

## 6,12-METHANODIPYRANO[4,3-*b*:4,3-*f*]DIOXOCINE-1,7-DIONE: THE REACTIVITY TOWARDS NITROGEN NUCLEOPHILES

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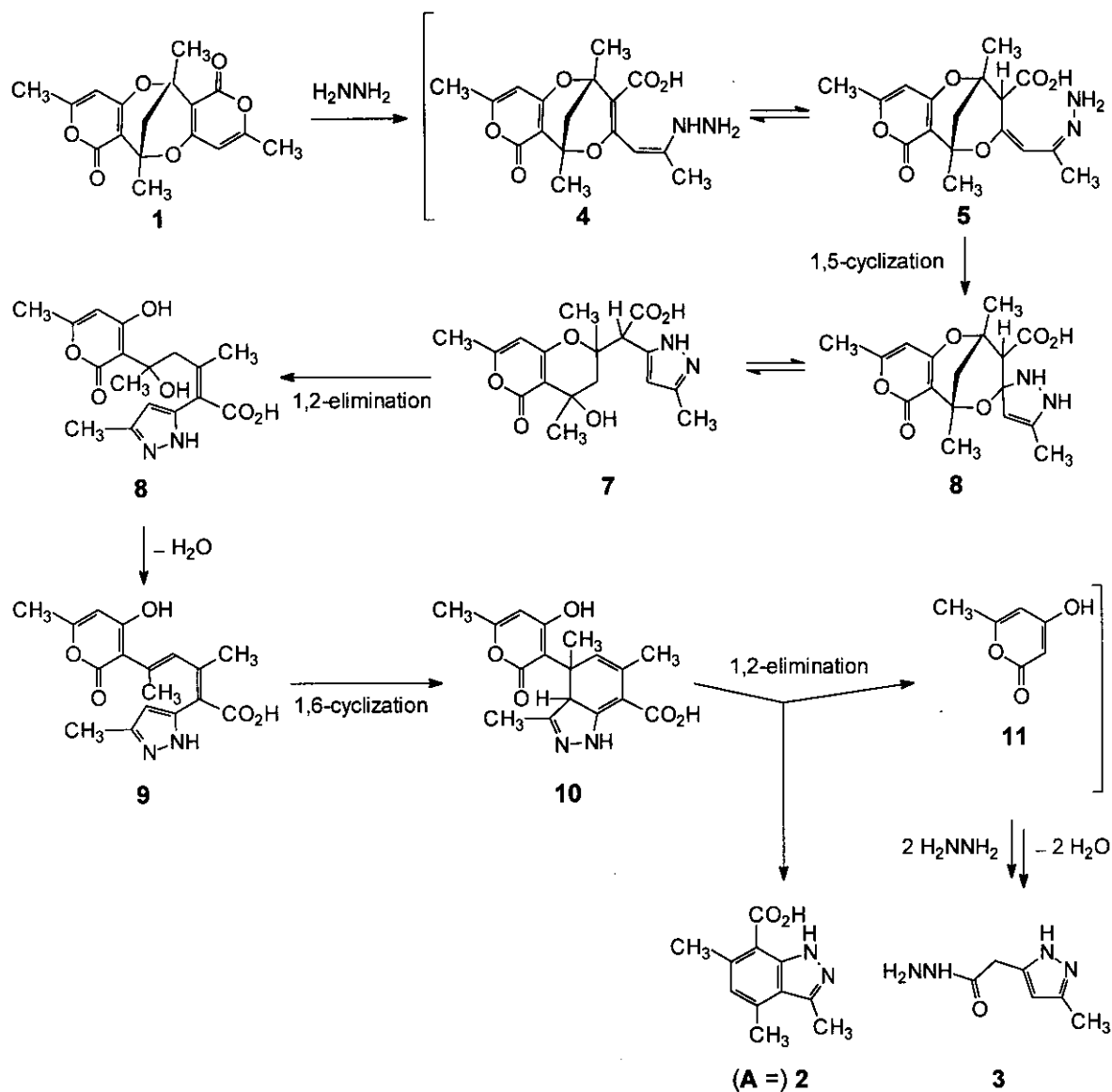
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**Abstract** - The reaction of the title compound (**1**) with hydrazine hydrate induces a complex ring transformation affording 3,4,6-trimethyl-1*H*-indazole-7-carboxylic acid (**2**) and (3-methyl-1*H*-pyrazol-5-yl)acetic acid hydrazide (**3**). The product structures have been elucidated by 2D-NMR techniques, and a mechanistic rationalization of this multistep reaction is presented. Methylhydrazine converts compound (**1**) into (1,3-dimethyl-1*H*-pyrazol-5-yl)acetic acid (**12**), while phenylhydrazine fails to affect **1**.

The ring system of 2*H*-pyran-2-one is known to react with nitrogen nucleophiles undergoing ring transformation and affording various nitrogen heterocycles.<sup>1-6</sup> The 3,6,9,12-tetramethyl-1*H*,6*H*,7*H*,12*H*-6,12-methanodipyrano[4,3-*b*:4,3-*f*][1,5]dioxocine-1,7-dione (**1**) is readily accessible from 4-hydroxy-6-methyl-2*H*-pyran-2-one (triacetic lactone, **11**) and pentane-2,4-dione.<sup>7</sup> The dioxocine (**1**) is an analogue of Tröger's base<sup>8</sup> with a relatively rigid concave molecular frame; the two  $\alpha$ -pyranone rings add to the multifunctionality of the molecule and confer an electrophilic character to the polycyclic compound (**1**). There appears to be no report on reactions of dioxocine (**1**). Our interest in conformationally restricted heterocycles<sup>9</sup> prompted us to examine the reactivity of compound (**1**) towards nitrogen nucleophiles. Dioxocine (**1**) proved surprisingly inert: Ammonia, primary (isobutylamine), and secondary amines (piperidine, morpholine) under various reaction conditions left compound (**1**) unchanged. However, hydrazine and methylhydrazine do react with dioxocine (**1**). By contrast, and surprisingly, phenylhydrazine did not affect substrate (**1**).

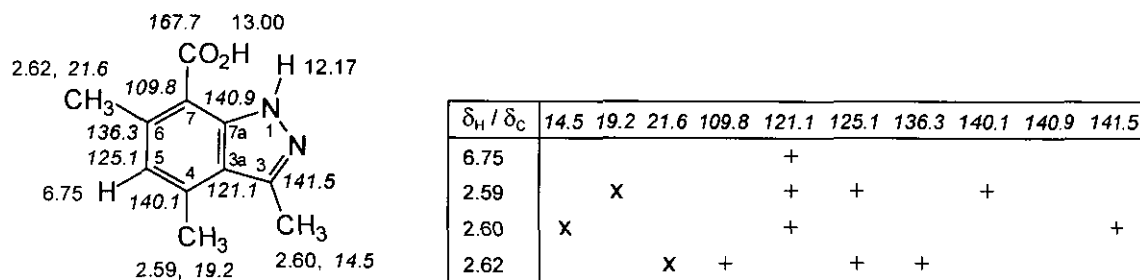


Scheme 1

Treatment of **1** with an excess of hydrazine hydrate in refluxing ethanol for 16 h afforded two products (**A**) and (**3**) (Scheme 1). Mass spectrometry and elemental analysis of compound (**A**) furnish the molecular formula  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2$  indicating the loss of a fragment of six carbon atoms from the original molecule (**1**). This can be accounted for by one pyranone unit being expelled in the course of the hydrazinolysis reaction.

The structure of **A** was elucidated mainly by NMR methods: The relatively simple  $^1\text{H}$ -NMR spectrum of **A** consists of three methyl singlets and one aromatic proton singlet. The  $^{13}\text{C}$ -NMR spectrum reveals three methyl groups, one  $\text{sp}^2$  methine, six quaternary  $\text{sp}^2$  carbons, and a carboxylic carbon ( $\delta_{\text{C}}$  167.7); the IR

spectrum ( $\nu_{\text{C=O}}$  at  $1693\text{ cm}^{-1}$  and broad  $\nu_{\text{OH}}$  centered at  $2477\text{ cm}^{-1}$ ) also confirms the carboxy function. The spectroscopic data and the degree of unsaturation suggest a carboxy- and trimethyl-substituted indazole structure for product (**A**). Comparison of the  $^{13}\text{C}$ -NMR spectra of **A** and 3-methylindazole<sup>10</sup> leads to attribute the  $^{13}\text{C}$  signals  $\delta_{\text{C}}$  141.5 and  $\delta_{\text{C}}$  140.9 to carbon atoms next to nitrogen atoms of indazole, *i.e.* 3-C and 7a-C; furthermore,  $\delta_{\text{C}}$  14.5 is assigned to 3-CH<sub>3</sub>. However, estimates<sup>11</sup> based on spectral simulation do not allow to distinguish between conceivable substitution patterns of the benzo moiety, and the ultimate structure proof was provided by extended application of 2D-NMR techniques (Figure 1): HSQC<sup>12</sup> experiments correlate  $^1\text{H}$  and  $^{13}\text{C}$  methyl signals ( $\delta_{\text{H}}$  2.60 and  $\delta_{\text{C}}$  14.5 of 3-CH<sub>3</sub>;  $\delta_{\text{H}}$  2.59 and  $\delta_{\text{C}}$  19.2,  $\delta_{\text{H}}$  2.62 and  $\delta_{\text{C}}$  21.6 of the two methyl substituents of the benzo ring); HMBC<sup>13</sup> experiments permit the assignment of  $^{13}\text{C}$  signals to the methyl-bearing carbon atoms ( $\delta_{\text{H}}$  2.60 and  $\delta_{\text{C}}$  141.5 of 3-C-CH<sub>3</sub>;  $\delta_{\text{H}}$  2.59 and  $\delta_{\text{C}}$  140.1;  $\delta_{\text{H}}$  2.62 and  $\delta_{\text{C}}$  136.3). Due to long-range couplings additional cross peaks arise from  $^1\text{H}$  methyl signals and other ring carbon signals:  $\delta_{\text{H}}$  2.59 and  $\delta_{\text{C}}$  125.1 (CH),  $\delta_{\text{C}}$  121.1 (quaternary);  $\delta_{\text{H}}$  2.60 and  $\delta_{\text{C}}$  121.1 (quaternary);  $\delta_{\text{H}}$  2.62 and  $\delta_{\text{C}}$  125.1 (CH),  $\delta_{\text{C}}$  109.8 (quaternary). These correlations (a) indicate the relative 1,3-position of the two methyl substituents in the benzo ring, (b) assign  $\delta_{\text{C}}$  121.1 to the ring fusion position 3a-C, (c) together with the cross peak between the signal of the aromatic methine proton ( $\delta_{\text{H}}$  6.75) and that of 3a-C ( $\delta_{\text{C}}$  121.1) determine the unsubstituted ring position 5 in structure (**2**). Signals  $\delta_{\text{C}}$  140.9 and  $\delta_{\text{C}}$  109.8 are assigned to 7a-C (fusion atom) and 7-C (carboxy-substituted ring position), respectively.



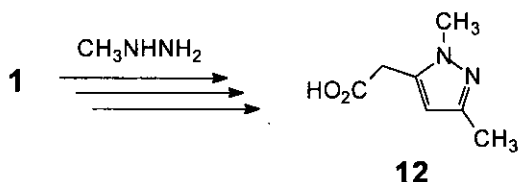
**Figure 1.**  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR data of **2** [ $\delta_{\text{C}}$  italicized], and 2D-NMR cross peaks: x (HSQC), + (HMBC).

The following tentative mechanism is offered to rationalize the conversion of dioxocine (**1**) with hydrazine into products (**2**) and (**3**) (Scheme 1). The reaction is presumed to be initiated by the attack of hydrazine at 3-C of substrate (**1**) inducing the opening of one pyranone ring. The resultant  $\omega$ -hydrazinodienoic acid (**4**) is considered to equilibrate with tautomer (**5**); the  $\alpha,\beta$ -unsaturated hydrazone moiety of the latter may undergo 1,5-electrocyclic ring-closure forming the 2,3-dihydropyrazole ring of intermediate (**6**) with both spiro rings participating in a hydrazinoaminal function (also a direct 5-*exo-trig* cyclization of **4** to **6** may be considered). Intermediate (**6**) is anticipated to undergo elimination and formation of the functional components, the pyrazole ring and the hydroxy group of intermediate (**7**). Two

subsequent elimination steps are conceivably driven by the extension of the conjugation range: 1,2-Elimination of the 4-hydroxypyranone moiety forming the  $\alpha,\beta$ -unsaturated acid (**8**) is followed by elimination of water affording the dienoid acid derivative (**9**) (the two elimination steps may occur also in reverse order). Electrocyclization involving the diene  $\pi$ -bonds and the 4,5- $\pi$ -bond of the pyrazole ring of **9** affords the 3a,4-dihydroindazole intermediate **10**. Elimination of 4-hydroxy-6-methyl-2H-pyran-2-one (**11**) provides one of the final products (**2**).

The presumed elimination product (**11**) was not found; instead, (3-methyl-1H-pyrazol-5-yl)acetic acid hydrazide (**3**) was isolated. The formation of product (**3**) is considered to result from the reaction of the intermediate (**11**) with hydrazine. Compound (**3**) proved identical in all aspects with an authentic sample prepared from triacetic lactone (**11**) with hydrazine,<sup>5</sup> and tautomer structure (**3**) has been assigned in analogy to the 1-methyl derivative (**12**) (*vide infra*).

Under similar conditions, the reaction of dioxocine (**1**) with methylhydrazine was slow and afforded only one isolable product, (1,3-dimethyl-1H-pyrazol-5-yl)acetic acid (**12**) in low yield (Scheme 2). No complementing product was found. Product structure (**12**) was confirmed by employing 2D-NMR methods: Cross peaks (HMBC) between the signals of the methylene group ( $\delta_{\text{H}}$  3.65) and those of the carboxy group ( $\delta_{\text{C}}$  170.8) and the quaternary ring carbon atom ( $\delta_{\text{C}}$  136.4) as well as between the latter and the *N*-methyl group ( $\delta_{\text{H}}$  3.61) are compatible only with the structure of the 1,3-dimethyl isomer (**12**).



Scheme 2

The reaction of phenylhydrazine with dioxocine (**1**) led only to recovery of the reactants. This is a remarkable and unexpected result in view of the known reactivity of substituted pyran-2-ones with phenylhydrazine under mild conditions.<sup>6</sup>

## EXPERIMENTAL

Spectroscopic data were recorded on the following instruments: MATTSON Galaxy Series GL-3020 (IR; KBr;  $[\text{cm}^{-1}]$ ); Bruker AM 300 ( $^1\text{H}$ -NMR, 300 MHz;  $^{13}\text{C}$ -NMR, 75 MHz;  $\text{DMSO}-d_6$ ;  $\delta$ ); Varian Unity (500 MHz); MAT 95 (EI-MS 70 eV  $[m/z]$  (%)). Melting points (mp [ $^\circ\text{C}$ ]) were determined with a Kofler hot stage microscope (Reichert). Thin layer chromatography was carried out on silica gel (Polygram Sil G/UV<sub>254</sub>),  $R_f$  values were determined with acetone as eluent.

**3,6,9,12-Tetramethyl-1*H*,6*H*,7*H*,12*H*-6,12-methanodipyrano[4,3-*b*;4,3-*f*][1,5]dioxocine-1,7-dione (1)**

The starting material (1) has been prepared following the reported protocol,<sup>7</sup> the reaction was carried out at 140°C for 1.5 h to yield **1** (60 %); mp 235-237°C (ethanol) (lit.,<sup>7</sup> mp 235-237°C); *R<sub>f</sub>* 0.78 (acetone); <sup>1</sup>H-NMR: δ 6.06 (s, 2H, 4,10-H), 2.17 (s, 2H, 13-CH<sub>2</sub>), 2.11 (s, 6H, 3,9-CH<sub>3</sub>), 1.87 (s, 6H, 6,12-CH<sub>3</sub>); <sup>13</sup>C-NMR: δ 166.6 (C=O), 163.5 (3,9-C), 160.7 (4a,10a-C), 99.3 (4,10-CH), 98.6 (6a,12a-C), 73.2 (6,12-C), 42.0 (13-CH<sub>2</sub>), 22.1 (6,12-CH<sub>3</sub>), 19.2 (3,9-CH<sub>3</sub>); signal assignments reflect suggestions by spectral simulation.<sup>11</sup>

**Reaction of Dioxocine (1) with Hydrazine: 3,4,6-Trimethyl-1*H*-indazole-7-carboxylic acid (2) and (3-Methyl-1*H*-pyrazol-5-yl)acetic acid hydrazide (3):**

After addition of hydrazine monohydrate (99 %, 1.60 mL, 31 mmol) to a warm solution of **1** (1.00 g, 3.16 mmol) in ethanol (100 mL) the reaction mixture was heated under reflux for 16 h. On cooling, colorless crystals of **2** precipitated and were collected (0.38 g); the filtrate was concentrated to yield another crop of **2** (0.03 g): Total yield 0.41 g (61 %); **2**; mp (sublime) 308°C (methanol); *R<sub>f</sub>* 0.59 (acetone); IR (KBr): 3399, 3385 (NH), 2477 (CO<sub>2</sub>H), 1693 cm<sup>-1</sup> (CO<sub>2</sub>H); <sup>1</sup>H-NMR: δ 13.00 (br s, 1H, CO<sub>2</sub>H, exchangeable with D<sub>2</sub>O), 12.17 (br s, 1H, NH, exchangeable with D<sub>2</sub>O), 6.75 (s, 1H, 5-H), 2.62 (s, 3H, 6-CH<sub>3</sub>), 2.60 (s, 3H, 3-CH<sub>3</sub>), 2.59 (s, 3H, 4-CH<sub>3</sub>). <sup>13</sup>C-NMR: δ 167.7 (C=O), 141.5 (3-C), 140.9 (7a-C), 140.1 (4-C), 136.3 (6-C), 125.1 (5-CH), 121.1 (3a-C), 109.8 (7-C), 21.6 (6-CH<sub>3</sub>), 19.2 (4-CH<sub>3</sub>), 14.5 (3-CH<sub>3</sub>); cross peaks resulting from 2D-NMR experiments are listed in Figure 1; MS: 204 (95, M<sup>+</sup>, C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>), 186 (100, C<sub>11</sub>H<sub>10</sub>N<sub>2</sub>O), 157 (29, C<sub>10</sub>H<sub>9</sub>N<sub>2</sub>), 129 (17, C<sub>10</sub>H<sub>9</sub>), 115 (23, C<sub>9</sub>H<sub>7</sub>). Anal. Calcd for C<sub>11</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.49; H, 6.08; N, 13.99.

The solvent of the second filtrate was evaporated. To the oily residue was added dioxane (10 mL), and the separated crystals were collected: 0.28 g (57 %) **3**; mp 148-150°C (dioxane) (lit.,<sup>5</sup> mp 145°C); *R<sub>f</sub>* 0.22 (acetone); IR (KBr): 3308 (sh), 3276, 3129 (NH), 1651 cm<sup>-1</sup> (C=O); <sup>1</sup>H-NMR: δ 11.95 (br s, 3H, NH, NH<sub>2</sub>, exchangeable with D<sub>2</sub>O), 9.06 (br s, 1H, NH, exchangeable with D<sub>2</sub>O), 5.83 (s, 1H, 4-H), 3.27\* (s, 2H, CH<sub>2</sub>), 2.13\*\* (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR: δ 168.8\* (C=O), 143.5\* (5-C), 141.1\*\* (3-C), 103.4 (4-CH), 33.0 (CH<sub>2</sub>), 11.3 (CH<sub>3</sub>); labels refer to corresponding signals giving rise to HMBC cross peaks; MS: 154 (49, M<sup>+</sup>, C<sub>6</sub>H<sub>10</sub>N<sub>4</sub>O), 123 (78, C<sub>6</sub>H<sub>7</sub>N<sub>2</sub>O), 95 (100, C<sub>5</sub>H<sub>7</sub>N<sub>2</sub>).

**Reaction of Compound (1) with Methylhydrazine: (1,3-Dimethyl-1*H*-pyrazol-5-yl)acetic acid (12):**

After addition of methylhydrazine (3.30 mL, 62 mmol) to a warm solution of **1** (1.00 g, 3.16 mmol) in ethanol (100 mL) the reaction mixture was heated under reflux for 32 h. After removal of the solvent the residual oil was treated with ethyl acetate/acetone (4:1, 10 mL) inducing crystallization; the collected crystals were washed with ether: 0.125 g (13 %) **13**; mp 193-194°C (ethyl acetate); *R<sub>f</sub>* 0.56 (acetone); IR (KBr): 2672, 2587, 2502 (CO<sub>2</sub>H), 1701 (C=O), 1327, 1208 cm<sup>-1</sup>; <sup>1</sup>H-NMR: δ 12.58 (br s, 1H, CO<sub>2</sub>H, exchangeable with D<sub>2</sub>O), 5.88 (s, 1H, 4-H), 3.65\* (s, 2H, CH<sub>2</sub>), 3.61<sup>#</sup> (3H, 1-CH<sub>3</sub>), 2.07\*\* (s, 3H, 3-CH<sub>3</sub>); <sup>13</sup>C-NMR: δ 170.8\* (C=O), 145.4\*\* (3-C), 136.4\*\* (5-C), 105.5 (4-CH), 35.8 (1-CH<sub>3</sub>), 31.1

(CH<sub>2</sub>), 13.2 (3-CH<sub>3</sub>); signals giving rise to HMBC cross peaks are correspondingly labeled; MS 154 (85, M<sup>+</sup>, C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>), 109 (100, C<sub>6</sub>H<sub>9</sub>N<sub>2</sub>, M-CO<sub>2</sub>H). Anal. Calcd for C<sub>7</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.69; H, 6.33; N, 18.01.

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