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-1H-indazole-7-carboxylic acid (2) and (3-methyl-1H-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-1H-pyrazol-5-yl)acetic acid (12), while phenylhydrazine fails to affect 1.

The ring system of 2H-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-1H,6H,7H,12H-6,12-methanodipyran[4,3-b:4,3-f][1,5]dioxocine-1,7-dione (1) is readily accessible from 4-hydroxy-6-methyl-2H-pyran-2-one (triacetic lactone, 11) and pentane-2,4-dione.7 The dioxocine (1) is an analogue of Tröger's base8 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 heterocycles9 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).
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_{13}N_{2}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 $^1$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 ($\delta_c 167.7$); the IR
spectrum ($\nu_{\text{C=O}}$ at 1693 cm$^{-1}$ and broad $\nu_{\text{OH}}$ 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 $\delta_{c}$ 141.5 and $\delta_{c}$ 140.9 to carbon atoms next to nitrogen atoms of indazole, $i.e.$ 3-C and 7a-C; furthermore, $\delta_{c}$ 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 $^1$H and $^{13}$C methyl signals ($\delta_{H}$ 2.60 and $\delta_{C}$ 14.5 of 3-CH$_3$; $\delta_{H}$ 2.59 and $\delta_{C}$ 19.2, $\delta_{H}$ 2.62 and $\delta_{C}$ 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 ($\delta_{H}$ 2.60 and $\delta_{C}$ 141.5 of 3-CH$_3$; $\delta_{H}$ 2.59 and $\delta_{C}$ 140.1; $\delta_{H}$ 2.62 and $\delta_{C}$ 136.3). Due to long-range couplings additional cross peaks arise from $^1$H methyl signals and other ring carbon signals: $\delta_{H}$ 2.59 and $\delta_{C}$ 125.1 (CH), $\delta_{C}$ 121.1 (quaternary); $\delta_{H}$ 2.60 and $\delta_{C}$ 121.1 (quaternary); $\delta_{H}$ 2.62 and $\delta_{C}$ 125.1 (CH), $\delta_{C}$ 109.8 (quaternary). These correlations (a) indicate the relative 1,3-position of the two methyl substituents in the benzo ring, (b) assign $\delta_{C}$ 121.1 to the ring fusion position 3a-C, (c) together with the cross peak between the signal of the aromatic methine proton ($\delta_{H}$ 6.75) and that of 3a-C ($\delta_{C}$ 121.1) determine the unsubstituted ring position 5 in structure (2). Signals $\delta_{C}$ 140.9 and $\delta_{C}$ 109.8 are assigned to 7a-C (fusion atom) and 7-C (carboxy-substituted ring position), respectively.

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 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-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, 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 (δH 3.65) and those of the carboxy group (δC 170.8) and the quarternary ring carbon atom (δC 136.4) as well as between the latter and the N-methyl group (δH 3.61) are compatible only with the structure of the 1,3-dimethyl isomer (12).

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.

**EXPERIMENTAL**

Spectroscopic data were recorded on the following instruments: MATTSON Galaxy Series GL-3020 (IR; KBr; [cm⁻¹]); Bruker AM 300 (¹H-NMR, 300 MHz; ¹³C-NMR, 75 MHz; DMSO-d₆); 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/UV₂₅₄), Rf values were determined with acetone as eluent.
The starting material (1) has been prepared following the reported protocol, the reaction was carried out at 140°C for 1.5 h to yield 1 (60%) mp 235-237°C (ethanol) (lit., mp 235-237°C); Rf 0.78 (acetone); \(^1\)H-NMR: δ 6.06 (s, 2H, 4,10-H), 2.17 (s, 2H, 13-CH,), 2.11 (s, 6H, 3,9-CH,), 1.87 (s, 6H, 6,12-CH,); \(^13\)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,) 22.1 (6,12-CH,), 19.2 (3,9-CH,); signal assignments reflect suggestions by spectral simulation.

Reaction of Dioxocine (1) with Hydrazine: 3,4,6-Trimethyl-1H-indazole-7-carboxylic acid (2) and (3-Methyl-1H-pyrazol-5-yl)acetic acid hydrazide (3): After addition of hydrazine monohydrate (99%, 1.60 mL, 3.1 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%); mp (sublime) 308°C (methanol); Rf 0.59 (acetone); IR (KBr): 3399, 3385 (NH), 2477 (CO, H), 1693 cm\(^{-1}\) (C=O); \(^1\)H-NMR: 6 13.00 (br s, 1H, CO2H, exchangeable with D2O), 12.17 (br s, 1H, NH, exchangeable with D,O), 6.75 (s, 1H, 5-H), 2.62 (s, 3H, 6-CH,), 2.60 (s, 3H, 3-CH,), 2.59 (s, 3H, 4-CH). \(^13\)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-CH3), 19.2 (4-CH3), 14.5 (3-CH3); cross peaks resulting from 2D-NMR experiments are listed in Figure 1; MS: 204 (95, M", C11H15N2O2), 186 (100, CllH10N2O), 157 (29, C10H7N2), 129 (17, C10H9), 115 (23, C9H7). Anal. Calcd for C11H12N2O2: 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., mp 145°C); Rf 0.22 (acetone); IR (KBr): 3308 (sh), 3276, 3129 (NH), 1651 cm\(^{-1}\) (C=O); \(^1\)H-NMR: δ 11.95 (br s, 1H, CO2H, exchangeable with D2O), 9.06 (br s, 1H, NH, exchangeable with D2O), 5.83 (s, 1H, 4-H), 3.27* (s, 2H, CH2), 2.13** (s, 3H, CH3); \(^13\)C-NMR: δ 168.8* (C=O), 143.5* (5-C), 141.1** (3-C), 103.4 (4-CH), 33.0 (CH2), 11.3 (CH3); labels refer to corresponding signals giving rise to HMBC cross peaks; MS: 154 (49, M**, C6H10N4O), 123 (78, C6H9N2O), 95 (100, C5H7N2).

Reaction of Compound (1) with Methylhydrazine: (1,3-Dimethyl-1H-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); Rf 0.56 (acetone); IR (KBr): 2672, 2587, 2502 (CO2H), 1701 (C=O), 1327, 1208 cm\(^{-1}\); \(^1\)H-NMR: δ 12.58 (br s, 1H, CO2H, exchangeable with D2O), 5.88 (s, 1H, 4-H), 3.65* (s, 2H, CH2), 3.61* (3H, 1-CH3), 2.07** (s, 3H, 3-CH3); \(^13\)C-NMR: δ 170.8* (C=O), 145.4** (3-C), 136.4** (5-C), 105.5 (4-CH), 35.8 (1-CH3), 31.1
(CH₂), 13.2 (3-CH₃); signals giving rise to HMBC cross peaks are correspondingly labeled; MS 154 (85, M⁺, C₇H₁₀N₂O₂), 109 (100, C₅H₇N₂, M-CO₂H). Anal. Calcd for C₇H₁₀N₂O₂: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.69; H, 6.33; N, 18.01.

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