 2.56 | 2.39 | 2.71 | 2.65 | 2.58 |
| 3-H | 5.12 | 5.12 | 5.12 | 5.12 | 4.52 | 4.48 | 5.17 | 4.58 | 4.54 |
| 3-Me-H | 1.23 | 1.23 | 1.24 | 1.24 | 1.45 | 1.39 | 1.28 | 1.50 | 1.41 |
| 9-H or 1′-H | 11.1 | 11.1 | 11.02 | 11.02 | 5.63 | 5.76 | 11.10 | 5.98 | 6.11 |
| 2′-H | 11.02 | 11.24 | 10.92 | 10.72 | 9.30 | 9.27 | 11.44 | 10.03 | 10.02 |
| R′′-H | 7.84 | 8.39 | 1.79 | 1.94 | 1.63[a] | 1.74[a] | 7.81 | *n.r.*[b] | *n.r.* |
| | − | − | − | − | − | − | 7.46 | *n.r.* | *n.r.* |
| | − | − | − | − | − | − | 7.54 | *n.r.* | *n.r.* |
| C-1 | 149.00 | 146.09 | 146.54 | 143.35 | 72.37 | 71.97 | 149.00 | 72.65 | 72.04 |
| C-2 | 37.43 | 37.18 | 37.29 | 36.92 | 31.80 | 33.45 | 37.40 | 32.05 | 33.66 |
| C-3 | 49.52 | 49.50 | 49.57 | 49.26 | 54.67 | 55.34 | 49.62 | 54.78 | 55.51 |
| C-3-Me | 19.02 | 18.96 | 19.02 | 18.98 | 19.40 | 18.49 | 19.09 | 19.51 | 18.50 |
| C-3′ | 156.65 | 164.37 | 165.06 | 171.23 | 169.06[a] | 169.25[a] | 162.70 | 166.41[a] | 166.56[a] |
| C-R′′ | − | − | 21.35 | 20.04 | 20.51[a] | 20.67[a] | 133.36 | 132.94[a] | 133.21[a] |
| | − | − | − | − | − | − | 127.46 | *n.r.* | *n.r.* |
| | − | − | − | − | − | − | 128.30 | *n.r.* | *n.r.* |
| | − | − | − | − | − | − | 131.52 | 131.24[a] | 131.37[a] |
| *J*(1,2*x*) | 5.4 | 5.4 | 5.5 | 5.4 | *n.r.* | *n.r.* | 5.4 | <1 | 7.6 |
| *J*(1,2*y*) | 5.4 | 5.4 | 5.5 | 5.4 | *n.r.* | *n.r.* | 5.5 | 7.3 | 1.7 |
| *J*(2*x*,2*y*) | *n.r.* | −14.3 | *n.r.* | −14.6 | *n.r.* | *n.r.* | −14.4 | −13.4 | −13.4 |
| *J*(2*x*,3) | *n.r.* | *n.r.* | *n.r.* | 8.8 | *n.r.* | *n.r.* | *n.r.* | <1 | 8.1 |
| *J*(2*y*,3) | *n.r.* | 8.6 | *n.r.* | 9.0 | *n.r.* | *n.r.* | 8.6 | *n.r.* | *n.r.* |
| *J*(3,3-Me) | 6.6 | 6.6 | 6.9 | 6.9 | 6.6 | 6.1 | 6.6 | 6.6 | 6.1 |
| *J*(1,1′) | − | − | − | − | 1.9 | 2.7 | − | 2.1 | 3.3 |
| *J*(1′,2′) | − | − | − | − | 5.2 | 5.1 | − | 5.4 | 5.1 |
| *J*(2′,3′) | 0 | 9.3 | − | − | − | − | − | − | − |

[a] May be vice versa. [b] *n.r.*: not resolved.

examined has been found[10,11] due to the well-known predominance of the (*E*) isomer characteristic for aldehyde hydrazones.

### 1-Hydrazino-3-methyl-2,3-dihydro-1*H*-pyrazolo[1,2-*a*]-pyridazine-5,8-diones IVa−c

These are the 3-methyl-substituted analogues of the first set of compounds. $^1$H and $^{13}$C NMR chemical shifts, selected $^1$H,$^1$H coupling constants, and relative amounts of the isomers for **IVa**−**c** are shown in Table 3. All spectra for these compounds were measured in [D$_6$]DMSO at 30 °C because of the low solubility in other solvents. The chemical shifts (not given) for the pyridazine-5,8-dione moiety were very similar to those for compounds **III**.

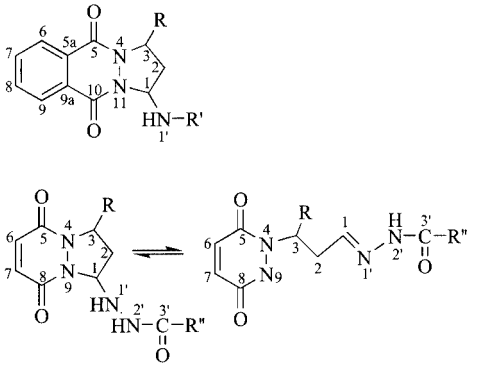
The 3-methyl substitution enables *cis*/*trans* isomerism of the cyclic tautomers. The observed amounts of the *cis* and *trans* isomers were equal, *cis* and *trans* isomers being identified from the values of the coupling constants for protons in position 2. For *cis* isomers, only very small vicinal coupling constants were observed for one of the protons (2*x*) in position 2. Thus the torsion angles between protons 2*x* and 1, and also between protons 2*x* and 3, were close to 90° (Karplus-like dependence[14]), meaning that both substituents were on the same side of the ring. Also, the proton chemical shifts (for position 2) showed a clear difference between the *cis* and *trans* isomers. The proton shifts for protons 2*x* and 2*y* were closer to each other in the *trans* forms than in the *cis* forms. This is easy to explain, since in the *cis* isomer the magnetic environment of proton 2*x* differs greatly from that of proton 2*y* (both substituents are on the same side of the ring). Also, the chemical shift of the methyl carbon atom is in each case larger for *cis* isomers than for *trans* isomers. The same trend was also observed in the shifts of the methyl protons. These effects were also observed for our starting materials **I**[4] and they were also seen clearly in the spectra of compounds **Va**−**c** (Table 3), in which the cyclic forms were present in larger amounts (vide infra).

The linear forms of **IV** behaved very similarly to the 3-unsubstituted compounds **III**. The amount of the (*Z*) form increased with the size and steric effects of the carbonyl substituent. The ratios of the linear and cyclic forms were also much the same as before. The only compound in which the cyclic forms were present to an appreciable extent was the phenyl-substituted one (Scheme 2, R′′=C$_6$H$_5$), as above. The cyclic forms were identified as (*Z*) rotamers by comparison of the chemical shift of the carbonyl carbon atom to those found for compounds **Va**−**c** (vide infra).

Table 3. Relative amounts of the isomers, $^1$H and $^{13}$C chemical shifts and selected $^1$H,$^1$H coupling constants for compounds **Va**−**c** recorded at 30 °C in [D$_6$]DMSO (referenced internally to the solvent signals using values δ = 2.49 ppm for $^1$H and δ = 39.50 ppm for $^{13}$C); chemical shifts are in ppm and coupling constants in Hz

| | **Va** | **Va** | **Va** | **Va** | **Va** | **Va** | **Vb** | **Vb** | **Vb** | **Vb** | **Vb** | **Vb** | **Vc** | **Vc** | **Vc** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | (*Z*-linear) | (*E*-linear) | (*Z*-*cis*) | (*E*-*cis*) | (*Z*-*trans*) | (*E*-*trans*) | (*Z*-linear) | (*E*-linear) | (*Z*-*cis*) | (*E*-*cis*) | (*Z*-*trans*) | (*E*-*trans*) | (*Z*-linear) | (*Z*-*cis*) | (*Z*-*trans*) |
| DMSO (%) | 5 | 25 | 21 | 19 | 16 | 14 | 8 | 21 | 29 | 7 | 24 | 11 | 12 | 42 | 46 |
| 1-H | 7.39 | 7.25 | 5.74 | 5.58 | 5.72 | 5.67 | 7.34 | 7.24 | 5.79 | 5.58 | 5.74 | 5.69 | 7.64 | 5.88 | 5.83 |
| 2*x*-H | 2.59 | 2.55 | 2.01 | 1.85 | 2.19 | 2.23 | 2.60 | 2.56 | 1.98 | 1.92 | 2.17 | 2.22 | 2.65 | 2.18 | 2.23 |
| 2*y*-H | 2.74 | 2.68 | 2.67 | 2.81 | 2.45 | 2.37 | 2.75 | 2.72 | 2.65 | 2.87 | 2.41 | 2.41 | 2.85 | 2.70 | 2.65 |
| 3-H | 5.28 | 5.28 | 4.67 | 4.65 | 4.66 | 4.60 | 5.31 | 5.31 | 4.70 | 4.68 | 4.67 | 4.63 | 5.33 | 4.73 | 4.68 |
| 3-Me-H | 1.33 | 1.33 | 1.55 | 1.50 | 1.45 | 1.45 | 1.33 | 1.32 | 1.54 | 1.50 | 1.46 | 1.44 | 1.36 | 1.59 | 1.49 |
| 11-H or 1′-H | *n.r.*[a] | *n.r.* | 5.81 | 5.96 | 5.90 | 6.09 | *n.r.* | *n.r.* | 5.91 | 6.00 | 5.95 | 6.03 | 11.63 | 6.02 | 6.13 |
| 2′-H | 10.98 | 11.91 | 9.47 | 9.13 | 9.39 | 9.20 | 11.25 | 11.26 | 9.66 | 9.22 | 9.57 | 9.29 | 11.39 | 10.05 | 10.01 |
| R′′-H | 7.81 | 8.35 | 7.94 | 8.05 | 7.84 | 8.06 | 3.59 | 3.77 | 3.53 | 3.84 | 3.49 | 3.89 | *n.r.* | 7.80 | 7.61 |
| | − | − | − | − | − | − | 3.59 | 3.84 | 3.53 | 3.84 | 3.49 | 3.89 | *n.r.* | 7.44 | 7.39 |
| | − | − | − | − | − | − | − | − | − | − | − | − | *n.r.* | 7.51 | 7.48 |
| C-1 | 149.18 | 146.31 | 72.59 | 73.94 | 72.15 | 73.24 | 149.44 | 146.17 | 71.85 | 73.88 | 71.74 | 73.39 | 149.25 | 72.47 | 71.63 |
| C-2 | 37.24 | 37.02 | 32.31 | 32.18 | 33.52 | 33.15 | 37.13 | 36.83 | 32.33 | 32.25 | 33.56 | 32.87 | 37.24 | 32.38 | 33.99 |
| C-3 | 49.16 | 49.16 | 54.45 | 53.96 | 54.64 | 54.08 | 49.14 | 48.77 | 54.49 | 53.85 | 54.64 | 53.87 | 49.32 | 54.65 | 55.24 |
| C-3-Me | 19.07 | 19.00 | 19.84 | 19.43 | 18.83 | 18.74 | 19.13 | 19.04 | 19.94 | 19.46 | 18.74 | 18.61 | 19.21 | 19.95 | 18.93 |
| C-3′ | 156.52 | 164.20 | 160.65 | 166.70 | 160.53 | 166.92 | 158.33 | 163.85 | 162.56 | 166.82 | 162.44 | 167.40 | 162.65 | 166.47 | 166.71 |
| C-R′′ | − | − | − | − | − | − | 24.50 | 23.73 | 23.90 | 23.61 | 23.84 | 23.88 | *n.r.* | 133.23 | 133.00 |
| | − | − | − | − | − | − | 115.66 | 115.74 | 115.70 | 116.24 | 115.61 | 116.30 | *n.r.* | 127.34 | 127.09 |
| | − | − | − | − | − | − | − | − | − | − | − | − | *n.r.* | 128.18 | 128.21 |
| | − | − | − | − | − | − | − | − | − | − | − | − | *n.r.* | 131.20 | 131.25 |
| *J*(1,2*x*) | 5.6 | 5.6 | 1.2 | 2.2 | 7.8 | 7.8 | 5.7 | 5.1 | <1 | 2.5 | 7.7 | 8.0 | *n.r.* | <1 | 7.0 |
| *J*(1,2*y*) | 5.6 | 5.6 | 9.2 | 9.0 | 3.0 | 4.0 | 5.7 | 5.1 | 7.9 | 8.8 | 2.9 | 4.5 | 5.3 | 7.9 | 1.3 |
| *J*(2*x*,2*y*) | *n.r.* | −14.0 | −13.4 | −13.9 | −13.4 | −13.5 | *n.r.* | *n.r.* | −13.4 | −13.1 | −13.4 | −13.7 | −14.5 | −13.2 | −13.5 |
| *J*(2*x*,3) | *n.r.* | *n.r.* | 1.2 | 2.2 | 7.5 | 6.6 | *n.r.* | *n.r.* | <1 | <1 | 7.4 | 6.3 | *n.r.* | <1 | 8.0 |
| *J*(2*y*,3) | *n.r.* | *n.r.* | *n.r.* | 9.5 | 7.8 | 8.0 | *n.r.* | *n.r.* | *n.r.* | 4.8 | 8.0 | 8.0 | 9.6 | 9.4 | 7.7 |
| *J*(3,3-Me) | 6.7 | 6.8 | 6.6 | 6.6 | 6.1 | 6.1 | 6.3 | 6.5 | 6.6 | 6.7 | 6.1 | 6.3 | 6.7 | 6.4 | 6.2 |
| *J*(1,1′) | − | − | 2.4 | 2.5 | 3.7 | 3.4 | − | − | 1.4 | 3.3 | 3.2 | 4.0 | − | *n.r.* | *n.r.* |
| *J*(1′,2′) | − | − | 4.6 | 0 | 4.4 | 0 | − | − | 4.5 | 0. | 3.5 | 0 | − | 2.3 | <1 |
| *J*(2′,3′) | 0 | 10.0 | 0 | 10.5 | 0 | 10.5 | − | − | − | − | − | − | − | − | − |

[a] *n.r.*: not resolved.



Scheme 3. The numbering system used for the compounds studied

### 1-Hydrazino-3-methyl-2,3-dihydro-1*H*-pyrazolo[1,2-*b*]-phthalazine-5,10-diones Va−c

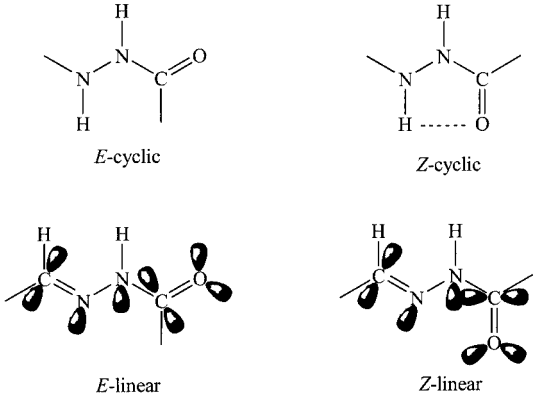
These were the most complicated and also the most interesting of the compounds studied. Compared with the pyridazine derivatives, the phthalazine derivatives favored the cyclic forms much more. It is therefore understandable that also the (*E*)/(*Z*) rotamers of the cyclic tautomers of these compounds could be seen. This means that all six possible isomers − *Z*-linear, *E*-linear, *Z*-*cis*, *E*-*cis*, *Z*-*trans* and *E*-*trans* − could be observed in the spectra (Scheme 2). $^1$H and $^{13}$C NMR chemical shifts, selected $^1$H,$^1$H coupling constants, and the relative amounts of the isomers for compounds **Va**−**c** are listed in Table 3. The chemical shifts of the phthalazine-5,10-dione moiety were not resolved properly, due to the presence of multiple forms in the spectra.

In compounds **Va** and **Vb** all six forms were observed in [D$_6$]DMSO at 30 °C. The signals did not overlap too badly and so it was possible to assign all chemical shifts for all isomers (excluding complete assignment of the phthalazine-5,10-dione moiety) by use of a number of NMR experiments, including, for example, long-range heteronuclear correlation spectra optimized for different long-range carbon-proton coupling constant values. Firstly, it was very easy to distinguish the linear tautomers from the cyclic ones through the sp$^2$-hybridized *C*=N carbon atom (δ = 145−150 ppm) and the proton attached to it (δ = 7.2−7.6 ppm). The *E*- and *Z*-linear forms were identified by the chemical shift differences in the *C*=N and N−*C*=O carbon signals, as mentioned before. In compound **Va**, the vicinal $^1$H,$^1$H coupling constant between the aldehyde and the N*H* protons also differentiated the (*E*) and (*Z*) forms, being large for the *E*-linear form. With the aid of the correlation spectra, it was easy to assign all signals by proceeding from the known signals to unknown

signals. The four cyclic tautomers were first distinguished into two (*E*) forms and two (*Z*) forms on the basis of their carbonyl carbon chemical shifts and, in the case of **Va**, also of the coupling constants. On the other hand, it was possible to distinguish two *cis* isomers from the two *trans* isomers, mainly on the basis of the chemical shifts and the coupling constants of the protons in position 2 (see above). Now, by following the correlations from, for example, the known signals (in position 2) of *cis* isomers it was possible to proceed through the structure to the carbonyl carbon atoms, in which the *E*-*cis* and *Z*-*cis* forms could be identified. Similarly, the starting point could be the two *trans* isomers, (*E*) isomers, or (*Z*) isomers, and thus all isomers could be identified and assigned.

The simplest case was that of compound **Vc**. The phenyl substituent makes the (*Z*) forms much more favored, so only three forms, *Z*-*cis*, *Z*-*trans* and *Z*-linear, were present. Identification of these forms was easy with the aid of the information available from the other compounds.

The relative amounts of the isomers of compounds **V** were interesting. The amounts of the cyclic forms were much higher than for compounds **III** and **IV**. Most probably, this was due to higher substitution and thereby higher conjugation in the phthalazine derivatives; that is, to the anellation effect. The ratios between the (*E*) and (*Z*) forms of the linear tautomers are logical in the light of those for pyridazine derivatives. For compounds **Va** and **Vb**, the (*E*) form was favored, but for **Vc** the (*Z*) form was the only rotamer observed. In cyclic isomers the situation was different. For the cyclic forms of **Va** and **Vb**, the (*Z*) isomer was favored. This can be explained by the delocalization of the π and the lone-pair electrons. We can assume that the (*Z*) form should be favored, if both nitrogen atoms in the hydrazino moiety are $sp^3$-hybridized,[8] like in the cyclic tautomers. A likely reason for this is the hydrogen bonding, which can occur between the C−N*H*−N proton and the carbonyl oxygen atom in the (*Z*) forms (Scheme 4). In the linear isomers, however, the C=N double bond changes the situation. When the $sp^2$-hybridized carbon and nitrogen atoms are present, the delocalization can happen through the structure C=N−N−C=O. By drawing the (*E*) and (*Z*) forms, it is easy to see that the more complete delocalization can occur in the (*E*) form (Scheme 4). Thus, there are two phenomena competing: the steric effects of the substituents are driving the equilibrium towards the (*Z*) forms, but the stabilization caused by the delocalization of the π and lone-pair electrons drives it towards the (*E*) forms. This also explains the (*E*)/(*Z*) ratios for the linear forms in pyridazine derivatives.

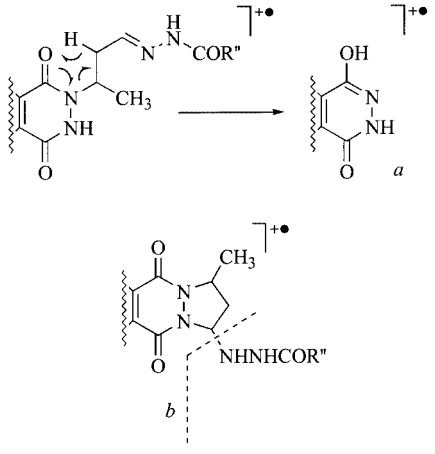



Scheme 4. Hydrogen bonding in the cyclic (*Z*) form and the delocalization of the π and lone-pair electrons through the structure C=N−N−C=O in the *E*-linear and *Z*-linear forms

The solubility also allowed us to measure the proton spectra of compounds **V** in $CDCl_3$. In this solvent only cyclic forms were observed. This phenomenon is known[15,16] for many other ring-chain tautomeric systems, being a result of the greater polarity of the linear tautomer than of the cyclic one. DMSO, as a strong hydrogen-bonding acceptor, has a capability to form stabilizing hydrogen bonds with the N*H* proton of the more polar linear form and thereby, unlike $CDCl_3$, to favor linear forms.

### Mass Spectrometry

To examine structural preferences in the absence of solvent effects and intermolecular interactions, electron-impact mass spectra of representative compounds **IVa** and **IVc** (80−100% linear form in DMSO) and **Va** and **Vc** (70−90% cyclic form in DMSO) were recorded. Somewhat surprisingly, the spectra of all four compounds were dominated by peaks of $[M - R''CONHNH]^+$ (ions *b* in Scheme 5), attributable to the cyclic (pyrazole) form of their $M^{+\cdot}$ ions. These ions were shown (by metastable ion analysis) to originate directly from $M^{+\cdot}$, which requires only a simple cleavage of the C−N bond, assuming the cyclic form of $M^{+\cdot}$, but would have involved two hydrogen shifts in open-chain $M^{+\cdot}$ structures.




Scheme 5. Mass spectrometric fragmentation of compounds **IV**−**V**

Table 4. Characteristic ions in the EI mass spectra of compounds **IV**−**V** (% TIC, see Scheme 5 for ion structures)

| Compound | $M^{+\cdot}$ | *a* | *a* + H | *b* | $[M - R''COC_2N_2H_4]$ | $PhCO^+$ |
|---|---|---|---|---|---|---|
| **IVa** | 2.3 | 11.2 | 7.6 | 20.6 | 6.0 | – |
| **IVc** | 2.4 | 2.1 | 1.1 | 19.4 | 2.4 | 19.5 |
| **Va** | 1.4 | 2.2 | 1.8 | 38.9 | 4.7 | – |
| **Vc** | 2.1 | 1.9 | 0.6 | 36.5 | 2.6 | 9.4 |

Although the *b* ions dominated the total ion current (TIC, Table 4), the presence of open-chain $M^{+\cdot}$ isomers was indicated by ions *a*, which also originated directly from $M^{+\cdot}$ and were probably formed by McLafferty rearrangement (Scheme 5). The presence of $[a + H]^+$ ions (Table 4) further confirmed the open-chain structure for the parent $M^{+\cdot}$ ions.

Abundant ions $[M - R''COC_2N_2H_4]^+$ cannot be unequivocally assigned to either of the $M^{+\cdot}$ isomers, as their formation directly from $M^{+\cdot}$ could not be confirmed by metastable ions.

The true ring/chain ratio of $M^{+\cdot}$ isomers could not be directly determined from the relative abundances of *b* and *a* ions, respectively. The former species are formed by a direct bond cleavage with the loss of well-stabilized acylhydrazinyl radicals, so that their higher relative abundance (with respect to ions *a*) may result from a lower activation barrier of fragmentation (rather than from higher gas-phase concentrations) of the cyclic $M^{+\cdot}$ ions. However, the general trends observed in solution were qualitatively reproduced in the mass spectrometric fragmentation of compounds **IV**−**V**. Thus, ions *b* were more abundant in compounds **V** than in **IV** (Table 4), and ions *a* were the most abundant in compound **IVa**, which is 100% open-chain in solution. The origin of cyclic $M^{+\cdot}$ structures in the case of compounds **IV** remains an open question. They may result from thermal cyclization of the corresponding neutral molecules in the ion source prior to electron impact, but also from isomerization of the $M^{+\cdot}$ ions initially formed as open-chain structures.

## Conclusion

The novel hydrazino derivatives **III**−**V** of previously studied hydroxypyrazolidines **I** were synthesized and their properties were studied by NMR spectroscopy.

Ring-chain tautomerism was observed in the acylhydrazino derivatives for the first time. The ring/chain ratio increased from pyridazine to phthalazine derivatives. Phenyl-substituted (Scheme 2, $R'' = C_6H_5$) compounds were also observed to favor cyclic forms in each subset of compounds compared to their smaller size analogues (Scheme 2, $R'' =$ H, $CH_3$, $CH_2CN$), which is most probably the result of steric effects.

(*E*)/(*Z*) rotamerism was observed with respect to the nitrogen−carbon amide bond. In cyclic forms the (*Z*) rotamer was the favored one. In linear forms the (*E*)/(*Z*) ratio decreased with the size of the substituent R''. For small substituents (Scheme 2, $R'' =$ H, $CH_3$, $CH_2CN$), the (*E*) form was favored due to the more complete delocalization of the π and the lone-pair electrons. For the phenyl substituent (Scheme 2, $R'' = C_6H_5$), steric repulsion shifted the equilibrium towards the (*Z*) form.

For cyclic forms, also *cis*/*trans* isomers were observed in 3-methyl-substituted compounds. In conclusion, NMR research revealed a complex set of stereochemical phenomena in addition to the ring-chain tautomerism of the studied compounds.

## Experimental Section

**NMR Measurements:** NMR spectra were measured with a JEOL JNM-A-500 spectrometer operating at 500.16 MHz for $^1H$ and 125.78 MHz for $^{13}C$ or a JEOL JNM-L-400 spectrometer operating at 399.78 MHz for $^1H$ and 100.54 MHz for $^{13}C$. Spectra were recorded at 30 °C in $[D_6]$DMSO and at 25 °C in $CDCl_3$. Proton and carbon spectra were referenced internally to the solvent signals, by using values of δ = 2.49 ppm for $^1H$ and δ = 39.50 ppm for $^{13}C$. 1D proton spectra were acquired with normal single-pulse excitation, 45° flip-angle consisting of 32 K data points. 1D carbon spectra were acquired with normal single-pulse excitation, broad-band proton decoupling, 45° flip-angle and with spectral widths of 30 kHz consisting of 65 K data points and with 0.3−0.5 Hz exponential weighting applied prior to Fourier transformation. DEPT spectra were acquired as carbon spectra. NOE difference experiments were acquired with saturation times of 6−8 s and enhancements are expressed as a percentage, integrated with respect to the irradiated spin (set to −100%). Prior to NOE measurements, samples were deoxygenated by nitrogen bubbling. 2D heteronuclear one-bond correlation experiments were acquired by using either carbon-detected CH-shift correlation with partial homonuclear decoupling in the f1 dimension or proton-detected HMQC with gradient selection. Long-range heteronuclear correlation experiments included either carbon-detected COLOC or proton-detected HMBC with gradient selection. The one-bond coupling constant was 145 Hz and the long-range coupling constants were 5−12 Hz in proton-carbon correlation spectra. 2D homonuclear H,H-correlation experiments were performed by using phase-sensitive double-quantum-filtered COSY. In long-range homonuclear correlation spectra, DQF-COSY was also used, now with the value 200000 ms as an initial waiting time. The spectral widths of 2D spectra were optimized from 1D spectra. All spectra were recorded using standard pulse sequences.[17]

**MS Measurements:** The electron-impact mass spectra were recorded with a VG ZabSpec mass spectrometer (Manchester, UK) at 70 eV (direct insertion probe, ion source temperature 160 °C). Elemental compositions of fragment ions were determined from accurate mass measurements at a resolution of 10000−12000 (10% valley definition) by the peak-matching technique, using perfluorokerosene (PFK) as a reference compound. Metastable ion spectra (B/E and $B^2/E$ linked scan technique, decompositions in the 1FFR) were recorded with the same instrument. All the fragmentation processes discussed in the text were confirmed by metastable ion spectra.

**Synthesis of Compounds III−V:** Compounds **Ia**−**c** were synthesized as described previously.[1] Their physicochemical characteristics corresponded to the literature data. A mixture of **Ia**−**b** (10 mmol) with amine or hydrazide **II** (10 mmol) was heated under reflux in 10 mL of benzene. After this, 5 mL of methanol and 5 drops of trifluoroacetic acid were added to the mixture. The reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure, and the residue was washed with diethyl ether and recrystallized from ethyl acetate/methanol (5:1). Characteristic properties for compounds **III**−**V** are given below.

***N*-(5,8-Dioxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-yl)-formohydrazide (cyclic), *N*-[(1*E*)-3-(3,6-Dioxo-3,6-dihydropyridazin-1(2*H*)-yl)propylidene]formohydrazide (linear) (IIIa):** Yield 64%. M.p. 203−205 °C (ethyl acetate/methanol, 5:1). $R_f$ = 0.36 (in chloroform/methanol, 10:0.3). $C_8H_{10}N_4O_3$ (210.2): calcd. C 45.71, H 4.80, N 26.66; found C 45.56, H 4.91, N 26.45. NMR spectroscopic data are in Table 1.

***N*-(5,8-Dioxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-yl)-acetohydrazide (cyclic), *N*-[(1*E*)-3-(3,6-Dioxo-3,6-dihydropyridazin-1(2*H*)-yl)propylidene]acetohydrazide (linear) (IIIb):** Yield 30%. M.p. 160−162 °C (ethyl acetate/methanol, 5:1). $R_f$ = 0.45 (in chloroform/methanol, 10:0.3). $C_9H_{12}N_4O_3$ (224.2): calcd. C 48.21, H 5.39, N 24.99; found C 48.12, H 5.42, N 25.12. NMR spectroscopic data are in Table 1.

**2-Cyano-*N*-(5,8-dioxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]-pyridazin-1-yl)acetohydrazide (cyclic), 2-Cyano-*N*-[(1*E*)-3-(3,6-dioxo-3,6-dihydropyridazin-1(2*H*)-yl)propylidene]acetohydrazide (linear) (IIIc):** Yield 34%. M.p. 170−172 °C (ethyl acetate/methanol, 5:1). $R_f$ = 0.30 (in chloroform/methanol, 10:0.3). $C_{10}H_{11}N_5O_3$ (249.2): calcd. C 48.19, H 4.45, N 28.10; found C 48.05, H 4.23, N 27.89. NMR spectroscopic data are in Table 1.

***N*-(5,8-Dioxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-yl)-benzohydrazide (cyclic), *N*-[(1*E*)-3-(3,6-Dioxo-3,6-dihydropyridazin-1(2*H*)-yl)propylidene]benzohydrazide (linear) (IIId):** Yield 76%. M.p. 170−172 °C (ethyl acetate/methanol, 5:1). $R_f$ = 0.44 (in chloroform/methanol, 10:0.3). $C_{14}H_{14}N_4O_3$ (286.3): calcd. C 58.74, H 4.93, N 19.57; found C 58.65, H 4.77, N 19.47. NMR spectroscopic data are in Table 1.

***N*-(3-Methyl-5,8-dioxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]-pyridazin-1-yl)formohydrazide (cyclic), *N*-[(1*E*)-3-(3,6-Dioxo-3,6-dihydropyridazin-1(2*H*)-yl)butylidene]formohydrazide (linear) (IVa):** Yield 30%. M.p. 203−204 °C (ethyl acetate/methanol, 5:1). $R_f$ = 0.37 (in chloroform/methanol, 10:0.3). MS (EI, 70 eV): *m*/*z* (%) = 224 (10) [M], 180 (8), 166 (10), 165 (100), 139 (29), 113 (37), 112 (55), 98(7), 82 (29), 80 (10), 69 (11), 68 (14), 55 (11), 54 (11). $C_9H_{12}N_4O_3$ (224.2): calcd. C 48.21, H 5.39, N 24.99; found C 48.11, H 5.63, N 25.18. NMR spectroscopic data are in Table 2.

***N*-(3-Methyl-5,8-dioxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]-pyridazin-1-yl)acetohydrazide (cyclic), *N*-[(1*E*)-3-(3,6-Dioxo-3,6-dihydropyridazin-1(2*H*)-yl)butylidene]acetohydrazide (linear) (IVb):** Yield 60%. M.p. 175−177 °C (ethyl acetate/methanol, 5:1). $R_f$ = 0.46 (in chloroform/methanol, 10:0.3). $C_{10}H_{14}N_4O_3$ (238.2): calcd. C 50.41, H 5.92, N 23.52; found C 50.63, H 6.12, N 24.08. NMR spectroscopic data are in Table 2.

***N*-(3-Methyl-5,8-dioxo-2,3,5,8-tetrahydro-1*H*-pyrazolo[1,2-*a*]pyridazin-1-yl)benzohydrazide (cyclic), *N*-[(1*E*)-3-(3,6-Dioxo-3,6-dihydropyridazin-1(2*H*)-yl)butylidene]benzohydrazide (linear) (IVc):** Yield 62%. M.p. 204−206 °C (ethyl acetate/methanol, 5:1). $R_f$ = 0.40 (in chloroform/methanol, 10:0.3). MS (EI, 70 eV): *m*/*z* (%) = 300 (10), [M], 189 (6), 188 (25), 173 (7), 166 (10), 165 (99), 139 (12), 122 (11), 121 (21), 113 (6), 112 (11), 106 (8), 105 (100), 82 (8), 77 (38), 51 (7). $C_{15}H_{16}N_4O_3$ (300.3): calcd. C 59.99, H 5.37, N 18.66; found C 60.17, H 5.21, N 18.85. NMR spectroscopic data are in Table 2.

***N*-(3-Methyl-5,10-dioxo-2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]-phthalazin-1-yl)formohydrazide (cyclic), *N*-[(1*E*)-3-(1,4-Dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)butylidene]formohydrazide (linear) (Va):** Yield 51%. M.p. 150−152 °C (ethyl acetate/methanol, 5:1). $R_f$ = 0.45 (in chloroform/methanol, 10:0.3). MS (EI, 70 eV): *m*/*z* (%) = 274 (3) [M], 216 (14), 215 (100), 189 (12), 173 (5), 163 (5), 162 (6), 148 (5), 130 (14), 104 (6), 76 (5). $C_{13}H_{14}N_4O_3$ (274.3): calcd. C 56.93, H 5.14, N 20.43; found C 57.12, H 5.38, N 20.68. NMR spectroscopic data are in Table 3.

**2-Cyano-*N*-(3-methyl-5,10-dioxo-2,3,5,10-tetrahydro-1*H*-pyrazolo-[1,2-*b*]phthalazin-1-yl)acetohydrazide (cyclic), 2-Cyano-*N*-[(1*E*)-3-(1,4-dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)butylidene]acetohydrazide (linear) (Vb):** Yield 40%. M.p. 118−120 °C (ethyl acetate/methanol, 5:1). $R_f$ = 0.34 (in chloroform/methanol, 10:0.3). $C_{15}H_{15}N_5O_3$ (313.3): calcd. C 57.50, H 4.83, N 22.35; found C 57.79, H 5.07, N 22.21. NMR spectroscopic data are in Table 3.

***N*-(3-Methyl-5,10-dioxo-2,3,5,10-tetrahydro-1*H*-pyrazolo[1,2-*b*]-phthalazin-1-yl)benzohydrazide (cyclic), *N*-[(1*E*)-3-(1,4-Dioxo-3,4-dihydrophthalazin-2(1*H*)-yl)butylidene]benzohydrazide (linear) (Vc):** Yield 47%. M.p. 165−167 °C (ethyl acetate/methanol, 5:1). $R_f$ = 0.71 (in chloroform/methanol, 10:0.3). MS (EI, 70 eV): *m*/*z* (%) = 350 (5) [M], 216 (15), 215 (100), 189 (7), 162 (5), 130 (9), 105 (26), 104 (4), 77 (15). $C_{19}H_{18}N_4O_3$ (350.4): calcd. C 65.13, H 5.18, N 15.99; found C 65.35, H 5.42, N 16.21. NMR spectroscopic data are in Table 3.

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