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

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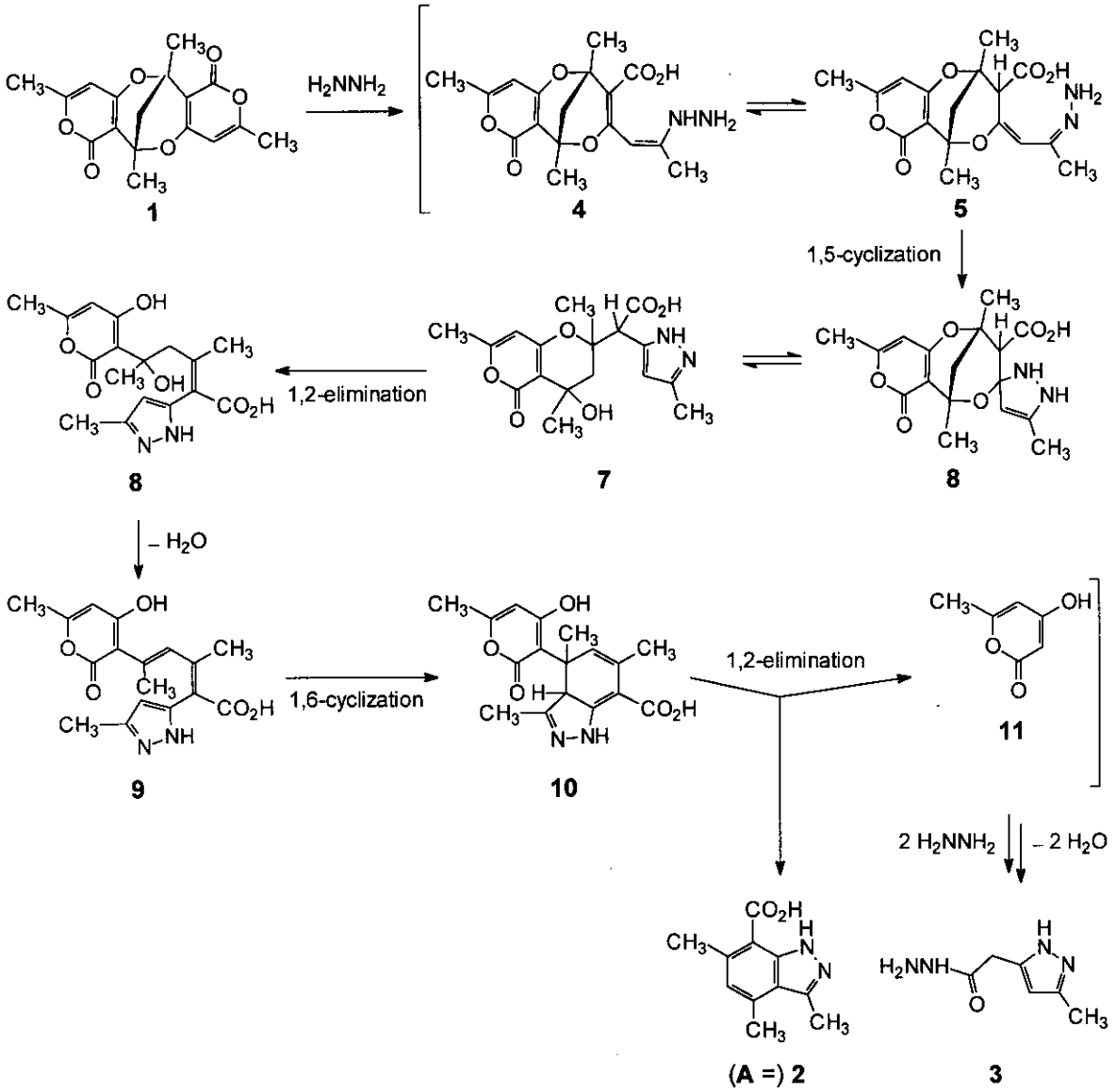
Abstract - The reaction of the title compound (**1**) with hydrazine hydrate induces a complex ring transformation affording 3,4,6-trimethyl-1*H*-indazole-7-carboxylic acid (**2**) and (3-methyl-1*H*-pyrazol-5-yl)acetic acid hydrazide (**3**). The product structures have been elucidated by 2D-NMR techniques, 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 phenyl hydrazine 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.[1-6] 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.[7] The dioxocine (**1**) is an analogue of Tröger's base[8] with a relatively rigid concave molecular frame; the two α-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[9] 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**).

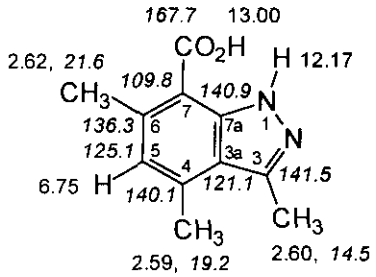


Scheme 1

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 $C_{11}H_{12}N_2O_2$ 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}H-NMR spectrum of **A** consists of three methyl singlets and one aromatic proton singlet. The ^{13}C-NMR spectrum reveals three methyl groups, one sp^2 methine, six quarternary sp^2 carbons, and a carboxylic carbon (δ_C 167.7); the IR

spectrum ($\nu_{C=O}$ at 1693 cm^{-1} and broad ν_{OH} centered at 2477 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}C-NMR spectra of **A** and 3-methylindazole[10] leads to attribute the ^{13}C signals δ_C 141.5 and δ_C 140.9 to carbon atoms next to nitrogen atoms of indazole, *i.e.* 3-C and 7a-C; furthermore, δ_C 14.5 is assigned to 3-CH_3. However, estimates[11] 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[12] experiments correlate ^1H and ^{13}C methyl signals (δ_H 2.60 and δ_C 14.5 of 3-CH_3; δ_H 2.59 and δ_C 19.2, δ_H 2.62 and δ_C 21.6 of the two methyl substituents of the benzo ring); HMBC[13] experiments permit the assignment of ^{13}C signals to the methyl-bearing carbon atoms (δ_H 2.60 and δ_C 141.5 of 3-$\underline{C}CH_3$; δ_H 2.59 and δ_C 140.1; δ_H 2.62 and δ_C 136.3). Due to long-range couplings additional cross peaks arise from ^1H methyl signals and other ring carbon signals: δ_H 2.59 and δ_C 125.1 (CH), δ_C 121.1 (quaternary); δ_H 2.60 and δ_C 121.1 (quaternary); δ_H 2.62 and δ_C 125.1 (CH), δ_C 109.8 (quaternary). These correlations (a) indicate the relative 1,3-position of the two methyl substituents in the benzo ring, (b) assign δ_C 121.1 to the ring fusion position 3a-C, (c) together with the cross peak between the signal of the aromatic methine proton (δ_H 6.75) and that of 3a-C (δ_C 121.1) determine the unsubstituted ring position 5 in structure (**2**). Signals δ_C 140.9 and δ_C 109.8 are assigned to 7a-C (fusion atom) and 7-C (carboxy-substituted ring position), respectively.



δ_H / δ_C	*14.5*	*19.2*	*21.6*	*109.8*	*121.1*	*125.1*	*136.3*	*140.1*	*140.9*	*141.5*
6.75					+					
2.59		x			+	+		+		
2.60	x				+					+
2.62			x	+		+	+			

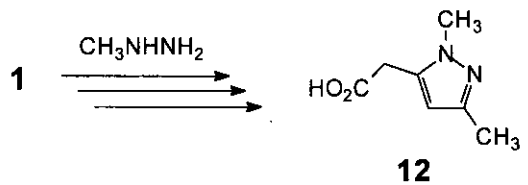
Figure 1. ^1H- and ^{13}C-NMR data of **2** [δ_C *italicized*], and 2D-NMR cross peaks: x (HSQC), + (HMBC).

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 ω-hydrazinodienoic acid (**4**) is considered to equilibrate with tautomer (**5**); the α,β-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 α,β-unsaturated acid (**8**) is followed by elimination of water affording the dienoic acid derivative (**9**) (the two elimination steps may occur also in reverse order). Electrocyclization involving the diene π-bonds and the 4,5-π-bond of the pyrazole ring of **9** affords the 3a,4-dihydroindazole intermediate **10**. Elimination of 4-hydroxy-6-methyl-2*H*-pyran-2-one (**11**) provides one of the final products (**2**).

The presumed elimination product (**11**) was not found; instead, (3-methyl-1*H*-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,[5] 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-1*H*-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 (δ_H 3.65) and those of the carboxy group (δ_C 170.8) and the quarternary ring carbon atom (δ_C 136.4) as well as between the latter and the *N*-methyl group (δ_H 3.61) are compatible only with the structure of the 1,3-dimethyl isomer (**12**).



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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.[6]

EXPERIMENTAL

Spectroscopic data were recorded on the following instruments: MATTSON Galaxy Series GL-3020 (IR; KBr; [cm^{-1}]); Bruker AM 300 (^{1}H-NMR, 300 MHz; ^{13}C-NMR, 75 MHz; DMSO-d_6; δ); Varian Unity (500 MHz); MAT 95 (EI-MS 70 eV [m/z] (%)). Melting points (mp [°C]) were determined with a Kofler hot stage microscope (Reichert). Thin layer chromatography was carried out on silica gel (Polygram Sil G/UV_{254}), 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,[7] the reaction was carried out at 140°C for 1.5 h to yield **1** (60 %); mp 235-237°C (ethanol) (lit.,[7] mp 235-237°C); R_f 0.78 (acetone); ^{1}H-NMR: δ 6.06 (s, 2H, 4,10-H), 2.17 (s, 2H, 13-CH_2), 2.11 (s, 6H, 3,9-CH_3), 1.87 (s, 6H, 6,12-CH_3); ^{13}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_2) 22.1 (6,12-CH_3), 19.2 (3,9-CH_3); signal assignments reflect suggestions by spectral simulation.[11]

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_f 0.59 (acetone); IR (KBr): 3399, 3385 (NH), 2477 (CO_2H), 1693 cm^{-1} (CO_2H); ^{1}H-NMR: δ 13.00 (br s, 1H, CO_2H, exchangeable with D_2O), 12.17 (br s, 1H, NH, exchangeable with D_2O), 6.75 (s, 1H, 5-H), 2.62 (s, 3H, 6-CH_3), 2.60 (s, 3H, 3-CH_3), 2.59 (s, 3H, 4-CH_3). ^{13}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_3), 19.2 (4-CH_3), 14.5 (3-CH_3); cross peaks resulting from 2D-NMR experiments are listed in Figure 1; MS: 204 (95, $M^{\bullet+}$, $C_{11}H_{12}N_2O_2$), 186 (100, $C_{11}H_{10}N_2O$), 157 (29, $C_{10}H_9N_2$), 129 (17, $C_{10}H_9$), 115 (23, C_9H_7). Anal. Calcd for $C_{11}H_{12}N_2O_2$: 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.,[5] mp 145°C); R_f 0.22 (acetone); IR (KBr): 3308 (sh), 3276, 3129 (NH), 1651 cm^{-1} (C=O); ^{1}H-NMR: δ 11.95 (br s, 3H, NH, NH_2, exchangeable with D_2O), 9.06 (br s, 1H, NH, exchangeable with D_2O), 5.83 (s, 1H, 4-H), 3.27* (s, 2H, CH_2), 2.13** (s, 3H, CH_3); ^{13}C-NMR: δ 168.8* (C=O), 143.5* (5-C), 141.1** (3-C), 103.4 (4-CH), 33.0 (CH_2), 11.3 (CH_3); labels refer to corresponding signals giving rise to HMBC cross peaks; MS: 154 (49, $M^{\bullet+}$, $C_6H_{10}N_4O$), 123 (78, $C_6H_7N_2O$), 95 (100, $C_5H_7N_2$).

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_f 0.56 (acetone); IR (KBr): 2672, 2587, 2502 (CO_2H), 1701 (C=O), 1327, 1208 cm^{-1}; ^{1}H-NMR: δ 12.58 (br s, 1H, CO_2H, exchangeable with D_2O), 5.88 (s, 1H, 4-H), 3.65* (s, 2H, CH_2), 3.61# (3H, 1-CH_3), 2.07** (s, 3H, 3-CH_3); ^{13}C-NMR: δ 170.8* (C=O), 145.4** (3-C), 136.4*# (5-C), 105.5 (4-CH), 35.8 (1-CH_3), 31.1

(CH_2), 13.2 (3-CH_3); signals giving rise to HMBC cross peaks are correspondingly labeled; MS 154 (85, $M^{\bullet+}$, $C_7H_{10}N_2O_2$), 109 (100, $C_6H_9N_2$, M-CO_2H). Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.69; H, 6.33; N, 18.01.

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