Isomerisation of 2-Aryl-4-oxo-2,3-dihydrobenzopyrano[2,3-*d*]pyrimidines to 2-Aryl-4-hydroxy-5*H*-benzopyrano[2,3-*d*]pyrimidines

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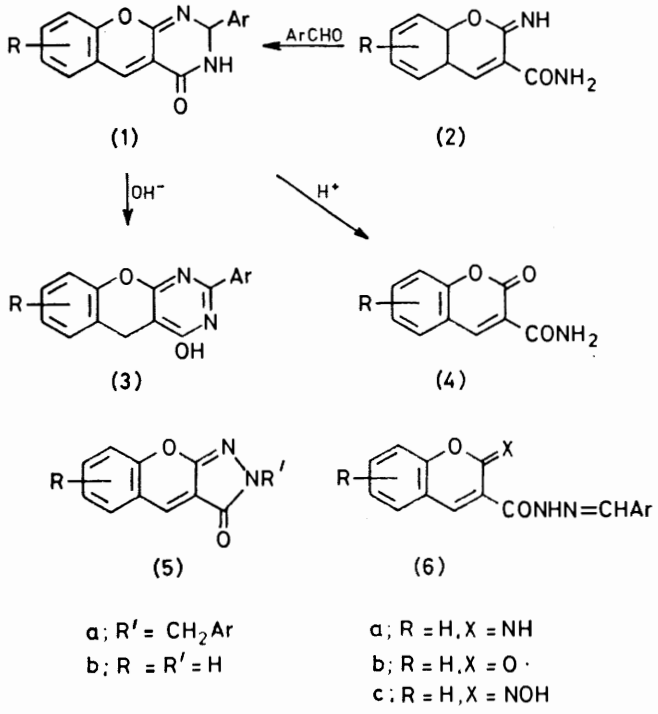
The base-catalysed condensation of 3-carbamoyl-2-iminochromen with aromatic aldehydes yields 2-aryl-4-oxo-2,3-dihydrobenzopyrano[2,3-*d*]pyrimidines, which isomerise to stable 2-aryl-4-hydroxy-5*H*-benzopyrano[2,3-*d*]-pyrimidines. The synthesis of 3-oxo-2*H*-benzopyrano[2,3-*c*]pyrazole is also described.

2-ARYL-4-OXO-2,3-DIHYDROBENZOPYRANO[2,3-*d*]PYRIMIDINE derivatives (1; R = H) have been synthesised by the base-catalysed condensation of 3-carbamoyl-2-iminochromen (2; R = H) with aromatic aldehydes.[1] A number of new derivatives are listed in Table 1. Aromatic aldehydes in general give satisfactory products, but while it is clear that aliphatic, aralkyl, and heterocyclic aldehydes react with the iminochromen (2; R = H), they form only viscous gums from which satisfactory crystalline products cannot be isolated.



(An exception is cyclohexanecarbaldehyde which yields 2-cyclohexyl-4-oxo-2,3-dihydrobenzopyrano[2,3-*d*]-pyrimidine.) As well as the compounds (1; R = H), some substituted derivatives (R ≠ H) have also been prepared, although yields tend to be smaller; using piperonal, a variety of substituted 2-(3,4-methylenedioxyphenyl)-4-oxo-2,3-dihydrobenzopyrano[2,3-*d*]-pyridimidines (1; Ar = 3,4-methylenedioxyphenyl, R ≠ H) have been prepared (*cf.* Table 1). (A minor by-product obtained from the reaction of piperonal with substituted 3-carbamoyl-2-iminochromens, is α-cyano-3,4-methylenedioxycinnamamide, obtained by displacement of the substituted salicylidene residue.)

Under mild acid conditions, the pyrimidine ring in the tricyclic compounds (1) readily undergoes ring-opening and cleavage; addition of semicarbazide hydrochloride to the compounds (1; R = H) results in the production of 3-carbamoylcoumarin (4; R = H) and the appropriate aldehyde semicarbazone.

Prolonged heating of the compounds (1) in ethanol containing piperidine causes rearrangement to take place with formation of the high-melting insoluble isomers (3). [The formation of small amounts of isomeric materials during the synthesis of a few derivatives of (1) had previously been noted;[1] it is now clear that they are obtainable from all the compounds (1).] The same rearrangement takes place thermally when the compounds (1) are heated above their melting points. Table 2 is a list of the new compounds (3) obtained either in the course of preparation of (1), or from (1) by thermal rearrangement or by prolonged heating in ethanol containing piperidine.

The compounds (1) are structurally similar to 2-aryl-4-oxo-2,3-dihydroquinazolines, which readily lose hydrogen with formation of the corresponding 4-quinazolones,[2] but it is clear from the analytical data in Table 2 that no loss of hydrogen occurs during rearrangement, and that only an internal transfer of hydrogen takes place. The products (3) are unreactive and are stable to acid [unlike the parent compounds (1) from which 3-carbamoylcoumarin is obtained in almost theoretical yield]. The C=O (1 680—1 690 cm^{-1}) and N–H (3 140 cm^{-1}) absorption characteristic of the compounds (1) is absent from the i.r. spectra of (3), in which a weak absorption at 2 600—2 800 cm^{-1} suggests the presence of bonded OH. The application of n.m.r. is limited by the lack of solubility of the hydroxy-compounds; 2-cyclohexyl-4-hydroxy 5*H*-benzopyrano[2,3-*d*]pyrimidine (which is the only one of the series sufficiently soluble for examination) shows that the pyran H-5 (7.9, s) and pyrimidine H-2 resonances (5.0, m), characteristic of the oxo-isomers (1), are replaced by CH_2 (3.65, s). Compounds of type (1) in which the hydrogen on the 3-position is replaced by a substituent [1] fail to undergo any rearrangement.

The oxo-compounds (1) display anti-tumour activity when tested against the P.388 lymphocytic leukaemia in mice, but the hydroxy-compounds (3) are inactive; full details will be published elsewhere.

Attempts to synthesise a third isomer (5a) were unsuccessful but the 2-unsubstituted parent compound (5b) has been synthesised. The hydrazono-derivatives (6a) cyclise in the presence of hydroxylamine, the aryl substituent Ar being eliminated as an aldoxime. The

TABLE 1

New 2-aryl-4-oxo-2,3-dihydrobenzopyrano[2,3-*d*]pyrimidine derivatives (1)

R	Ar	M.p.[a] (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
H	C_6H_4Me-2	235—237	74.2	4.8	9.6	$C_{18}H_{14}N_2O_2$	74.5	4.8	9.7
H	$C_6H_3(OMe)_2$-3,4	212—213	67.5	4.8	8.2	$C_{19}H_{16}N_2O_4$	67.9	4.8	8.3
H	$C_6H_4NHCOMe$-4	245—247	68.1	4.5	12.5	$C_{19}H_{15}N_3O_3$	68.5	4.5	12.6
H	CH=CHPh	230	75.3	4.6	9.2	$C_{19}H_{14}N_2O_2$	75.5	4.6	9.3
H	Cyclohexyl	251—252	72.6	6.5	9.7	$C_{17}H_{18}N_2O_2$	72.3	6.4	9.9
7-OCH_3	$C_6H_3(OCH_2O)$-3,4 [b]	250—252	64.7	4.0	7.9	$C_{19}H_{14}N_2O_5$	65.1	4.0	8.0
9-OCH_3	$C_6H_3(OCH_2O)$-3,4 [b]	256—258	65.2	4.1	8.3	$C_{19}H_{14}N_2O_5$	65.1	4.0	8.0
9-OC_2H_5	$C_6H_3(OCH_2O)$-3,4 [b]	245—246	65.8	4.5	7.5	$C_{20}H_{16}N_2O_5$	65.9	4.4	7.7
7-Cl	$C_6H_3(OCH_2O)$-3,4 [b]	245	60.6	3.0	8.0	$C_{18}H_{11}ClN_2O_4$	60.9	3.1	7.9

[a] Resolidification takes place above the m.p. [b] 3,4-Methylenedioxyphenyl.

dark red 3-oxo-2*H*-benzopyrano[2,3-*c*]pyrazole (5b) displays the anticipated N–H (3 170 cm^{-1}) and C=O (1 685 cm^{-1}) absorption. Among the by-products of the reaction, the coumarin derivatives (6b) and 2-hydroxyiminochromen derivatives (6c) have been identified. When the latter are refluxed in ethanol no reaction occurs, but addition of hydroxylamine hydrochloride brings about formation of the cyclised compound (5b), with elimination of the arylidene residue as an aldoxime.

EXPERIMENTAL

T.l.c. was performed on Merck silica gel, and the products were detected using a u.v. lamp. Satisfactory analyses, within the following tolerances, were obtained for all new compounds: C ±0.4%; H ±0.2%; N ±0.3%. I.r. spectra were recorded on Nujol mulls, and n.m.r. spectra in dimethyl sulphoxide; for 2-cyclohexyl-4-hydroxy-5*H*-benzopyrano[2,3-*d*]pyrimidine a saturated solution at 115 °C was used.

Preparation of (1) *and* (3).—The following preparation is typical. A solution of 3-carbamoyl-2-iminochromen [3] (1.88 g) and 3,4-dimethoxybenzaldehyde (1.66 g) in ethanol (100 ml) containing piperidine (0.2 ml) was refluxed for 3 h, then stored at 20 °C overnight. The crude material which separated was collected and dried, and then repeatedly extracted with boiling ethanol. This left undissolved 2-(3,4-*dimethoxyphenyl*)-4-*hydroxy*-5H-*benzopyrano*[2,3-d]-*pyrimidine* [3; R = H, Ar = 3,4-$(OMe)_2C_6H_3$] which, following repeated recrystallisation from dimethylformamide, had m.p. 293—295 °C; $\nu_{max.}$ 2 600—2 800w (bonded OH) and 1 635 (–C=N–) cm^{-1}; 0.29 g (9%). From the ethanol extracts, 2-(3,4-*dimethoxyphenyl*)-4-*oxo*-2,3-*dihydrobenzopyrano*[2,3-d]*pyrimidine* (1; R = H, Ar = C_6H_3-$(OMe)_2$-3,4) crystallised and, after recrystallisation from ethanol, had m.p. 212 °C (with re-solidification and subsequent re-melting at 288—293 °C); $\nu_{max.}$ 3 170 (N–H) and 1 695 (C=O) cm^{-1}; 0.55 g (16%).

With most aldehydes it was found that an increase in the heating period to 6 h resulted in an increased yield of the hydroxy-compounds (3), with a corresponding decrease in the amount of oxo-compounds (1). However, from benzaldehyde, *o*-toluic aldehyde, and cyclohexanecarbaldehyde, only the oxo-compounds (1) were obtained; subsequently the corresponding hydroxy-compounds (3) were obtained by thermal rearrangement of the oxo-compounds.

After the reaction of piperonal with a number of substituted 3-carbamoyl-2-iminochromens (2; R ≠ H) and removal of the products [(1; R ≠ H, Ar = 3,4-methylenedioxyphenyl) and (3; R ≠ H, Ar = 3,4-methylenedioxyphenyl)], the residues yielded small amounts (*ca.* 3%) of a benzene-soluble material identified as α-cyano-3,4-methylenedioxycinnamamide.[4]

Acid Degradation of the Oxo-compounds (1).—The following sequence is typical. To a solution of 4-oxo-2-phenyl-2,3-dihydrobenzopyrano[2,3-*d*]pyrimidine (1; R = H, Ar = Ph) (0.276 g) in ethanol–water (90 ml : 10 ml) was added 2N hydrochloric acid (2 ml). The mixture was refluxed for

TABLE 2

2-Aryl-4-hydroxy-5*H*-benzopyrano[2,3-*d*]pyrimidines (3)

R	Ar	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N	Formula less 2 H would require H
H	C_6H_5	295—298	74.0	4.4	10.2	$C_{17}H_{12}N_2O_2$	73.9	4.3	10.1	3.6
H	C_6H_4Me-2	>300	74.8	4.7	9.7	$C_{18}H_{14}N_2O_2$	74.5	4.8	9.7	4.2
H	C_6H_4Me-4	291—294	74.1	4.8	9.6	$C_{18}H_{14}N_2O_2$	74.5	4.8	9.7	4.2
H	C_6H_4OH-2	300—301	69.7	4.2	9.3	$C_{17}H_{12}N_2O_3$	69.9	4.1	9.6	3.4
H	C_6H_4OH-4	285—287	69.5	4.0	9.7	$C_{17}H_{12}N_2O_3$	69.9	4.1	9.6	3.4
H	$C_6H_4OMe_3$-4	285—288	70.2	4.7	9.2	$C_{18}H_{14}N_2O_3$	70.6	4.6	9.1	3.9
H	$C_6H_3(OMe)_2$-3,4	293—295	67.7	4.8	8.5	$C_{19}H_{16}N_2O_4$	67.9	4.8	8.3	4.2
H	$C_6H_4NHCOMe$-4	>300	68.2	4.7	12.2	$C_{19}H_{15}N_3O_3$	68.5	4.5	12.6	3.9
H	C_6H_4Cl-4	310	65.4	3.7	8.9	$C_{17}H_{11}ClN_2O_2$	65.7	3.5	9.0	2.9
H	CH=CHPh	281—283	75.2	4.6	9.2	$C_{19}H_{14}N_2O_2$	75.5	4.6	9.3	4.0
H	Cyclohexyl	296—299	71.9	6.5	9.6	$C_{17}H_{18}N_2O_2$	72.3	6.4	9.9	5.7
H	$C_6H_3(OCH_2O)$-3,4 *	>300	67.4	3.6	9.1	$C_{18}H_{12}N_2O_4$	67.5	3.8	8.8	3.1
7-OCH_3	$C_6H_3(OCH_2O)$-3,4 *	283—285	65.2	4.1	8.0	$C_{19}H_{14}N_2O_5$	65.1	4.0	8.0	3.4
9-OCH_3	$C_6H_3(OCH_2O)$-3,4 *	290—291	64.8	4.2	8.0	$C_{19}H_{14}N_2O_5$	65.1	4.0	8.0	3.4
9-OC_2H_5	$C_6H_3(OCH_2O)$-3,4 *	>300	65.5	4.5	7.5	$C_{20}H_{16}N_2O_5$	65.9	4.4	7.7	3.9
7-Cl	$C_6H_3(OCH_2O)$-3,4 *	>300	60.5	2.8	8.0	$C_{18}H_{11}ClN_2O_4$	60.9	3.1	7.9	2.6

* 3,4-Methylenedioxyphenyl.

45 min, then cooled to −20 °C, when 3-carbamoylcoumarin (4; R = H) [5] separated, and was collected by filtration. Another crop of the same product separated when the filtrate was concentrated to 50 ml (total yield 0.186 g, 98%).

When the hydroxy-compound (3; R = H, Ar = Ph) (0.276 g) in dimethylformamide (DMF) (50 ml) was treated with 2N hydrochloric acid (5 ml) and the solution heated at 100 °C for 4 h, the starting material was recovered unchanged.

Reaction of the Oxo-compounds (1) *with Semicarbazide Hydrochloride*.—The following sequence is typical. To a suspension of 2-(4-chlorophenyl)-4-oxo-2,3-dihydrobenzopyrano[2,3-*d*]pyrimidine (1; R = H, Ar = C_6H_4Cl-4) (0.311 g) in ethanol (25 ml) was added a solution of semicarbazide hydrochloride (0.166 g) in water (10 ml). The solution was refluxed for 30 min, then stored at 20 °C overnight, when 3-carbamoylcoumarin (4, R = H) [5] (0.18 g, 95%) crystallised out. The filtered solution was evaporated to dryness, and the residues recrystallised from methanol, yielding 4-chlorobenzaldehyde semicarbazone [6] (0.11 g, 56%).

Similar results were obtained with other 2-aryl-4-oxo-2,3-dihydrobenzopyrano[2,3-*d*]pyrimidines, but the hydroxy-compounds (3) were recovered unchanged from similar treatment.

Rearrangement of the Oxo-compounds (1).—(a) *Base-catalysed rearrangement*. When 2-(4-chlorophenyl)-4-oxo-2,3-dihydrobenzopyrano[2,3-*d*]pyrimidine (1; R = H, Ar = C_6H_4Cl-4) (0.311 g) was refluxed in ethanol (120 ml) containing piperidine (0.2 ml) for 6 h, the hydroxy-compound (3; R = H, Ar = C_6H_4Cl-4) separated from the hot solution. This was removed by filtration and the filtrate concentrated to 60 ml, when a further crop of the same product was obtained. Following recrystallisation from DMF, the yield of product, m.p. 310 °C [1] was 0.268 g (86%).

(b) *Thermal rearrangement*. 2-Cyclohexyl-4-oxo-2,3-dihydrobenzopyrano[2,3-*d*]pyrimidine (1; R = H, Ar = cyclohexyl) was placed in a flask which was heated to 255 °C, and then allowed to cool to 20 °C. It was clear that melting and re-solidification had occurred. The contents were extracted with hot DMF, from which the *hydroxy-compound* (3; R = H, Ar = cyclohexyl) separated, m.p. 296—299 °C; $\nu_{max.}$ 2 600—2 800w (bonded OH) and 1 650 (−C=N−) cm^{-1}; δ 3.65 (s, pyran CH_2); *m/e* 282 (M^+); (0.127 g, 90%).

No rearrangement was observed when the 3-*N*-substituted compound 2-(2-hydroxyphenyl)-4-oxo-3-salicylideneamino-2,3-dihydrobenzopyrano[2,3-*d*]pyrimidine [1] was similarly heated beyond its melting point.

3-*Oxo*-2H-*benzopyrano*[2,3-c]*pyrazole* (5b).—To a suspension of N-(2-iminochromen-3-carbonyl)-N′-(4-chlorobenzylidene)carbohydrazine (6a; Ar = C_6H_4Cl-4) [7] (1.085 g) in ethanol (100 ml) was added hydroxylamine hydrochloride (0.463 g) and the solution heated under reflux. The starting-material dissolved, and a yellow product which separated was removed by filtration from the hot, dark red solution after 3 h. Following recrystallisation from a large volume of ethanol, this was identified as N′-(4-*chlorobenzylidene*)-2-*hydroxyiminochromen*-3-*carbohydrazide* (6c; Ar = C_6H_4Cl-4), m.p. 280—281 °C (Found: C, 59.5; H, 3.6; Cl, 10.6; N, 12.6. $C_{17}H_{12}ClN_3O_3$ requires C, 59.7; H, 3.5; Cl, 10.4; N, 12.3%); $\nu_{max.}$ 1 665 cm^{-1}; (0.11 g, 10%). As the filtrate cooled to 20 °C, 3-*oxo*-2,3-*dihydrobenzopyrano*[2,3-c]*pyrazole* (5b) separated as shining dark red crystals. Recrystallised from ethanol, it had m.p. 302—304 °C (Found: C, 64.6; H, 3.4; N, 14.8. $C_{10}H_6N_2O_2$ requires C, 64.5; H, 3.2; N, 15.1%); $\nu_{max.}$ 3 170 (N−H) and 1 695 (C=O) cm^{-1}. The filtered solution was evaporated, and from the residues 4-chlorobenzaldehyde α-oxime (0.31 g) was obtained by sublimation. The remaining residues were a mixture of small quantities of the product (5b) and the coumarin (6b; Ar = C_6H_4Cl-4),[7] which were separated by repeated recrystallisation from ethanol. The yield of product (5b) was 0.285 g (46%), and of the coumarin (6b) 0.053 g (5%).

Similar results were obtained when N′-(2,4-dichlorobenzylidene)-2-iminochromen-3-carbohydrazide (6a; Ar = $C_6H_3Cl_2$-2,4) [7] was treated with hydroxylamine hydrochloride; when the salicylidene derivative (6a, Ar = C_6H_4-OH-2) [7] was similarly treated, the tricyclic product (5b) was again obtained, together with the coumarin (6b; Ar = C_6H_4OH-2) [7] and salicylaldehyde oxime, but no hydroxyiminochromen (6c) was isolated.

Conversion of Simple 2-*Iminochromen Derivatives to* 2-*Hydroxyiminochromens*.—When a solution of 3-carbamoyl-2-imino-8-methoxychromen (2; R = 8-OMe) [8] (1.01 g) and hydroxylamine hydrochloride (0.695 g) in ethanol (100 ml) was refluxed for 1.5 h, and then stored at 20 °C overnight, 3-*carbamoyl*-2-*hydroxyimino*-8-*methoxychromen* separated, m.p. 238—240 °C (ethanol) (Found: C, 56.6; H, 4.5; N, 11.7. $C_{11}H_{10}N_2O_4$ requires C, 56.4; H, 4.3; N, 12.0%); $\nu_{max.}$ 3 320, 3 200br, and 1 660 cm^{-1} (0.875 g). Similarly prepared were 3-carbamoyl-2-hydroxyiminochromen,[9] and, from the appropriate parent imines,[10,11] 3-*ethylcarbamoyl*-2-*hydroxyimino*-8-*methoxychromen*, m.p. 189—191 °C (Found: C, 59.6; H, 5.5; N, 10.8. $C_{13}H_{14}N_2O_4$ requires C, 59.5; H, 5.3; N, 10.7%), and 3-(1,2-*dihydroxypropyl*)*carbamoyl*-2-*hydroxyiminochromen*, m.p. 180—182 °C (Found: C, 55.7; H, 5.1; N, 10.1. $C_{13}H_{14}N_2O_5$ requires C, 56.1; H, 5.0; N, 10.1%).

Conversion of (6c) *into* (5b).—When the oxime (6c; Ar = C_6H_4Cl-4) (0.114 g) was refluxed in ethanol (60 ml) for several hours, no change occurred. Addition of hydroxylamine hydrochloride (0.046 g) brought about an almost immediate colour change. After 2 h, undissolved oxime (6c) (0.056 g) was removed by filtration, and the filtrate on concentration yielded the pyrazolone derivative (5b) (0.024 g). Evaporation of the remaining solvent and sublimation of the residues yielded 4-chlorobenzaldehyde α-oxime.

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