Reactions of 4-Oxo-4*H*-1-benzopyran-3-carboxylic Acids with Phenylhydrazine, Guanidine, and Hydroxylamine

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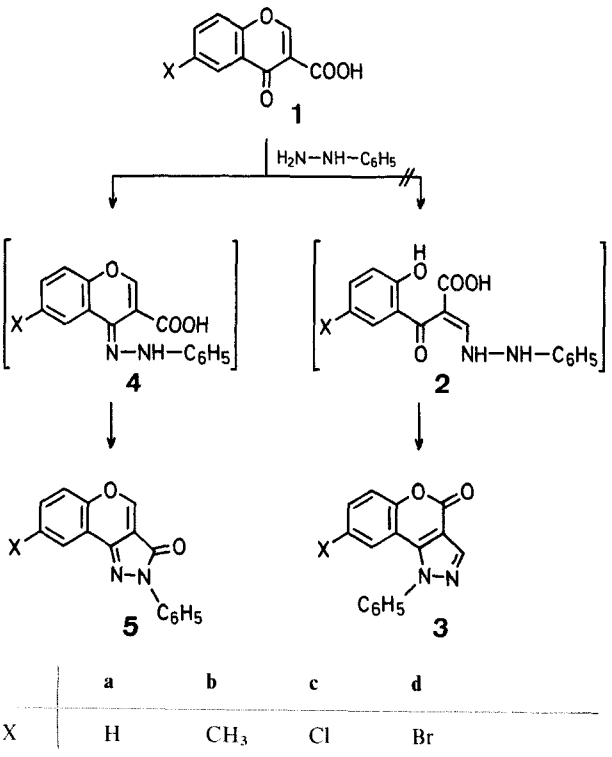
4-Oxo-4*H*-1-benzopyrans (chromones) react with hydrazine or phenylhydrazine to produce 3(5)-*o*-hydroxyphenylpyrazoles[1,2]. Chromone-3-carboxaldehydes react with guanidine to form 2-amino-5-hydroxy-5*H*-[1]benzopyrano[4,3-*d*] pyrimidines[3]. Chromone-3-carboxylic esters and 3-haloacylchromones, on treatment with mild alkali, rearrange to give 3-acyl-4-hydroxycoumarins[4,5,6] and 3,5-dioxo-2,3-dihydro-1-benzoxepin-4-carboxaldehydes[7], respectively. Chromone-3-carbonitriles react with acetylacetone in the presence of piperidine to afford 3-acetyl-2-methyl-[1]benzopyrano[2,3-*b*]pyridin-5(5*H*)-ones[8]. In all these reactions, the nucleophiles undergo Michael addition to the γ-pyrone system with concomitant opening of the pyrone ring followed by new cyclisation(s). We thus anticipated that phenylhydrazine would likewise undergo [1,4]-addition to the α,β-unsaturated keto-function of chromone-3-carboxylic acid (**1**) with consequent cleavage of the pyrone ring, and the intermediate **2**, thus formed, would further lactonise and cyclise to yield the 1-phenyl-[1]benzopyrano[4,3-*c*]pyrazol-4-(1*H*)-one (**3**) [Scheme A]. It should be mentioned here that the coumarinopyrazole system **3** has so far been synthesised by reacting either 4-chloro- or 4-hydroxy-3-formylcoumarins with phenylhydrazine[9,10].

However, by refluxing an equimolar mixture of chromone-3-carboxylic acid (**1a**) and phenylhydrazine or phenylhydrazine hydrochloride in ethanol or acetic acid, a compound different from, but isomeric with, the pyrazolone **3a**[9] was obtained. On the basis of its spectral data, this compound was assigned as 2-phenyl-[1]benzopyrano[4,3-*c*]pyrazol-3(2*H*)-one (**5a**), and its formation can be rationalised as follows: with phenylhydrazine the keto-function of **1a** is first derivatised, the intermediate **4a** (non-isolable) thus formed undergoing further cyclisation (Scheme A). Various 8-substituted benzopyrano-pyrazoles **5** were synthesised by reacting the appropriate 6-substituted chromone-3-carboxylic acids **1** with phenylhydrazine.



	a	b	c	d
X	H	CH_3	Cl	Br

Scheme A

Application of the same reasonings as put forward in Scheme A reveals that [1,4]-addition of guanidine to the chromones **1** would ultimately lead to the formation of 2-amino-[1]benzopyrano[4,3-*d*]pyrimidin-5(5*H*)-ones (**6**), whereas [1,2]-addition would give 2-amino-[1]benzopyrano[4,3-*d*]pyrimidin-4(4*H*)-ones (**7**).

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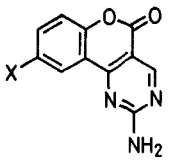

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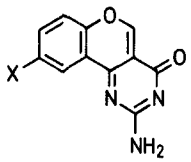

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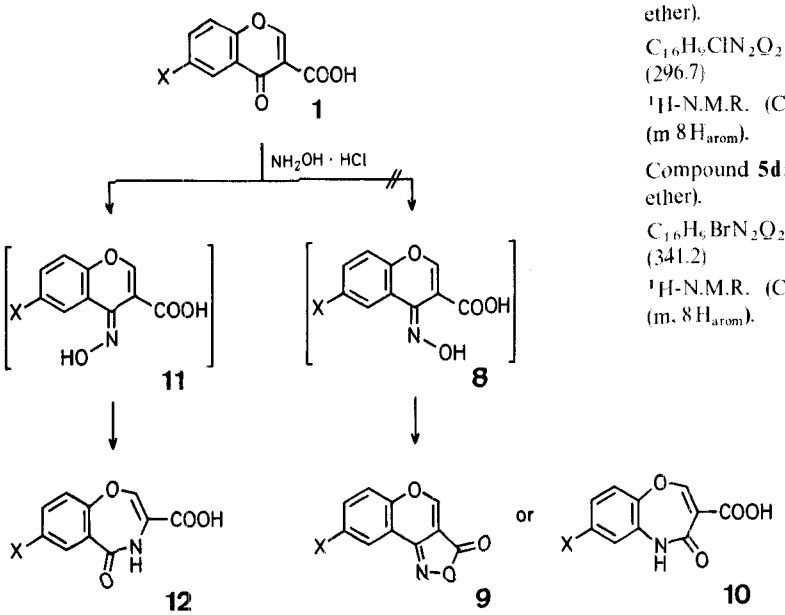
The product obtained by refluxing **1a** with an equivalent amount of guanidine carbonate in ethanol, although analysing for $C_{11}H_7N_3O_2$ ($M^{\oplus}$, 213), was found to be different (comparison of I.R. spectra) from an authentic sample of **6a** prepared according to the method of Petersen and Heitzer[3]; so the structure of 2-amino-[1]benzopyrano[4,3-*d*]pyrimidin-4(4*H*)-one (**7a**) was assigned to it. Structure **7a** is also supported by its N.M.R. spectrum. The other chromones **1b–d** reacted similarly with guanidine carbonate to afford the pyrimidinones **7b–d**.

Hydroxylamine hydrochloride underwent likewise [1,2]-addition to the chromone-carboxylic acid **1** to give an oxime as the intermediate. Had this intermediate existed in (*Z*)-isomeric form **8**, it would either cyclise to the oxazolone **9** or undergo Beckmann transformation (migration of the bond *anti* to OH group) to yield the oxazepin **10**, whereas its (*E*)-isomeric form **11** would rearrange to the oxazepin **12** [Scheme **B**]. Interaction of 6-methylchromone-3-carboxylic acid (**1b**) with hydroxylamine hydrochloride, however, gave an acidic compound that might be assigned as either **10b** or **12b**. ^{1}H-N.M.R. spectra of this compound and its methyl ester could not distinguish between these two structures. However, its mass spectral fragmentation can be explained only by the structure of 7-methylbenzo[*f*]1,4-oxazepin-3-carboxylic acid (**12b**).



	a	b	c	d
X	H	CH_3	Cl	Br

Scheme **B**

The exclusive formation of the oxazepin **12** by interaction of **1** with hydroxylamine hydrochloride indicates that the intermediate oxime is formed in the (*E*)-isomeric form **11**, and the latter undergoes Beckmann transformation at a faster rate than its isomerisation to the (*Z*)-form **8**. In reactions of **1** with phenylhydrazine and guanidine, it may be assumed that the intermediates are initially formed in the (*E*)-isomeric forms that isomerise to the (*Z*)-forms under the reaction conditions, and the latter cyclise to give **5** and **7**, respectively. Though a proper explanation for [1,2]-instead of [1,4]-addition of the nucleophiles considered here to the γ-pyrone system **1** is lacking, it is speculated that the negative dipole of the COOH group or the carboxylate anion reduces the electrophilicity at C-2 and thereby supresses the addition of the nucleophiles at this position.

2-Phenyl-[1]benzopyrano[4,3-*c*]pyrazol-3(2*H*)-one (5a); Typical Procedure:

A mixture of **1a**[11,12] (0.38 g, 0.002 mol) and phenylhydrazine (0.21 g, 0.002 mol) or phenylhydrazine hydrochloride (0.28 g, 0.002 mol) is heated under reflux in acetic acid (10 ml) or ethanol (15 ml) for 3 h. The mixture is then concentrated and cooled to precipitate **5a**; yield: 0.45 g (85%); m.p. 191° (benzene/light petroleum ether).

$C_{16}H_{10}N_2O_2$	calc.	C 73.27	H 3.84	N 10.68
(262.3)	found	73.21	3.61	10.71

I.R. ($CHCl_3$): ν_{max} = 1740 (lactam C=O), 1620 cm^{-1} (C=N or C=C).

^{1}H-N.M.R. ($CDCl_3$): δ = 8.25 (s, 1H, H-4); 7.79–7.01 ppm (m, 9H_{arom}).

M.S. (70 eV): m/e = 262 ($M^{\oplus}$, 100%).

Similarly prepared are compounds **5b**; yield: 83%; m.p. 204° (chloroform).

$C_{17}H_{12}N_2O_2$	calc.	C 73.90	H 4.38	N 10.14
(276.3)	found	74.02	4.21	10.22

^{1}H-N.M.R. ($CDCl_3$): δ = 8.32 (s, 1H, H-4); 7.62–6.87 (m, 8H_{arom}); 2.17 ppm (s, 3H, CH_3).

Compound **5c**; yield: 80%; m.p. 222° (benzene/light petroleum ether).

$C_{16}H_9ClN_2O_2$	calc.	C 64.76	H 3.06	N 9.44
(296.7)	found	64.48	2.88	9.41

^{1}H-N.M.R. ($CDCl_3$): δ = 8.28 (s, 1H, H-4); 7.82–6.89 ppm (m 8H_{arom}).

Compound **5d**; yield: 81%; m.p. 205° (benzene/light petroleum ether).

$C_{16}H_9BrN_2O_2$	calc.	C 56.32	H 2.66	N 8.21
(341.2)	found	56.45	2.89	8.07

^{1}H-N.M.R. ($CDCl_3$): δ = 8.24 (s, 1H, H-4); 7.80–7.02 ppm (m, 8H_{arom}).

2-Amino-[1]benzopyrano[4,3-*d*]pyrimidin-4(4*H*)-one (7a); Typical Procedure:

A mixture of **1a** (0.38 g, 0.002 mol) and guanidine carbonate (0.18 g, 0.001 mol) is heated under reflux in ethanol (20 ml) for 4 h, then cooled and the product **7a** filtered; yield: 0.25 g (60%); m.p. 290° dec. (acetic acid/water).

$C_{11}H_7N_3O_2$	calc.	C 61.97	H 3.31	N 19.71
(213.2)	found	61.72	3.06	19.52

I.R. (KBr): ν_{max} = 3475, 3340 (NH_2), 1730 (lactam C=O), 1660 (pyrone C=O), 1640 (C=N), 1605 cm^{-1} (C=C).

^{1}H-N.M.R. (DMSO-d_6): δ = 8.42 (s, 1 H, H-5); 8.31–7.20 ppm (m, 6 H, H_{arom} + NH_2).

M.S. (70 eV): m/e = 213 ($M^{\oplus}$, 100 %); 185 (M – CO, 18 %); 171 (M – NH_2CN, 69 %); 143 (M – CO—NH_2CN, 31 %).

Similarly prepared are compounds **7b**; yield: 51 %; m.p. 300° dec. (acetic acid).

$C_{12}H_9N_3O_2$	calc.	C 63.43	H 4.00	N 18.49
(227.2)	found	63.65	3.87	18.62

^{1}H-N.M.R. (DMSO-d_6): δ = 8.48 (s, 1 H, H-5); 8.21–7.02 (m, 5 H, H_{arom} + NH_2); 2.21 ppm (s, 3 H, CH_3).

Compound **7c**; yield: 47 %; m.p. 218–221° (ethanol).

$C_{11}H_6ClN_3O_2$	calc.	C 53.36	H 2.44	N 16.97
(247.6)	found	53.58	2.46	17.12

^{1}H-N.M.R. (DMSO-d_6): δ = 8.47 (s, 1 H, H-5); 8.35–7.15 ppm (m, 5 H, H_{arom} + NH_2).

Compound **7d**; yield: 49 %; m.p. 193° dec. (ethanol).

$C_{11}H_6BrN_3O_2$	calc.	C 45.22	H 2.07	N 14.38
(292.1)	found	45.41	2.21	14.49

^{1}H-N.M.R. (DMSO-d_6): δ = 8.45 (s, 1 H, H-5); 8.26–7.26 ppm (m, 5 H, H_{arom} + NH_2).

7-Methyl-5-oxo-4,5-dihydrobenzo[*f*]-1,4-oxazepin-3-carboxylic Acid (12b); Typical Procedure:

A mixture of **1b**[11, 12] (0.41 g, 0.002 mol) and hydroxylamine hydrochloride (0.14 g, 0.002 mol) is heated under refluxed in petroleum ether (30 ml) for 4 h, concentrated, and then diluted with water, and the precipitated solid filtered and crystallised from chloroform to give pure **12b**; yield: 0.32 g (73 %); m.p. 178°.

$C_{11}H_9NO_4$	calc.	C 60.27	H 4.14	N 6.39
(219.2)	found	59.98	3.94	6.32

I.R. ($CHCl_3$): ν_{max} = 3675 (carboxylic OH), 3540 (NH), 1610 cm^{-1} (C=O).

^{1}H-N.M.R.: δ = 10.30 (s, 1 H, exchangeable with D_2O, COOH); 8.60 (d, J = 2 Hz, 1 H, H-6); 7.63 (s, 1 H, H-2); 7.20–6.87 (m, 3 H, 2 H_{arom} + NH); 2.30 ppm (s, 3 H, CH_3).

M.S. (70 eV): m/e = 175 (M – CO_2, 100 %); 148 (M – CO_2 – C_2H_2 – H, 20 %); 135 (M – CO_2 – CH_2CN, 77 %); 119 (38 %).

Similarly prepared are compounds **12a**; yield: 77 %; m.p. 192° (benzene).

$C_{10}H_7NO_4$	calc.	C 58.53	H 3.44	N 6.82
(205.2)	found	58.42	3.20	6.75

^{1}H-N.M.R. (DMSO-d_6): δ = 10.32 (s, 1 H, COOH); 8.52–6.90 ppm (m, 6 H, H_{arom} + NH_2).

M.S. (70 eV): m/e = 161 (M – CO_2, 100 %); 134 (M – C_2H_2 – H; 18 %); 121 (M – CO_2 – CH_2CN, 76 %); 105 (36 %); 93 (33 %).

Compound **12c**; yield: 72 %; m.p. 198° (benzene).

$C_{10}H_6ClNO_4$	calc.	C 50.12	H 2.52	N 5.85
(239.6)	found	50.37	2.41	5.93

^{1}H-N.M.R. (DMSO-d_6): δ = 10.34 (s, 1 H, COOH); 8.62 (d, J = 3 Hz, 1 H, H-6); 7.61 (s, 1 H, H-2); 7.22–6.84 ppm (m, 3 H, H_{arom} + NH).

Compound **12d**; yield: 69 %; m.p. 208–212° (chloroform).

$C_{10}H_6BrNO_4$	calc.	C 42.27	H 2.13	N 4.93
(284.1)	found	42.50	2.20	5.15

^{1}H-N.M.R. (DMSO-d_6): δ = 10.32 (s, 1 H, COOH); 8.63 (d, J = 3 Hz, 1 H, H-6); 7.62 (s, 1 H, H-2), 7.23–6.82 ppm (m, 3 H, H_{arom} + NH).

Methyl 7-Methyl-5-oxo-4,5-dihydrobenzo[*f*]-1,4-oxazepin-3-carboxylate (Methyl Ester of 12b):

Usual treatment of acid **12b** (0.22 g, 0.001 mol) in methanol (7 ml) with an ethereal solution (30 ml) of diazomethane [prepared from nitrosomethylurea (1.2 g)] gives the crude methyl ester of **12b**; yield: 0.20 g (90 %); m.p. 118–124°. Recrystallisation from chloroform/light petroleum ether gives pure crystals; yield: 0.18 g (75 %); m.p. 127–29°.

$C_{12}H_{11}NO_4$	calc.	C 61.80	H 4.76	N 6.01
(233.2)	found	62.05	H 4.63	6.12

^{1}H-N.M.R. ($CDCl_3$): δ = 8.27 (d, J = 2 Hz, 1 H, H-6); 7.72 (s, 1 H, H-2); 7.27–6.67 (m, 3 H, 2 H_{arom} + NH); 3.87 (s, 3 H, $COOCH_3$); 2.33 ppm (s, 3 H, H_3C—C-7).

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