Reaction of β-Cyano Esters with Hydrazine Hydrate. Unexpected Formation of Dipyrrolo[1,2-*b*:1',2'-*e*][1,2,4,5]tetrazine, a Novel Ring System

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Some intermediates and by-products of the title reaction, known to yield 6-hydrazinopyridazine-3-one derivatives, were isolated or detected when the amount of hydrazine hydrate used to react with two model β-cyano esters was reduced to less than two equivalents. *N*'-(1-amino-4-hydrazino-4-oxo-2-phenylbutylidene)-4-hydrazino-4-oxo-2-phenylbutanehydrazonamide and 3,3,8,8-tetramethyl-2,3,7,8-tetrahydro-1*H*,6*H*-dipyrrolo[1,2-*b*:1',2'-*e*][1,2,4,5]tetrazine-1,6-dione were isolated as the terminal products of side-reactions; they were unreactive to hydrazine. The latter compound is a derivative of a novel ring system. Mechanism of the reaction was proposed.

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The reaction of 3-cyanopropionic esters (**1**) with hydrazine hydrate, once mistakenly believed to be a matter-of-course method for the preparation of the corresponding 3-cyanopropanohydrazides [1], revealed to be a rather complex process. As it is known now, it gives a high yield of the appropriate 6-hydrazino-4,5-dihydro-2*H*-pyridazin-3-ones (**2**) [2], convenient building blocks in the synthesis of bicyclic pyridazine structures [3-5]. Unsubstituted **2** and a phthalazine analog of **2** were also prepared earlier by ring expansion of 5-iminopyrrolidin-2-one and an isoindolinone derivative, respectively, under the action of hydrazine hydrate [6-8].

With a sufficiently large excess of hydrazine (≥15 mol) the reaction was routinely carried out in this laboratory by simply leaving the reagents standing for a long time at room temperature. Elevation of the reaction temperature enhanced the formation of hardly removable by-products. However, even under optimal reaction conditions, poor solubility of the reaction products caused in the preparative-scale runs some purification problems. On the other hand, if insufficiently pure **2** are used as the substrates in further reactions, the results may be surprising and rather hard to rationalize at first sight.

Thus, when a roughly purified 5,5-dimethyl-6-hydrazino-4,5-dihydro-2*H*-pyridazin-3-one (**2a**) was once used by us in the cyclocondensation with ethyl pyruvate [3] and the resulting crude 3,9,9-trimethyl-8,9-dihydro-4*H*-pyridazino[6,1-*c*][1,2,4]triazine-4,7(6*H*)-dione (**3**) was hydrogenated on a palladium catalyst, the product isolated in a very low yield (3.5%) was later identified by crystallography as 3,3,8,8-tetramethyl-2,3,7,8-tetrahydro-1*H*,6*H*-dipyrrolo[1,2-*b*:1',2'-*e*][1,2,4,5]-tetrazine-1,6-dione (**4a**), a derivative of a novel ring system (Figure 1) [9,10]. When thoroughly purified **2a** was recently used in the same reaction sequence, the final hydrogenation gave the expected 3,9,9-trimethyl-8,9-dihydro-2*H*-pyridazino[6,1-*c*][1,2,4]-triazine-4,7(3*H*,6*H*)-dione (**5**) as the only product. Since the formation of **4a** from **3** was considered highly unlikely, it was assumed that **4a** must have been formed in the cyanoester-hydrazine reaction and that it passed unchanged through the subsequent steps to be finally isolated once the solubility conditions became more favorable (**5**, unlike **4**, is quite readily soluble in water). In order to verify this assumption, the title reaction was recently reinvestigated in detail with ethyl 3-cyano-3-methylbutyrate (**1a**) and ethyl 3-cyano-3-phenylpropionate (**1b**) as the model starting esters.

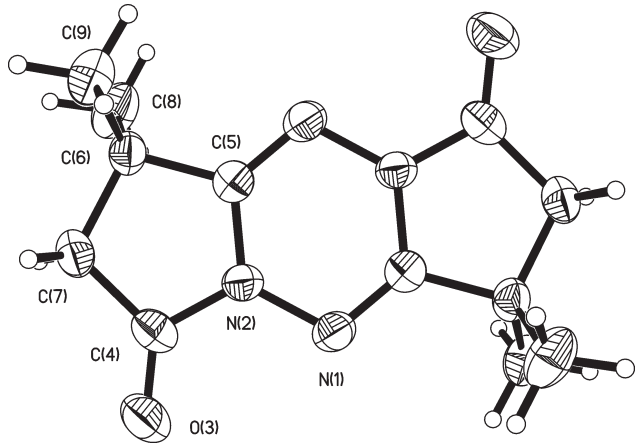


Figure 1. ORTEP drawing of the molecule of **4a**. Atom labels given only for the crystallographically independent part of the molecule [9].

Theoretically, the conversion of **1** into **2** requires two equivalents of hydrazine hydrate whereas one is enough to produce **4**. It seemed logical, therefore, to assume that the formation of **4** occurred mostly at the phase boundary, where a rapid uptake of hydrazine in the main reaction

(**1** → **2**) caused a local deficiency of this reagent in the initially heterogeneous un-agitated reaction mixture. Following that line of reasoning, in a series of experiments we performed presently, the cyanoester-hydrazine molar ratio was reduced to 1:1.1-2.0. All the reactions were carried out under standard conditions, *i.e.*, without agitation and at ambient temperature; in some experiments, a small amount of ethanol was added in order to make the two phases come into a better contact with one another. The reaction progress was monitored by GC and/or GC/MS and the reactions were arrested for the first time when the ester content dropped by 30-35% and any amount of a solid product appeared. Upon separation of the solid, the homogeneous filtrate deposited slowly on standing another portion of a solid which was separated when a reasonable amount had accumulated. This operation was repeated 2-4 times at suitable intervals. Changes in the hydrazine hydrate concentration (40-98%) affected the reaction rate but had little effect upon the reaction course, if any.

In experiments with **1a**, when the amount of hydrazine hydrate (40%) was reduced to the stoichiometry level (2 mol as required for the formation of **2a**), the first portion of the solid product revealed to be a mixture of **2a** and two other compounds. Elution with chloroform made it possible to separate the practically insoluble **2a** while the residue was resolved by column chromatography. The structures of the new compounds, 1-amino-3,3-dimethyl-pyrrolidine-2,5-dione 2[(3,3-dimethyl-5-oxopyrrolidin-2-ylidene)-hydrazone] (**6a**, Figure 2) and 6-amino-5-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one (**7a**, Figure 3), respectively, were elucidated by X-ray crystallography. The second crop, filtered after a few weeks, was a mixture of **6a** and **2a** (Scheme 1).

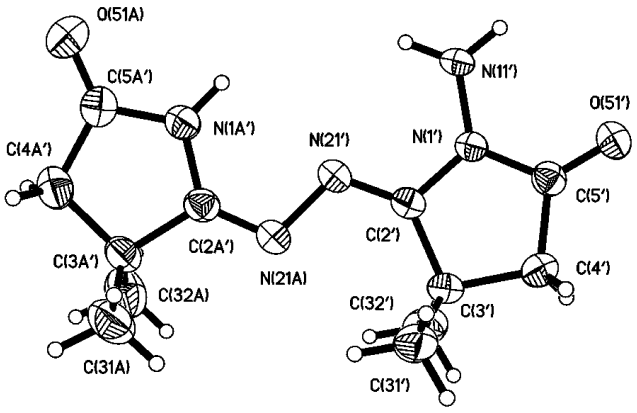


Figure 2. ORTEP drawing of one of the two independent and identical molecules of **6a** (primed atom labels).

Similar results were noted with 24% hydrazine hydrate used without any diluent. However, the formation of **4a** was not observed in these experiments. Both **6a** and **7a** have to be considered as intermediates in the formation of **2a**, into which they are readily converted upon treatment with hydrazine hydrate.

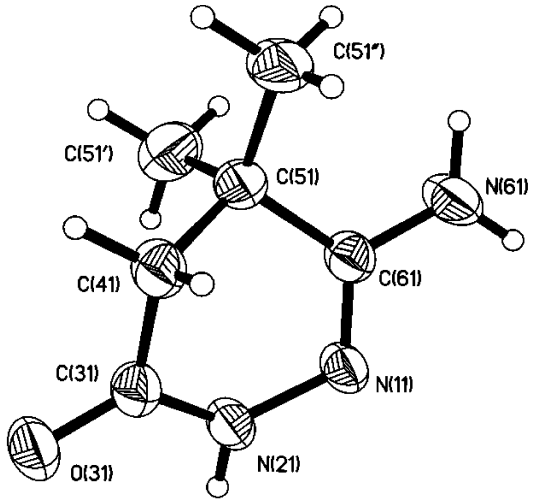


Figure 3. ORTEP drawing of one of the three crystallographically independent units of **7**.

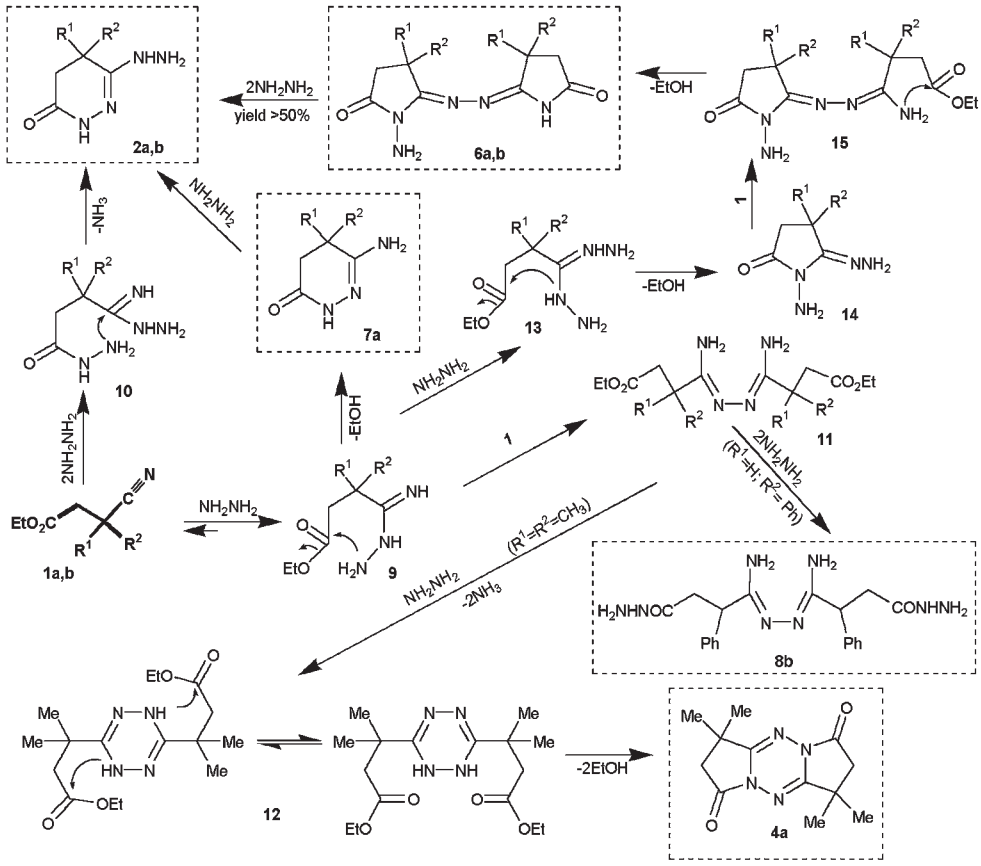
When the cyanoester-to-hydrazine hydrate (98%) ratio was reduced further down to 1:1.5 mol and the reaction was carried out with a small amount of ethanol added, the isolated solid product was pure **6a** (47% yield). The filtrate left standing for 3 weeks deposited a mixture of **6a** and **2a** which was separated by column chromatography.

Finally, the reaction with 1.1 mol of hydrazine hydrate (98%) was carried out under analogous conditions. The solid product that gradually deposited in the reaction mixture was portionwise removed by filtration at intervals of a few weeks. The first portions contained more or less pure **6a** but the last portion contained also **4a** (3.5% yield) which was isolated by column chromatography.

When **1b** was treated with 1.1 mol of hydrazine hydrate (98%) with some ethanol added, crystals which separated after 7 days at room temperature (28% yield relative to hydrazine) were identified by NMR and MS as *N*'-(1-amino-4-hydrazino-4-oxo-2-phenylbutylidene)-4-hydrazino-4-oxo-2-phenylbutanehydrazonamide (**8b**). The filtrate left standing 18 days deposited a small amount of **6b**, the phenyl analog of **6a**. **8b** was a terminal compound of this reaction pathway (Scheme 1) as it did not react with hydrazine hydrate.

The results show that the reaction of β-cyano esters with hydrazine hydrate is a multidirectional process involving intra- and intermolecular mechanisms. The main reaction product, the hydrazinopyridazinone **2**, is presumably formed by an intramolecular 6-*exo-trig* [11] cyclization of the intermediate **9** resulting from the addition of hydrazine

Scheme 1



Proposed mechanisms of the reactions between cyano esters **1** and hydrazine hydrate. Letters in compound labels denote: **a** - $R^1 = R^2 = CH_3$; **b** - $R^1 = C_6H_5$, $R^2 = H$. Compounds in dashed frames were isolated and characterized.

across the C≡N nitrile bond. Isolation of the cyclization intermediate, the aminopyridazinone **7**, constitutes a strong support for this reaction pathway since **7** is readily converted into **2** in the reaction with hydrazine hydrate; similar reactions were observed earlier [12]. An alternative pathway may lead to **2** *via* the intermediate **10** formed from **1** and 2 mol of hydrazine. Although the intramolecular cyclization of **10** also conforms to the Baldwin's ring closure rules [11] this reaction pathway seems to be disfavored since the electrophilicity of the amidrazone carbon atom in **10** is much lower than that of the ester carbon atom in **9** [13].

As far as the formation of the dipyrrolotetrazine **4a** is concerned, it should be noticed that the formation of *s*-tetrazine compounds in the reaction of hydrazine with nitriles was observed long ago [14-16]. In our case, the intermediate **9** may participate in this reaction. Thus, addition of **9** with its hydrazino fragment across the C≡N bond of **1** may lead to the symmetric open-chain diester **11** which in the reaction with hydrazine hydrate either is simply converted into the corresponding dihydrazide **8b** or cyclizes with elimination of ammonia to give **12** and, further on, **4a**. It is noteworthy that the reaction course depends here on the substituents R^1 and R^2. In the reaction starting with **1b**, GC/MS monitoring revealed no trace of the phenyl analog of **4a**. Similarly, no dimethyl analog of **8b** could be detected in the reaction mixture starting with **1a**. The effect of substituents on the behavior of **11** is hardly explicable; some steric and/or electronic factors may here decide upon the reaction course.

Since **8b** did not react with hydrazine hydrate, at least under the conditions of the present experiments (room temperature), participation of the **9** → **11** → **8** pathway in the formation of the pyridazinones **2** and **7** can be ruled out.

The formation of the dissymetric azines **6**, readily convertible by the action of hydrazine hydrate into the hydrazinopyridazinones **2**, has to be considered as another

evidence of the key role of the intermediate **9**. In the reaction with hydrazine, the amidrazone moiety of **9** is converted into a hydrazonohydrazine (**13**). Intramolecular acylation of the secondary nitrogen atom in **13** with elimination of ethanol gives rise to the formation of the *N*-aminopyrrolone **14** which subsequently reacts with **1**. The thus formed azine **15** undergoes a similar intramolecular cyclization to yield **6**. Both intramolecular cyclizations (**13** → **14** and **15** → **6**) are of the favored 5-*exo-trig* type [11].

It is of particular interest that the conversion of **6** into **2** proceeds in yields exceeding 50%. That means that both "halves" of **6** have active centers capable of reacting with hydrazine. Since similar unrecognized centers may be present in other reaction intermediates, formulation of a more precise and fully proven mechanism is hardly possible. For instance, an alternative pathway leading to **6** may involve acylation of the carbon-attached nitrogen atom in **9** and in its hydrazono tautomer (5-*exo-trig* cyclizations) as shown in Scheme 1. However, the interaction of the thus formed pyrrolones (**16** and **17**, respectively) is for statistical reasons rather doubtful.

The crystallographic determination of the enamino tautomeric form in solid **7a** (Figure 3) was of particular assistance in the interpretation of the ^{1}H NMR spectrum. Thus, the low-field one-proton signal at δ = 10.28 ppm observed in a deuteriodimethylsulfoxide solution could be unequivocally attributed to the endocyclic NH group, while the two-proton singlet at δ = 5.35 ppm, to the amino function. Similar chemical shifts of the nitrogen-attached protons were also noted in the spectra of **2** (*e.g.*, 7.07 and 9.90 ppm signals in **2a**). It seems therefore legitimate to assume that the tautomeric form found in crystals predominates also in a solution and that it is characteristic of other 3-amino- and 3-hydrazinosubstituted pyridazin-6-ones.

EXPERIMENTAL

General Methods.

Melting points were determined in open glass capillaries (Büchi apparatus) and are reported uncorrected. IR spectra were recorded with a Carl Zeiss Specord M-80 apparatus as potassium bromide pellets. ^{1}H and ^{13}C nmr spectra were taken with Varian 400 MHz or Brucker DPX 400 MHz instruments. Mass spectra were obtained on an AMD-604 Intectra GmbH instrument by routine electron ionization at 70 eV; in the case of thermally unstable compounds, the liquid secondary ion (LSI) and electron spray ionization (ESI) techniques were used. Microanalyses were carried out on a Perkin-Elmer C-H-N analyzer. Merck AG DC-Alufolien with Kieselgel 60 F_{254} were used in TLC purity monitoring. Column chromatography was performed on silicagel 60 Merck AG, granulation 0.063-0.200 mm, with chloroform gradually supplemented in 2.5% increments with ethanol up to 10% v/v. Unless otherwise stated, all yield data refer to recrystallized, chromatographically homogeneous compounds with consistent elemental analysis results.

X-Ray Structure Determination.

The crystal and molecular structures of **6a** and **7a** were determined by X-ray diffraction studies. Crystals were prepared by leaving the dilute solutions in acetonitrile to evaporate freely at room temperature. The measurements were performed at room temperature on a Kuma 4CCDκ-axis diffractometer with graphite-monochromated MoKα radiation (λ = 0.71073Å). Data were corrected for Lorentz and polarization effects. No absorption correction was applied. The structures were solved by direct methods [17] and refined using SHELXL [18]. The full-matrix least-squares refinement was based on F^2. The positions of all H-atoms were found from electron density $\Delta\rho$ map and refined in riding model with the isotropic displacement parameters of 1.5 times the respective U_{eq} values for the parent atoms. Atomic scattering factors were those as in SHELXL [18].

Reactions of **1a** and **1b** with 6 Mol of Hydrazine Hydrate.

Compound **1a** (1.001 g, 6.45 mmol) and 5 mL of 40% hydrazine hydrate (39 mmol) were left standing at room temperature (20 ± 2 °C). The solid product (0.63 g), which began to separate on the 13th day of the experiment and was collected by filtration 10 days later, was **2a** (yield 62%) [2]. **2b** was prepared in an analogous procedure (yield 58%) [2]; ^{1}H nmr of **2a** (deuteriodimethyl sulfoxide): δ 1.06 (s, 6H, 2 x CH_3), 2.11 (s, 2H, CH_2), 3.76 (s, 2H, NH_2), 7.07 (s, 1H, exocyclic NH), 9.90 ppm (s, 1H, endocyclic NH). ^{1}H nmr of **2b** (deuteriodimethyl sulfoxide): δ 2.38 (dd, 1H, ^2J = 16.6 Hz, ^3J = 1.6 Hz, C*H*H), 2.76 (dd, 1H, ^2J = 16.6 Hz, ^3J = 7.2 Hz, CH*H*), 3.72 (dd, 1H, ^3J = 1.6 and 7.2 Hz, CH), 3.91 (s, 2H, NH_2), 7.22-7.32 (m, 6H, C_6H_5 and exocyclic NH), 9.92 ppm (s, 1H, endocyclic NH). ^{13}C nmr of **2b** (deuteriodimethyl sulfoxide): 27.3 (CH_2), 44.7 (CH), 126.4, 127.9, 128.05, and 142.35 (C_6H_5), 156.35 (C=N), 170.3 ppm (C=O).

Reaction of **1a** with 2 Mol of Hydrazine Hydrate.

Compound **1a** (0.997 g, 6.42 mmol) and 1.6 mL of 40% hydrazine hydrate (13 mmol) left standing at room temperature yielded after 35 days 0.670 g of a solid product. Trituration with chloroform (3 x 4 mL) left 0.25 g of **2a** (25% yield) as the undissolved fraction while evaporation of the extract yielded 0.35 g of a mixture of two compounds (TLC). Column chromatography made it possible to isolate 0.159 g of **6a** (18.7% yield) and 0.087 g (9.6% yield) of **7a**.

1-Amino-3,3-dimethylpyrrolidine-2,5-dione 2[(3,3-Dimethyl-5-oxopyrrolidin-2-ylidene)-hydrazone] (**6a**).

This compound was obtained as colorless crystals (ethanol), mp 195-198º; ir: ν 3304, 3248, and 3188 (NH), 1728 and 1644 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.36 (s, 6H, 2 x CH_3), 1.54 (s, 6H, 2 x CH_3), 2.46 (s, 2H, CH_2), 2.47 (s, 2H, CH_2), 4.72 (s, 2H, NH_2), 10.16 ppm (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 26.2 and 27.3 (CH_3), 37.5 (*C*CH_3), 44.5 and 45.2 (CH_2), 163.4 and 163.7 (C=N), 170.9 and 176.5 ppm (C=O); ms: *m/z* 265 (M^+, 45%), 233 (100%).

Anal. Calcd. for $C_{12}H_{19}N_5O_2$ (265.31): C, 54.32; H, 7.22; N, 26.40. Found: C, 54.35; H, 7.18; N, 26.32.

Crystal data: $C_{12}H_{19}N_5O_2$; mol. mass 265.31; triclinic, P-1 (No. 1), a = 9.681(2), b = 11.634(2), c = 12.017(2) Å, α = 83.00(3), β = 89.64(3), γ = 82.83(3)°, V = 1357.6(4) Å^3, Z = 4, d_x = 1.298; Mg/m^3; μ = 0.092 mm^{-1}; F(000) = 568; final $R_{gt}(F)$ = 0.0486, $wRref(F^2)$ = 0.1425 for 3572 reflections [I>4σ(*I*)].

6-Amino-5-dimethyl-4,5-dihydro-2*H*-pyridazin-3-one (**7a**).

This compound was obtained as colorless crystals (acetonitrile), mp 191-194 °C; ir: ν 3500, 3436, 3316, and 3192 (NH), 1640 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.21 (s, 6H, CH_3), 2.29 (s, 2H, CH_2), 5.35 (s, 2H, NH_2), 10.28 ppm (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 24.2 (CH_3), 33.5 (CH_2), 41.4 (*C*CH_3), 159.5 (C=N), 167.9 ppm (C=O); ms (LSI, 3-nitrobenzyl alcohol): *m/z* 164 [$(M + Na)^+$, 10%], 142 [$(M + H)^+$, 100%].

Anal. Calcd. for $C_6H_{11}N_3O$ (141.17): C, 51.05; H, 7.85; N, 29.77. Found: C, 51.07; H, 7.70; N, 29.58.

Crystal data: $C_6H_{11}N_3O$; mol. mass 141.18; monoclinic, $P2_1/c$ (No. 14), a = 10.540(2), b = 21.879(4), c = 10.229(2) Å, β = 105.82(3)°, V = 2269.5(8)Å^3, Z = 12, d_x = 1.240; Mg/m^3; μ = 0.088 mm^{-1}; $F(000)$ = 912; final $R_{gt}(F)$ = 0.0632, $wRref(F^2)$ = 0.1941 for 3374 reflections [$I>4\sigma(I)$].

Reaction of **1a** with 1.5 Mol of Hydrazine Hydrate in Ethanol.

Compound **1a** (1.001 g, 6.44 mmol), 0.48 mL (9.78 mmol) of 99% hydrazine hydrate and 1 mL of ethanol were left standing at room temperature. The crystals (0.43 g) which were collected by filtration on the 37th day of the experiment were identified as 98% pure **6a** (47% yield). A small amount (0.042 g) of the second crop, which was collected by filtration 14 days later, revealed to be a roughly 1:1 mixture of **6a** and **2a**.

Reaction of **1a** with 1.1 Mol of Hydrazine Hydrate in Ethanol.

The reaction of 2.001 g (12.9 mmol) of **1a** with 0.70 mL (14.2 mmol) of 99% hydrazine hydrate and 2 mL of ethanol was carried out as above to give after 16 days 0.474 g (27% yield) of pure **6a**. The filtrate left standing over 37 days deposited 0.196 g of a mixture containing mostly **6a** and some **4a**. Extraction with chloroform (1 x 1 mL and 2 x 0.6 mL) left 0.066 g of **4a**, while the chloroform solution was subjected to column chromatography as above; the head fractions consisted of **4a** (0.053 g) whereas 0.067 g of **6a** was obtained in the tail fractions. The total yield of **4a** was 0.119 g (7.48%), and that of **6a**, 0.541 g (31.7%).

3,3,8,8-Tetramethyl-2,3,7,8-tetrahydro-1*H*,6*H*-dipyrrolo[1,2-*b*:1',2'-*e*][1,2,4,5]-tetrazine-1,6-dione (**4a**).

This compound was obtained as colorless crystals (ethanol), mp 335-338 ºC (decompn.); ir: ν 2968, 2932, and 2872 (NH), 1716 and 1656 cm^{-1} (C=O); ^{1}H nmr (deuteriochloroform): δ 1.40 (s, 12H, 4 x CH_3), 2.48 ppm (s, 4H, 2 x CH_2); ^{13}C nmr (deuteriochloroform): δ 26.4 (CH_3), 35.2 (CH_2), 42.9 (*C*CH_3), 160.1 (C=N), 165.4 ppm (C=O); ms: *m/z* 248 (M^+, 79%), 233 (100%).

Anal. Calcd. for $C_{12}H_{16}N_4O_2$ (248.28): C, 58.05; H, 6.50; N, 22.56. Found: C, 58.12; H, 6.35; N, 22.47.

Reaction of **1b** with 1.11 Mol of 99% Hydrazine Hydrate in Ethanol.

Compound **1b** (2.89 g, 14.23 mmol), 0.77 mL (15.80 mmol) of 99% hydrazine hydrate, and 3 mL of ethanol were left standing at room temperature. The first fraction of the solid product was collected by filtration after 6 days to give upon a thorough washing with ethanol (5 x 2 mL) 0.537 g (1.31 mmol) of practically pure **8b** (18.4% yield relative to **1b** and 24.8% relative to hydrazine hydrate). An analytical sample was obtained by recrystallization from methanol. The filtrate deposited on standing another portion of the reaction products which were removed by filtration when a reasonable amount had accumulated. Repetition of this procedure with successive filtrates made it possible to isolate: a mixture of **8b** and **6b** (15th day of the experiment, 0.111 g) and crude **6b** (30th day, 0.049 g; 60th day, 0.072 g; 220th day, 0.097 g). The total yield of crude **6b** was 0.218 g (8.5% relative to **1b**) An analytical sample was obtained by recrystallization from methanol.

N'-(1-Amino-4-hydrazino-4-oxo-2-phenylbutylidene)-4-hydrazino-4-oxo-2-phenylbutanehydrazonamide (**8b**).

This compound was obtained as colorless crystals (methanol), mp 161-163 ºC (decompn); ir: ν 3476, 3352, 3304, and 3196 (NH), 1628 and 1608 cm^{-1} (C=O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.34 (dd, 2H, ^2J = 14.8 Hz, ^3J = 7.6 Hz, 2 x CH*H*), 2.85 (dd, 2H, ^2J = 14.8 Hz, ^3J = 7.6 Hz, 2 x C*H*H), 3.90 (t, 2H, J = 7.6 Hz, 2 x CH), 4.03 (s, 4H, 2 x NH_2), 5.75 (s, 4H, 2 x NH_2), 7.17-7.33 (m, 10H, 2 x C_6H_5), 8.89 ppm (s, 2H, 2 x NH); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 37.3 (CH_2), 44.7 (CH), 126.4, 127.91 128.1, and 142.4 (C_6H_5), 156.4 (C=N), 170.3 ppm (C=O); ms (ESI, methanol/formic acid): *m/z* 411 [$(M + H)^+$, 100%].

Anal. Calcd. for $C_{20}H_{26}N_8O_2$ (410.47): C, 58.52; H, 6.38; N, 27.30. Found: C, 58.41; H, 6.29; N, 27.05.

1-Amino-3-phenylpyrrolidine-2,5-dione 2-(5-Oxo-3-phenylpyrrolidin-2-ylidene)hydrazone (**6b**).

This compound was obtained as colorless crystals (methanol), mp 234-237º (decompn.); ir: ν 3472 and 3316 (NH), 1624 and 1572 cm^{-1} (C=O); ^{1}H nmr (deuteriodimethyl sulfoxide): δ 2.23 (dd, 1H, ^2J = 18.0 Hz, ^3J = 2.0 Hz, C*H*H), 2.44 (dd, 1H. ^2J = 18.0 Hz, ^3J = 5.6 Hz, CH*H*), 3.04 (dd, 1H, ^2J = 18.0 Hz, ^3J = 10.0 Hz, C*H*H), 3.07 (dd, 1H, ^2J = 18.0 Hz, ^3J = 10.0 Hz, CH*H*), 4.25 (dd, 1H, J = 2.0 and 5.6 Hz, CH), 4.40 (dd, 1H, J = 10.0 Hz, CH), 5.42 (s, 2H, NH_2), 6.92-6.94 (m, 5H, C_6H_5), 7.11-7.18 (m, 5H, C_6H_5), 10.92 ppm (s, 1H, NH); ^{13}C nmr (deuteriodimethyl sulfoxide): δ 37.12 and 38.1 (CH_2), 38.3 and 41.7 (CH), 126.9, 127.3, 128.3, 128.4, 140.1 and 140.6 (C_6H_5), 159.6 and 159.7 (C=N), 170.4 and 175.45 ppm (C=O); ms (ESI): *m/z* 362 ([M + H]$^+$,100%).

Anal. Calcd. for $C_{20}H_{19}N_5O_2$ (361.40): C, 66.47; H, 5.30; N, 19.38). Found: C, 66.31; H, 5.22; N, 19.19.

Reaction of **6a** with Hydrazine Hydrate.

Compound **6a** (0.134 g, 1.6 mmol) and 2.0 mL (16 mmol) of 40% hydrazine hydrate were left standing at room temperature. Slow evolution of ammonia was observed although the mixture did not turn homogeneous. First portion of the product was collected by filtration on the 16th day, while the filtrate was concentrated *in vacuo* to approximately one-third of the initial volume and left standing for 33 days to deposit the second crop of crystals. The combined fractions (0.093 g) were identified as **2a** of 97% purity; the contaminant was unreacted **6a**. The overall yield of **2a** was 56%.

Hydrogenation of 3,9,9-Trimethyl-8,9-dihydro-4*H*-pyridazino-[6,1-*c*][1,2,4]triazine-4,7(6*H*)-dione (**3**).

A mixture of 1.519 g (7.3 mmol) of **3** [3], 75 mL of acetic acid and 0.313 g of 10% palladized carbon was hydrogenated 13 h under 50 psig in a Parr apparatus. Upon removal of the catalyst the filtrate was concentrated *in vacuo*. The solid residue was recrystallized twice from methanol to yield 1.128 g (73% yield) of **5**.

3,9,9-Trimethyl-8,9-dihydro-2*H*-pyridazino[6,1-*c*][1,2,4triazine-4,7(3*H*,6*H*)-dione (**5**).

This compound was obtained as colorless crystals (methanol), mp 154-157º; ir: ν 3412, 3192, and 3112 (NH), 1724 and 1684

cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.32 (s, 3H, 9-CH_3), 1.33 (s, 3H, 9-CH_3), 1.40 (d, 3H, *J* = 6.8 Hz, 3-CH_3), 2.50 (s, 2H, CH_2), 3.70 (q, 1H, *J* = 6.8 Hz, CH), 5.29 (s, 1H, 2-NH), 9.43 ppm (s, 1H, 6-NH) ^{13}C nmr (deuteriochloroform): δ 13.75 (3-CH_3), 25.6 and 25.9 (9-CH_3), 34.4 (9-C), 43.6 (CH_2), 51.7 (CH), 141.5 (C=N), 161.0 and 165.7 ppm (C=O); ms: *m/z* 210 (M^+, 17%), 195 (22%), 167 (100%).

Anal. Calcd. for $C_9H_{14}N_4O_2$ (210.23): C, 51.42; H, 6.71; N, 26.65. Found: C, 51.59; H, 6.65; N, 26.50.

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