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TRANSFORMATION OF 5,6,7,8-TETRAHYDRO-2*H*-1-BENZOPYRAN-2,8-DIONES WITH HYDRAZINES AND HYDRAZOIC ACID: SYNTHESIS OF 8-HYDRAZONO-5,6,7,8-TETRAHYDRO-2-OXO-2*H*-1-BENZOPYRANS, PYRANO[2,3-*c*]AZEPINES AND PYRIDO[2,3-*c*]AZEPINES[#]

Polonca Trebše,[¶,a] Lidija Vraničar,[a] Irena Mušič,[a] Slovenko Polanc,[a] William C. Stevens,[b] and Marijan Kočevar*[,a]

[a]Faculty of Chemistry and Chemical Technology, University of Ljubljana, Aškerčeva 5, SI-1000 Ljubljana, Slovenia
[b]Nuclear Magnetic Resonance Facility, Southern Illinois University at Carbondale, Carbondale, IL 62901 USA

Abstract – *N*-(5,6,7,8-Tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl)benzamide (**1a**) reacts with nitrogen-containing nucleophiles (**2**) (hydrazines and hydroxylamine) to give the corresponding 8-hydrazono derivatives (**3a**–**i**) and the related hydroxyimino derivative (**3j**). The action of hydrazoic acid on **1a**–**b** or **3a**–**b** and **3e** resulted in the formation of pyrano[2,3-*c*]azepines (**4a**–**b**). The pyranoazepine (**4a**) can be debenzoylated to **4b** or transformed into pyrido[2,3-*c*]azepines (**5a**–**b**).

2*H*-Pyran-2-ones and fused pyran-2-ones are important synthons and building blocks in organic synthesis.[1] Fused pyran-2-ones, such as 5-, 6-, 7-, or 8-oxo substituted 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones possess several reactive centers. For example, nucleophiles might react either with the lactone ring or with the keto group. Previous results have shown that *N*-(5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl)benzamides gave the corresponding quinolines[2a–c] when reacted with nitrogen-containing nucleophiles, such as ammonia, hydroxylamine, aniline, amino acids, hydrazine and *N*,*N*-dimethylhydrazine. On the other hand, hydrazides, phenylhydrazines and heterocyclic hydrazines converted benzopyran-2,5-diones selectively into 5-hydrazonobenzopyrans.[2c–f] These reactions were

[#] Dedicated with deep respect to Professor Richard Neidlein on the ocassion of his 70th birthday.

[¶] Present address: Nova Gorica Polytechnic, Vipavska 13, SI-5000 Nova Gorica, Slovenia

carried out in anhydrous ethanol under the influence of acidic catalysts. The hydrazones, when treated with a mixture of ethanol, water and triethylamine, were selectively converted to the corresponding quinoline-2,5-diones *via* an open-ring intermediate.[2e] In the case of a cyclopenta[*b*]pyran-2,5-dione derivative the corresponding fused pyridines were obtained as the only products.[2f] Heats of formation of some hydrazone or imine–fused pyridinone product pairs have shown that the obtained products are generally thermodynamically favored over the hypothetical isomers.[2b,e–g] In the 2*H*-pyran-2-one series, the corresponding 5-hydrazonoethyl-2*H*-pyran-2-ones can also be isolated under acidic conditions, but under basic conditions (*E*)-α,β-didehydroamino acid derivatives containing a pyrazolyl residue were isolated.[2e,h] With hydrazoic acid (the Schmidt reaction[3]) benzopyran-2,5-diones yielded derivatives of the pyrano[3,2-*c*]azepine system.[2a,c] These results stimulated us to investigate the reactivity of the benzopyran-2,8-dione derivatives in which the reactivity of the pyranone ring is mutually influenced by the 8-oxo group or *vice versa*.

Our starting 8-oxobenzopyran derivative (**1a**)[4] reacted with nitrogen-containing nucleophiles (**2**) (hydrazine hydrate, *N*,*N*-dimethylhydrazine, phenylhydrazine, heterocyclic hydrazines, acetylhydrazine and hydroxylamine) on heating in anhydrous ethanol in the presence of an acidic catalyst (*p*-toluenesulfonic acid or $BF_3 \bullet Et_2O$) to give the corresponding 8-hydrazono derivatives (**3a**–**i**) (Scheme 1, Table 1) and the 8-hydroxyimino derivative **(3j)**. In most experiments equimolar amounts or 10 % excess of the appropriate nitrogen-containing nucleophiles were used. In the case of hydrazine hydrate, *N*,*N*-dimethylhydrazine and phenylhydrazine, two equivalents of the nucleophilic reagent were used. The structures of products (**3**) were determined using several methods. Since the comparison of their IR data with those of the products resulting from 5-oxo derivatives[2b–f] did not give satisfactory results concerning their structures, we decided to study some of these products by some chemical conversions and by NMR techniques. In this manner, the compound (**3a**) was hydrolysed by 18% hydrochloric acid to give the benzopyran (**1a**). The Schmidt reaction, with a large excess of hydrazoic acid, converted hydrazones (**3a**–**b**) or (**3e**) into the pyrano[2,3-*c*]azepine derivative (**4a**), thus the ring enlargement was accompanied by the hydrolysis. The structure (**4a**) was also confirmed by the Schmidt reaction applied to benzopyran (**1a**). On the basis of these experiments, the structures (**3**) are more probable than the isomeric quinoline structures. In the ^{13}C NMR spectrum of the starting compound (**1a**) the signal for C-8 appears at 187.1 ppm, while hydrazones (**3**) did not give signals in this region.

A possible synthetic potential of the pyrano[2,3-*c*]azepine derivative (**4a**) was shown in its transformation to the debenzoylated product (**4b**) by gentle heating with concentrated sulfuric acid[2a] and, albeit in poor yield in one case, to pyrido[2,3-*c*]azepines (**5a**–**b**) with hydrazine hydrate in ethanolic solution and with phenylhydrazine, which was used as a solvent and reagent. Pyrano[2,3-*c*]azepine derivative (**4b**) can also

be obtained by a debenzoylation of the starting compound (**1a**) yielding **1b** (80% yield), followed by the application of the Schmidt reaction to **1b**.

Scheme 1

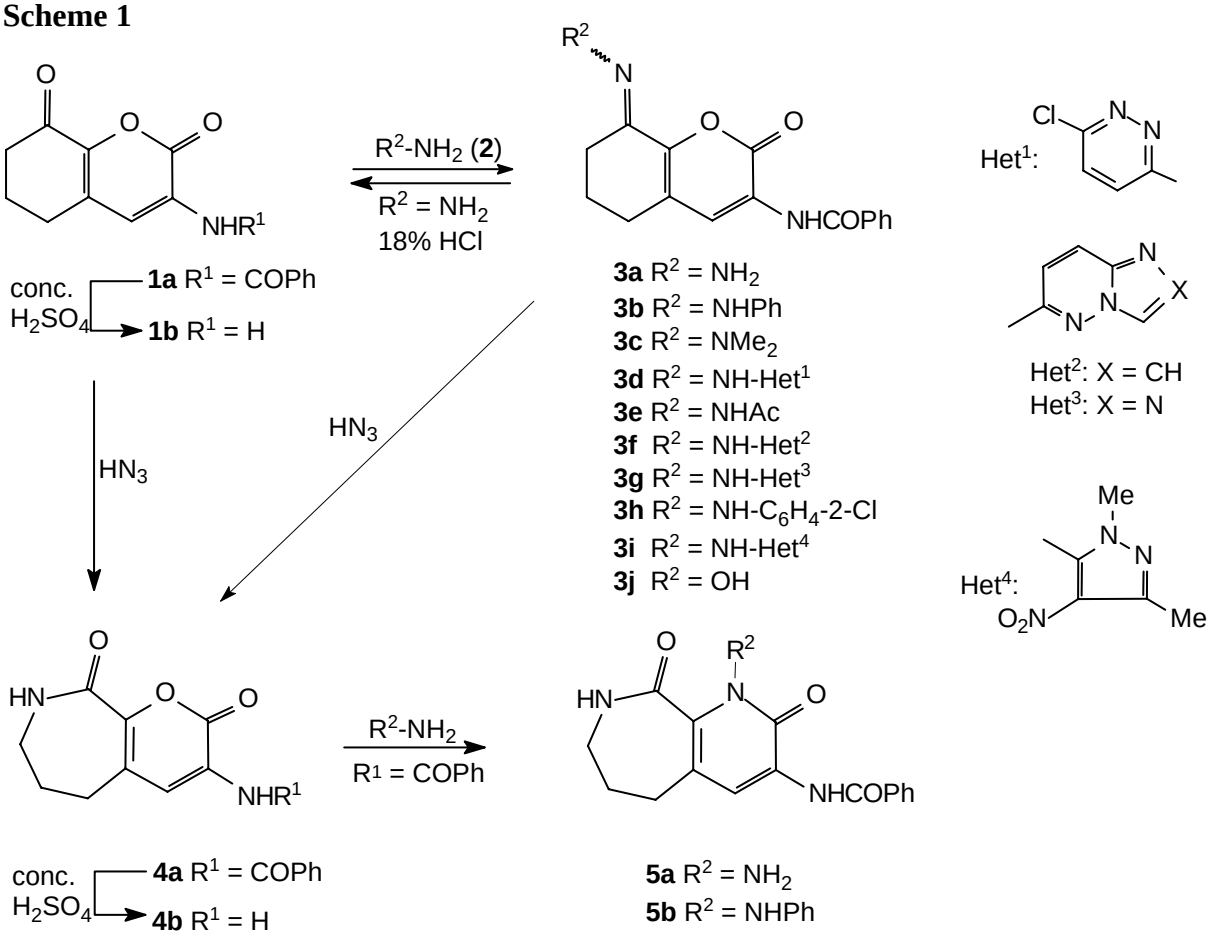

Table 1. Synthesis of 8-hydrazono-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyrans (**3a**–**i**):

2 (R^2=, mmol)	Catalyst (mmol)	Reflux (h)	Product	Yield (%)
NH_2 (2)	BF_3•Et_2O (0.15)	3	**3a**	69
PhNH (2)	BF_3•Et_2O (0.15)	7	**3b**	97
NMe_2 (2)	BF_3•Et_2O (0.15)	6	**3c**	83
Het^1NH (1)	BF_3•Et_2O (0.15)	3.5	**3d**	75
AcNH (1)	BF_3•Et_2O (0.15)	8	**3e**	91
Het^2NH (1.1)	TsOH (0.1)	13	**3f**	81
Het^3NH (1)	TsOH (0.1)	16	**3g**	77
2-ClC_6H_4NH (1)	TsOH (0.1)	5	**3h**	88
Het^4NH (1)	TsOH (0.1)	9	**3i**	93

In conclusion, we have presented the first synthesis of 8-hydrazono-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran derivatives, thus demonstrating derivatisation of the 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-one ring at the position 8. We also described the use of these derivatives in subsequent synthesis, in the formation of pyrano[2,3-*c*]azepines and pyrido[2,3-*c*]azepine derivatives. These results lead to the conclusion that the 8-oxobenzopyran system behaves differently from the isomeric 5-oxo derivatives and other related systems.[2] Namely, in this particular case all the reactions with nitrogen-containing nucleophiles take place at the 8-oxo group yielding the corresponding 8-hydrazono (or 8-hydroxyimino) derivatives. In no case fused pyran-2-one ring is transformed to the corresponding pyridin-2-one ring. To our knowledge, products (**3**) are the first representatives of the 2*H*-1-benzopyran system containing an exocyclic C=N double bond at the position 8. It is also important to mention that until now only a single derivative of the pyrano[2,3-*c*]azepine system has been described, namely, 6,7,8,9-tetrahydro-9-oxo-2-phenyl-5*H*-pyrano[2,3-*c*]azepin-1-ium perchlorate.[5] However, there are some methods for the synthesis of pyrido[2,3-*c*]azepines, for example, the photo-induced ring expansion of azidoquinolines,[6a–d] or the transformation of 8-nitroquinolines with dimethyl phosphite *via* a nitrene intermediate.[6e–f]

EXPERIMENTAL

Melting points were determined on a Kofler micro hot stage, and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with the Varian EM 360C, Varian VXR-300 and Bruker Avance DPX 300 spectrometers, using TMS as an internal standard. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin Elmer 1310 spectrophotometer. MS spectra were recorded with a VG-Analytical AutoSpec Q instrument. Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 CHN Analyzer. Thin-layer chromatography was carried out on Fluka silica gel TLC-cards.

3-Amino-5,6,7,8-tetrahydro-2*H*-1-benzopyran-2,8-dione (1b).

A mixture of 1 g (3.53 mmol) of 2*H*-1-benzopyran (**1a**) and 4 mL of concentrated sulfuric acid was heated for 90 min at 60–70 °C. After cooling, the solution was added to 40 g of ice, the separated solid was filtered and washed with a small amount of water to give 270 mg (63%) of benzoic acid. The filtrate was neutralized with solid $NaHCO_3$, the separated product was filtered and washed with a small amount of water to give 425 mg (67%) of compound (**1b**). An additional amount of product (82 mg, 13%) was obtained by extraction of filtrate with chloroform (4x100 mL). mp 236–239 °C (MeOH); ν_{max}/cm^{-1} 1690; ^{1}H NMR (60 MHz, DMSO-d_6) δ 1.90 (2H, m, CH_2), 2.30–2.75 (4H, m, two CH_2), 6.19 (1H, s, 4-H), 6.71 (2H, br s, NH_2). Anal. Calcd for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.32; H, 5.08; N, 7.89.

General procedure for the preparation of 8-hydrazono substituted *N*-(5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl)benzamides (3a–i).

A substituted hydrazine or amine (**2**) (1–2 mmol) was added to the mixture of benzopyran (**1a**) (1 mmol) in anhydrous ethanol (5 mL), followed by the addition of the appropriate catalyst. The reaction mixture was heated under reflux and, after cooling, the products were separated by filtration. Reaction conditions and yields are given in Table 1.

Procedure for the preparation of *N*-(5,6,7,8-tetrahydro- 8-hydroxyimino-2-oxo-2*H*-1-benzopyran-3-yl)benzamide (3j).

Hydroxylamine hydrochloride (70 mg, 1 mmol), benzopyran (**1a**) (283 mg, 1 mmol) and BF_3•Et_2O (21 mg, 0.15 mmol) were added to a solution prepared from 23 mg (1 mmol) of sodium and 2 mL of methanol. The reaction mixture was heated for 10 h and evaporated. After the addition of water (2 mL), the product was separated by filtration and crystallised from DMF/MeOH. Yield: 225 mg (80%).

Analytical and spectroscopic data of products (3a–j):

***N*-(8-Hydrazono-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl)benzamide (3a):** mp 204–206 °C (MeOH); ν_{max}/cm^{-1} 1615, 1655 br, 1680; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.80 (2H, m, 6-CH_2), 2.38 (2H, m) and 2.54 (2H, m) (5-CH_2, 7-CH_2), 7.03 (2H, s, NH_2), 7.53 (2H, m, Ph), 7.62 (1H, m, Ph), 7.93 (2H, m, Ph), 8.00 (1H, s, 4-H), 9.47 (1H, s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 80 °C) δ 19.8, 21.7, 25.4, 114.3, 122.5, 126.6, 128.0, 128.2, 131.4, 133.3, 134.6, 146.9, 158.2, 164.9; MS *m/z* 297 (M^+, 33%). Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.60; H, 5.15; N, 13.86.

***N*-(5,6,7,8-Tetrahydro-2-oxo-8-phenylhydrazono-2*H*-1-benzopyran-3-yl)benzamide (3b):** mp 257-260 °C (DMF/EtOH); ν_{max}/cm^{-1} 1665 br; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.89 (2H, m, 6-CH_2), 2.62 (4H, m, 5-CH_2, 7-CH_2), 6.83 (1H, m, 4-H of *N*-Ph), 7.24 (4H, m, *N*-Ph), 7.55 (2H, m, COPh), 7.63 (1H, m, COPh), 7.94 (2H, m, COPh), 8.06 (1H, s, 4-H), 9.55 (1H, br s, NH), 9.65 (1H, s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 80 °C) δ 20.0, 23.4, 25.5, 113.1, 116.0, 119.5, 123.0, 127.0, 128.2, 128.4, 128.5, 131.6, 133.3, 133.5, 144.9, 146.5, 158.2, 165.1; MS *m/z* 373 (M^+, 46%). Anal.Calcd for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.60; H, 5.16; N, 10.95.

***N*-(8-Dimethylhydrazono-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl)benzamide (3c):** mp 173-174 °C (DMF/EtOH); ν_{max}/cm^{-1} 1670 br; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.80 (2H, m, 6-CH_2), 2.62 (10H, m, 5-CH_2, 7-CH_2, *N*Me_2), 7.54 (2H, m, Ph), 7.63 (1H, m, Ph), 7.94 (2H, m, Ph), 8.08 (1H, s, 4-H), 9.55 (1H, s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 21.2, 25.9, 26.3, 47.0, 119.6, 125.2, 127.5, 128.2, 128.5, 132.2, 133.3, 145.2, 150.7, 158.1, 165.6; MS *m/z* 325 (M^+, 56%), 105 (100%). Anal.Calcd for $C_{18}H_{19}N_3O_3$: C, 66.45; H, 5.89; N, 12.91. Found: C, 66.26; H, 5.58; N, 13.01.

***N*-[8-(6-Chloropyridazin-3-yl)hydrazono-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl]benzamide (3d):** mp 300–302 °C (DMF/EtOH); ν_{max}/cm^{-1} 1695, 1668; ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ1.87 (2H, m, 6-CH_2), 2.63 (2H, m) and 2.74 (2H, m) (5-CH_2, 7-CH_2), 7.52–7.65 (4H, m, 3H of Ph, 4'-H), 7.75 (1H, d, 5'-H), 7.94 (2H, m, Ph), 8.10 (1H, s, 4-H), 9.60 (1H, br s, NH), 10.97 (1H, br s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 90 °C) δ19.9, 23.9, 25.5, 116.0, 118.6, 124.5, 126.9, 127.6, 128.1, 129.5, 131.6, 133.2, 139.6, 145.1, 148.0, 157.7, 158.8, 165.2; MS *m/z* 409 (M^+, 20%), 105 (100%). Anal. Calcd for $C_{20}H_{16}N_5O_3Cl$: C, 58.61; H, 3.94; N, 17.09. Found: C, 58.49; H, 3.69; N, 17.39.

***N*-(8-Acetylhydrazono-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl)benzamide (3e):** mp 291–293 °C (MeOH/DMF); ν_{max}/cm^{-1} 1660 br, 1698; ^{1}H NMR (300 MHz, DMSO-d_6, 60 °C) δ1.84 (2H, pseudo quintet, 6-CH_2), 2.18 (3H, br s, COMe), 2.60 (4H, m, 5-CH_2, 7-CH_2), 7.53 (2H, m, Ph), 7.61 (1H, m, Ph), 7.93 (2H, m, Ph), 8.08 (1H, s, 4-H), 9.43 (1H, br s, NH), 10.36 (1H, br s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 60 °C) δ20.1, 20.5, 24.1, 25.6, 119.8, 125.1, 127.2, 127.7, 128.3, 131.9, 133.2, 140.7, 144.9, 157.8, 165.5, 173 (signals at 20.5 and 140.7 were obtained by HMBC experiment); MS *m/z* 339 (M^+, 44%). Anal. Calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 64.03; H, 4.78; N, 12.23.

***N*-[8-(Imidazo[1,2-*b*]pyridazin-6-yl)hydrazono-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl]benzamide (3f):** mp 175–178 °C (DMF); ν_{max}/cm^{-1} 1662 br; ^{1}H NMR (300 MHz, DMSO-d_6) δ1.88 (2H, m, 6-CH_2), 2.63 (2H, m) and 2.71 (2H, m) (5-CH_2, 7-CH_2), 7.38 (1H, d, *J* 9.9, 7'-H), 7.59 (4H, m, 3H of Ph, 2'-H), 7.94 (2H, m, Ph), 8.02 (2H, m, 3'-H, 8'-H), 8.11 (1H, s, 4-H), 9.59 (1H, s, NH), 10.47 (1H, s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ20.2, 24.3, 25.7, 109.5, 116.4, 118.6, 124.4, 126.5, 127.5, 128.5, 129.0, 132.0, 132.2, 133.3, 136.7, 138.6, 145.8, 152.6, 158.2, 165.7; MS *m/z* 414 (M^+, 18%), 105 (100%). Anal.Calcd for $C_{22}H_{18}N_6O_3$: C, 63.76; H, 4.38; N, 20.28. Found: C, 63.67; H, 4.25; N, 20.37.

***N*-{5,6,7,8-Tetrahydro-2-oxo-8-[(1,2,4-triazolo[4,3-*b*]pyridazin-6-yl)hydrazono]-2*H*-1-benzopyran-3-yl}benzamide (3g):** mp 297–298 °C (DMF); ν_{max}/cm^{-1} 1628, 1674 br, 1705; ^{1}H NMR (300 MHz, DMSO-d_6) δ1.90 (2H, m, 6-CH_2), 2.64 (2H, m) and 2.72 (2H, m) (5-CH_2, 7-CH_2), 7.47 (1H, d, *J* 10.0, 7'-H), 7.54 (2H, m, Ph),7.64 (1H, m, Ph), 7.95 (2H, m, Ph), 8.12 (1H, s, 4-H), 8.22 (1H, dd, J_1 10.0, J_2 0.5, 8'-H), 9.39 (1H, d, *J* 0.5, 3'-H), 9.63 (1H, s, NH), 10.60 (1H, br s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 60 °C) δ 20.1, 24.3, 25.6, 114.4, 119.3, 124.6, 124.8, 127.2, 128.0, 128.3, 131.9, 133.2, 138.1, 140.5, 142.3, 145.1, 153.1, 157.9, 165.5; MS *m/z* 415 (M^+, 29%), 105 (100%). Anal. Calcd for $C_{21}H_{17}N_7O_3$: C, 60.72; H, 4.12; N, 23.60. Found: C, 60.37; H, 4.17; N, 23.29.

***N*-[8-(2-Chlorophenyl)hydrazono-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl]benzamide (3h):** mp 257–259 °C (DMF); ν_{max}/cm^{-1} 1670 br; ^{1}H NMR (300 MHz, DMSO-d_6, 60 °C) δ1.91 (2H, m, 6-CH_2), 2.63 (2H, m) and 2.71 (2H, m) (5-CH_2, 7-CH_2), 6.90 (1H, m, 4'-H), 7.33 (1H, m, 5'-H), 7.38 (1H, m, 3'-H), 7.58 (4H, m, 3H of Ph, 6'-H), 7.94 (2H, m, Ph), 8.08 (1H, s, 4-H), 8.52 (1H, br s, NH), 9.41 (1H, s,

NH); ^{13}C NMR (75.5 MHz, DMSO-d_6, 60 °C) δ20.0, 23.0, 25.5, 114.8, 117.7, 117.9, 120.8, 124.1, 127.2, 127.8, 128.3, 128.5, 128.9, 131.9, 133.3, 137.8, 140.4, 145.6, 158.0, 165.4; MS *m/z* 407 (M^+, 53%), 105 (100%). Anal. Calcd for $C_{22}H_{18}N_3O_3Cl$: C, 64.79; H, 4.45; N, 10.30. Found: C, 64.74; H, 4.52; N, 10.18.

***N*-{8-[(1,3-Dimethyl-4-nitropyrazol-5-yl)hydrazono]-5,6,7,8-tetrahydro-2-oxo-2*H*-1-benzopyran-3-yl}benzamide (3i):** mp 285–286 °C (DMF); ν_{max}/cm^{-1} 1670, 1700; ^{1}H NMR (300 MHz, $CDCl_3$) δ2.07 (2H, m, 6-CH_2), 2.49 (3H, s, Me), 2.68 (4H, m, 5-CH_2, 7-CH_2), 4.19 (3H, s, Me), 7.53 (2H, m, Ph), 7.60 (1H, m, Ph), 7.90 (2H, m, Ph), 8.36 (1H, s, 4-H), 8.82 (1H, br s, NH), 10.21 (1H, br s, NH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ14.6, 20.9, 23.6, 26.8, 40.7, 118.3, 121.4, 125.0, 126.5, 127.6, 129.4, 133.1, 133.7, 141.2, 142.5, 144.4, 145.5, 159.1, 166.5 (signal at 118.3 was obtained by HMBC experiment); MS *m/z* 436 (M^+, 25%), 105 (100%). Anal. Calcd for $C_{21}H_{20}N_6O_5$: C, 57.79; H, 4.62; N, 19.26. Found: C, 57.73; H, 4.72; N, 19.19.

***N*-(5,6,7,8-Tetrahydro-8-hydroxyimino-2-oxo-2*H*-1-benzopyran-3-yl)benzamide (3j):** mp 234–236 °C (decomp) (DMF/MeOH); ν_{max}/cm^{-1} 1645, 1695; ^{1}H NMR (300 MHz, DMSO-d_6) δ1.78 (2H, m, 6-CH_2), 2.58 (2H, m) and 2.62 (2H, m) (5-CH_2, 7-CH_2), 7.55 (2H, m, Ph), 7.61 (1H, m, Ph), 7.93 (2H, m, Ph), 8.07 (1H, s, 4-H), 9.57 (1H, s, NH), 11.68 (1H, s, OH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ20.1, 22.2, 25.8, 118.6, 125.1, 127.5, 128.4, 128.5, 132.2, 133.3, 144.5, 146.8, 157.9, 165.6; MS *m/z* 298 (M^+, 28%), 105 (100%). Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.25; H, 4.86; N, 9.52.

Hydrolysis of hydrazono derivative (3a).

A mixture of 10 mg (0.03 mmol) of compound (**3a**) and 1 mL of 18% hydrochloric acid was left at rt for 16.5 h. After neutralisation of the solution with solid $NaHCO_3$ the separated product was filtered and washed with a small amount of water to give 3.5 mg (37%) of compound (**1a**). mp 248–250 °C (DMF/MeOH) (lit.,[4] 248–250 °C).

***N*-(2,5,6,7,8,9-Hexahydro-2,9-dioxopyrano[2,3-*c*]azepin-3-yl)benzamide (4a).**

Method A. Sodium azide (2 g, 30.76 mmol) was added over a period of 30 min to a stirred mixture of the compound (**1a**) (1.5 g, 5.30 mmol) in chloroform (200 mL) and concentrated sulfuric acid (7.5 mL) at 0 °C. The reaction mixture was then stirred for 1.5 h at 0 °C and 2 h at rt. After the addition of ice and water (200 g) the p*H* value of the mixture was adjusted to 6 with solid $NaHCO_3$, the layers were separated, and the water layer was extracted with chloroform (3x200 mL). For the analysis the crude product (**4a**) (1.46 g, 93%) was crystallised from DMF/MeOH. mp 298–301 °C (decomp); ν_{max}/cm^{-1} 1710, 1655; ^{1}H NMR (300 MHz, DMSO-d_6) δ1.94 (2H, pseudo quintet, 6-CH_2), 2.61 (2H, pseudo t, 5-CH_2), 3.14 (2H, app. dt, $J_1 = J_2$ *ca*. 6, 7-CH_2), 7.55 (2H, m, Ph), 7.64 (1H, m, Ph), 7.95 (2H, m, Ph), 8.17 (1H, s, 4-H), 8.36 (1H, br

t, 8-H), 9.65 (1H, br s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 26.2, 29.1, 38.3, 119.7, 126.5, 127.6, 128.6, 128.8, 132.3, 133.3, 143.8, 157.8, 163.6, 165.9; MS *m/z* 298 (M^+, 28%), 105 (100%). Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.61; H, 4.68; N, 9.61.

Method B. Sodium azide (200 mg, 3.07 mmol) was added over a period of 10 min to a stirred solution of the hydrazono compound (**3a**) (149 mg, 0.50 mmol) in 20 mL of chloroform and 0.75 mL of concentrated sulfuric acid at 0 °C. Stirring for 1.5 h at 0 °C and 1.5 h at rt was followed by neutralisation and extraction with chloroform (3x30 mL) to give 114 mg (96%) of **4a**.

Method C. From 50 mg (0.14 mmol) of derivative (**3b**), 67 mg (1.03 mmol) of sodium azide, 6.7 mL of chloroform and 0.25 mL of concentrated sulfuric acid by method B. Yield: 23 mg (55%) of **4a**.

Method D. From 339 mg (1 mmol) of derivative (**3e**), 500 mg (8 mmol) of sodium azide, 40 mL of chloroform and 1.5 mL of concentrated sulfuric acid by method B. Yield: 285 mg (96%) of **4a**.

3-Amino-5,6,7,8-tetrahydropyrano[2,3-*c*]azepine-2,9-dione (4b).

Method A. A mixture of 298 mg (0.999 mmol) of pyranoazepine (**4a**) and 1.2 mL of concentrated sulfuric acid was heated for 2.5 h at 60 °C. After cooling, the solution was added to 12 g of ice, the separated benzoic acid (86 mg, 70%) was filtered and washed with a small amount of water. The p*H* value of the filtrate was adjusted to 5 with solid $NaHCO_3$. The separated **4b** (100 mg, 52%) was filtered and washed with a small amount of water. An additional amount (15 mg, 8%) of the same product was obtained by extraction of the filtrate with chloroform (5x20 mL). mp 257–260 °C (decomp) (MeOH); ν_{max}/cm^{-1} 1690, 1650; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.86 (2H, pseudo quintet, 6-CH_2), 2.47 (2H, pseudo t, 5-CH_2), 3.06 (2H, app. dt, $J_1 = J_2$ *ca.* 6, 7-CH_2), 6.00 (2H, s, NH_2), 6.19 (1H, s, 4-H), 8.97 (1H, br t, 8-H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 26.9, 29.1, 38.9, 110.6, 122.7, 136.3, 137.1, 158.5, 164.6; MS *m/z* 194 (M^+, 100%). Anal.Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.89; H, 5.26; N, 14.31.

Method B. Sodium azide (240 mg, 3.69 mmol) was added over a period of 10 min to a stirred solution of the compound (**1b**) (100 mg, 0.56 mmol) in chloroform (24 mL) and concentrated sulfuric acid (0.9 mL) at 0 °C. The reaction mixture was then stirred for 1.5 h at 0 °C and 1.5 h at rt. After the addition of ice and water (24 g) the p*H* value of the mixture was adjusted to 6 with solid $NaHCO_3$, the layers were separated and the water layer was extracted with chloroform (5x30 mL). Yield: 45 mg (42%) of **4b**.

***N*-[(1-Amino-2,5,6,7,8,9-hexahydro-2,9-dioxo-1*H*-pyrido[2,3-*c*]azepin-3-yl]benzamide (5a).**

A mixture of 149 mg (0.5 mmol) of pyranoazepine (**4a**), 90 mg (1.8 mmol) of 98% hydrazine hydrate and 3 mL of anhydrous ethanol was refluxed for 6 h. After cooling, the solid was filtered under nitrogen atmosphere and washed with ethanol to give 103 mg (66%) of **5a**. mp 240–242 °C (MeOH); ν_{max}/cm^{-1} 1650; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.90 (2H, pseudo quintet, 6-CH_2), 2.58 (2H, pseudo t, 5-CH_2),

3.10 (2H, app. dt, $J_1 = J_2$ *ca*. 6, 7-CH_2), 6.55 (2H, s, NH_2), 7.60 (3H, m, Ph), 7.93 (2H, m, Ph), 8.21 (1H, s, 4-H), 8.73 (1H, br t, 8-H), 9.43 (1H, br s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 27.1, 29.7, 37.9, 116.5, 122.2, 127.2, 128.2, 128.8, 129.6, 132.2, 133.7, 152.4, 164.4, 165.1; MS *m/z* 312 (M^+, 56%), 105 (100%). Anal. Calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.65; H, 5.05; N, 17.96.

***N*-[(2,5,6,7,8,9-Hexahydro-2,9-dioxo-1-phenylamino-1*H*-pyrido[2,3-*c*]azepin-3-yl]benzamide (5b).**
A mixture of 149 mg (0.5 mmol) of pyranoazepine (**4a**) and 1 mL (9.85 mmol) of 97% phenylhydrazine was refluxed for 50 min. After cooling, 1 mL of ethanol and 20 mL of ether were added, the separated product was filtered and washed with ether. Yield 60 mg (31%). mp 256–258 °C (DMF/EtOH); ν_{max}/cm^{-1} 1658; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.92 (2H, pseudo quintet, 6-CH_2), 2.62 (2H, pseudo t, 5-CH_2), 3.09 (2H, app. dt, $J_1 = J_2$ *ca*. 6, 7-CH_2), 6.57 (1H, m, 4-H of *N*-Ph), 6.78 (2H, m, *N*-Ph), 7.09 (2H, m, *N*-Ph), 7.61 (3H, m, COPh), 7.93 (2H, m, COPh), 8.28 (1H, s, 4-H), 8.36 (1H, br t, 8-H), 8.92 (1H, br s, NH), 9.40 (1H, s, NH); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 27.6, 29.5, 38.6, 111.5, 116.6, 117.8, 124.6, 127.1, 128.4, 128.9, 130.1, 130.7, 132.2, 133.6, 152.5, 156.4, 164.9, 165.6; MS *m/z* 388 (M^+, 35%). Anal. Calcd for $C_{22}H_{20}N_4O_3$: C, 68.03; H, 5.19; N, 14.42. Found: C, 68.00; H, 5.02; N, 14.21.

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