2-Alkyl-5-imino-1-benzopyrano[3,4-*c*]pyridin-4(3*H*,5*H*)-ones and Related Compounds from Reaction of 3-Carbamoyl-2-iminochromens with Methyl Ketones

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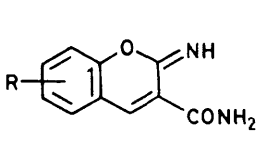
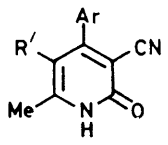
The base-catalysed condensation of 3-carbamoyl-2-iminochromens with methyl ketones yields 2-alkyl-5-imino-1-benzopyrano[3,4-*c*]pyridin-4(3*H*,5*H*)-ones, 2-alkyl-1-benzopyrano[3,4-*c*]pyridin-4(3*H*),5-diones, and 3-cyano-4-(2-hydroxyphenyl)-6-methyl-3,4-dihydropyridin-2-ones (which exist in two tautomeric forms).

THE base-catalysed condensation of 3-carbamoyl-2-iminochromen (1; R = H) with aromatic aldehydes yielded 2-aryl-4-oxo-2,3-dihydrobenzopyrano[2,3-*d*]-pyrimidines.[1] With acetone, however, the imino-group does not react, and 5-imino-2-methyl-1-benzopyrano-[3,4-*c*]pyridin-4(3*H*,5*H*)-one (2; R = R′ = H) is produced instead, together with the related 4,5-dione (3; R = R′ = H). Similar compounds are obtained using other 3-carbamoyl-2-iminochromens (1; R ≠ H) and methyl ketones. These compounds tend to be hygroscopic; conversion of the imines (2) to the oximes (4) for the purpose of further characterisation also causes some formation of the 4,5-diones (3) except under very mild conditions.



(1)



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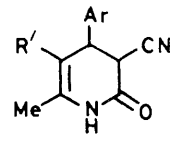

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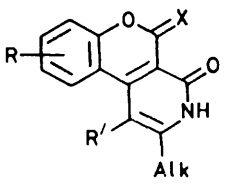
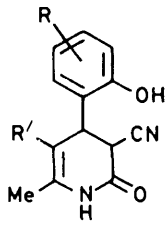


(2) X = NH, Alk = Me
(3) X = O, Alk = Me
(4) X = NOH, Alk = Et
(9) X = NH, Alk = Et
(10) X = O, Alk = Et
(12) X = NOH, Alk = Et



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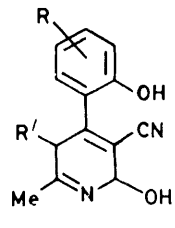
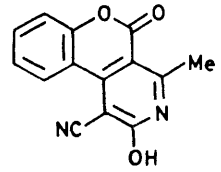


(8)



(11)

The pyridone formation represented by the reaction (1) ⟶ (2) resembles the formation of 6-alkyl-4-aryl-3-cyano-2-pyridones (5), using different but related starting materials. Thus, the 2-pyridones (5) have been obtained from the condensation of αβ-unsaturated ketones with cyanoacetamide [2-5] (or with ethyl cyanoacetate and ammonium acetate [6]) and also from the reaction of ethyl 2-cyanoacrylates with methyl ketones in the presence of ammonium acetate.[7]

Production of the 2-pyridones (5) has been accompanied by the formation of their parent dihydro-derivatives which have generally been isolated, either in the same experiment or using altered conditions. The formulation of these dihydro-compounds has been the subject of discussion (*cf.* ref. 3); recent workers [4,5] have assigned to them the 3,4-dihydro-structure (6). A corresponding dihydropyridin-2-one is not obtained from the imine (1; R = H) in acetone, but under altered experimental conditions a dihydropyridin-2-one is produced, having 3-cyano- and 4-(2-hydroxyphenyl)-substituents, clearly the result of fission of the pyran ring. The i.r. spectrum accords with the formulation (7; R = R′ = H) [$\nu_{max.}$ 3 210, 3 110, and 1 670 cm^{-1} (CONH); 2 260 cm^{-1} (saturated C≡N)].

Similar 3-cyano-4-(2-hydroxyphenyl)-3,4-dihydropyridin-2-ones are more readily obtained during the reaction of other 3-carbamoyl-2-iminochromens (1; R = 6-Cl, 6-NO_2, 8-OMe) with methyl ketones. Although their i.r. spectra are otherwise very similar to that of (7; R = R′ = H), the appearance in some of them of $\nu_{max.}$ 3 300 cm^{-1} suggests the presence in the solid state of a hydroxy-tautomer. The n.m.r. spectra of all these dihydropyridin-2-ones indicate that in solution in Me_2SO they exist exclusively in the tautomeric form (8) [δ 3.3—3.5 (d, C*H*OH), 4.5 (d, CHO*H*, disappearing on addition of D_2O, when the broadened signal at 3.3—3.5 is seen more clearly as a doublet)]. In the compounds (8; R′ = H) signals are at δ 1.7 (s, 6-Me) and 2.2 (br d, $-CH_2-$); in compounds (8; R′ = Me) signals are at δ 1.2 (d, 5-Me), 1.5 (s, 6-Me), and 2.3 (br m, C*H*Me). The tautomerisation of the amide group represented in (8) is unusual but not unique.[8] [It is of interest that the i.r. spectra of the compounds (5) agreed with the lactam formulation, but n.m.r. evidence showed that in solution in Me_2SO a hydroxy-form existed.[7]]

When butan-2-one is used in the reaction (1) ⟶ (2) instead of acetone, the imines obtained are the mono-ethyl derivatives (9; R′ = H); for solubility reasons, however, n.m.r. examination was carried out not on the imines [*e.g.* (9; R = R′ = H)] but on the diones [*e.g.* (10; R = R′ = H)] derived from them [δ 1.3 (t, CH_2-*Me*) and 2.75—2.98 (m, CH_2Me)]. In contrast to this,

the only dihydro-derivatives (*i.e.* nitriles) isolated in the same experiments are the dimethyl compounds (7; R′ = Me).

From the condensation of the imine (1; R = H) with pentane-2,4-dione, the only product isolated was the acetyl derivative (3; R = H, R′ = COMe). From ethyl acetoacetate, the two products (3; R = H, R′ = CO_2Et) and (11) were obtained. In the case of the latter, which resembles products previously obtained from the condensation of the imines (1) with ethyl cyanoacetate,[9] it is presumed that initial Michael addition at the 4-position of (1; R = H) is accompanied by fission of the pyran ring.

EXPERIMENTAL

T.l.c. of benzopyranopyridine derivatives was performed on Merck silica gel, and the products were detected using a u.v. lamp. The compounds were dried at 110 °C and 0.1 mm-Hg, but tended to pick up traces of moisture which slightly altered the analytical data. I.r. spectra were recorded on Nujol mulls, and n.m.r. spectra were measured at 60 MHz for solutions in dimethyl sulphoxide.

Reaction of 3-carbamoyl-2-iminochromen Derivatives with Ketones.—The following reaction is typical. (*a*) 3-Carbamoyl-2-imino-8-methoxychromen [10] (436 mg) in acetone (30 ml) containing piperidine (0.1 ml) was refluxed gently for 1 h, filtered to remove unchanged starting-material (120 mg), and heated again for a further 3 h. The crystalline product which separated on storing was collected, and the solution was then refluxed for a total of 20 h; at 4-hourly intervals it was cooled to 20 °C and the solid product removed. The first two crops, identified by i.r. examination, were the imine (2; R = 7-OMe, R′ = H); the third was the nitrile (7; R = 3′-OMe, R′ = H) [formulated as (8; R = 3′-OMe, R′ = H) in solution in dimethyl sulphoxide], the fourth a mixture of the imine (2; R = 7-OMe, R′ = H) and the dioxo-compound (3; R = 7-OMe, R′ = H), and the fifth the dioxo-compound (3; R = 7-OMe, R′ = H).

When the *imine* (2; R = 7-OMe, R′ = H) was recrystallised from methanol, it had m.p. 268—271 °C (decomp.) (63 mg, 17%); $\nu_{max.}$ 3 240 (=NH), 1 670, and 1 630 cm^{-1} (Found: C, 61.9; H, 4.7; N, 10.2. $C_{14}H_{12}N_2O_3 \cdot 0.75H_2O$ requires C, 62.3; H, 5.0; N, 10.4%). The *4,5-dioxo-compound* (3; R = 7-OMe, R′ = H) had m.p. >300 °C (ethanol) (21 mg, 6%); $\nu_{max.}$ 1 745 (lactone), 1 645, and 1 615 cm^{-1} (Found: C, 63.4; H, 4.7; N, 5.2. $C_{14}H_{11}NO_4 \cdot 0.5H_2O$ requires C, 63.2; H, 4.5; N, 5.3%). The *nitrile* (7; R = 3′-OMe, R′ = H) had m.p. 218—221 °C (ethanol) (166 mg, 45%); $\nu_{max.}$ 3 300 (CHOH), 2 255 (saturated C≡N), and 1 680 cm^{-1}; δ 1.7 (s, 6-Me), 2.2 (br d, $-CH_2-$), 3.5 (C*H*OH), and 4.5 (d, CHO*H*) (the latter signal disappears on addition of D_2O and the broadened signal at δ 3.5 is seen more clearly as a doublet) (Found: C, 64.8; H, 5.5; N, 10.7. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.4; N, 10.9%).

This method was used, with some variations, in the other preparations. Small crops of the products were collected at regular intervals, because this gave more satisfactory results than attempting to separate the mixture of products obtained after a long, uninterrupted period of heating. In cases in which it was clear that products were being formed relatively quickly, these were collected at 2-hourly intervals. The nitrile products (7) did not always crystallise readily, and accordingly in a few cases it was necessary to remove the solvent and recrystallise the residual gum from methanol. The proportions of the products varied according to the substituents and, to some extent, the length of heating. 3-Carbamoyl-2-imino-6-nitrochromen [11] (1; R = 6-NO_2) with acetone yielded only the nitrile derivative (7; R = 5′-NO_2, R′ = H) (47%), while only the imine (2; R = R′ = H) (19%) and the 4,5-dioxo-product (3; R = R′ = H) (6%) were obtained from the reaction of acetone with 3-carbamoyl-2-iminochromen (1; R = H), and also from the condensation of salicylaldehyde with cyanoacetamide in acetone by method (*b*); the nitrile derivative (7; R = R′ = H) was, however, obtained by methods (*c*) and (*d*) outlined below.

(*b*) Salicylaldehyde (2.24 g) and cyanoacetamide (1.68 g) in acetone (60 ml) containing piperidine (0.2 ml), refluxed for 2 h and then stored, yielded the imine (2; R = R′ = H) (0.34 g); concentration of the solution yielded the 2,3-dioxo-compound (3; R = R′ = H) (1.30 g).

(*c*) The imine (1; R = H) (1.88 g) heated at 60 °C with acetone (4 ml) in propanol (30 ml) containing piperidine (0.2 ml) for 2 h, then stored at 20 °C for 2 h, yielded a mixture of the imine (2; R = R′ = H) and the dioxo-product (3; R = R′ = H) (0.6 g). After filtration, the solution was concentrated to 15 ml, when the nitrile (7; R = R′ = H) (0.17 g) crystallised.

(*d*) A solution of 4-(2-hydroxyphenyl)but-3-en-2-one (1.62 g) and cyanoacetamide (0.84 g) in propanol (20 ml) containing piperidine (0.2 ml) was heated for 7 h. On concentrating and storing the solution, a mixture was obtained of the nitrile (7; R = R′ = H) (0.315 g) and the 2,3-dioxo-compound (3; R = R′ = H) (0.335 g); separation of the components was effected by recrystallisation.

Analytical data for new 2-alkyl-5-imino-1-benzopyrano-[3,4-*c*]pyridin-4(3*H*,5*H*)-ones, 2-alkyl-1-benzopyrano-[3,4-*c*]pyridine-4(3*H*),5-diones, and 3-cyano-4-(2-hydroxyphenyl)-6-methyl-3,4-dihydropyridin-2-ones are recorded in Tables 1, 2, and 3, respectively. The i.r. spectra of the imines in Table 1 are very similar to that recorded for the imine (2; R = 7-OMe, R′ = H), with characteristic =NH (3 250—3 270 cm^{-1}) absorption, and the i.r. spectra of the 2,3-dioxo-compounds in Table 2 are very similar to that of (3; R = 7-OMe, R′ = H), with strong lactone (1 740—1 750 cm^{-1}) absorption. The i.r. spectra of most of the nitrile derivatives resemble that of the 3′-methoxy-derivative (7; R = 3′-OMe, R′ = H); in the case of the two compounds (7; R = R′ = H) and (7; R = 5′-Cl, R′ = H), however, the absorption at 3 300 cm^{-1} is completely absent, being replaced by $-CONH-$ absorption at 3 110 and 3 210 cm^{-1}. For n.m.r. examination, the imine (2; R = R′ = H) [δ 2.3 (s, 5-Me), 3.3 (s, H_2O)] was sufficiently soluble, but the monoethyl imines (9; R = R′ = H) and (9; R = 7-OMe, R′ = H) were converted, by heating on the water-bath with dilute hydrochloric acid in aqueous ethanol, into the respective dioxo-compounds (10; R = R′ = H) [δ 1.32 (t, CH_2Me), 2.75—2.98 (m, CH_2Me), and 3.14 (s, H_2O)], and (10; R = 7-OMe, R′ = H) [δ 1.25 (t, CH_2Me), 2.35—2.8 (m, CH_2Me), and 3.3 (s, H_2O)]. N.m.r. spectra of the nitrile compounds in Table 3 resemble that recorded for the methoxy-derivative (8; R = 3′-OMe, R′ = H), but whereas monomethyl compounds had δ 1.7 (s, 6-Me), dimethyl derivatives had δ 1.2 (d, 5-Me) and 1.5 (s, 6-Me).

Preparation of 5-Hydroxyimino-2-methyl-1-benzopyrano-(3,4-c)pyridin-4(3H,5H)-one.—To a suspension of the imine (2; R = H) (226 mg) in ethanol (40 ml) at 40 °C was added

TABLE 1

2-Alkyl-5-imino-1-benzopyrano[3,4-*c*]pyridin-4(3*H*,5*H*)-one derivatives

Compound	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
(2; R = 9-Cl, R′ = H)	262—267	57.8	3.7	10.4	$C_{13}H_9ClN_2O_2 \cdot 0.5H_2O$ *	57.9	3.7	10.3
(2; R = R′ = H)	280—284 (decomp.)	65.1	4.6	11.6	$C_{13}H_{10}N_2O_2 \cdot 0.67H_2O$	65.5	4.8	11.8
(9; R = R′ = H)	259—262	69.6	5.1	11.4	$C_{14}H_{12}N_2O_2$	70.0	5.0	11.7
(9; R = 7-OMe, R′ = H)	237—241	66.3	5.2	10.3	$C_{15}H_{14}N_2O_3$	66.7	5.2	10.4

* Found: Cl, 13.0. Required: Cl, 13.2%.

TABLE 2

2-Alkyl-1-benzopyrano[3,4-*c*]pyridine-4,5-dione derivatives

Compound	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
(3; R = 9-Cl, R′ = H)	>300	58.3	3.2	5.6	$C_{13}H_8ClNO_3 \cdot 0.33H_2O$ *	58.3	3.2	5.2
(3; R = R′ = H)	>300	68.6	4.1	6.2	$C_{13}H_9NO_3$	68.7	4.0	6.2
(10; R = R′ = H)	298—301	68.5	4.5	5.7	$C_{14}H_{11}NO_3 \cdot 0.25H_2O$	68.4	4.7	5.7
(10; R = 7-OMe, R′ = H)	275—279	65.0	4.9	5.4	$C_{15}H_{13}NO_4 \cdot 0.33H_2O$	65.0	4.9	5.1

* Found: Cl, 13.0. Required: Cl, 13.2%.

TABLE 3

3-Cyano-4-(2-hydroxyphenyl)-6-methyl-3,4-dihydropyridin-2-one derivatives (7)

R	R′	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
5′-Cl	H	226—229	59.5	4.1	10.5	$C_{13}H_{11}ClN_2O_2$	59.4	4.2	10.7
5′-NO_2	H	202—204	57.4	4.2	15.7	$C_{13}H_{11}N_3O_4$	57.1	4.0	15.4
H	H	211—213	68.1	5.3	12.0	$C_{13}H_{12}N_2O_2$	68.4	5.3	12.3
H	CH_3	217—219	69.3	6.0	11.6	$C_{14}H_{14}N_2O_2$	69.4	5.8	11.6
3′-OMe	CH_3	228—229	65.8	6.0	10.4	$C_{15}H_{16}N_2O_3$	66.2	5.9	10.3

TABLE 4

5-Hydroxyimino-2-methyl-1-benzopyrano[3,4-*c*]pyridine derivatives

Compound	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
(4; R = 9-Cl, R′ = H)	>300	56.3	3.3	9.7	$C_{13}H_9ClN_2O_3$	56.4	3.3	10.1
(12; R = R′ = H)	265—268	65.4	4.6	10.6	$C_{14}H_{12}N_2O_3$	65.6	4.7	10.9
(4; R = 7-OMe, R′ = H)	290 (decomp.)	61.8	4.6	10.6	$C_{14}H_{12}N_2O_4$	61.7	4.4	10.3
(12; R = 7-OMe, R′ = H)	267—271	62.7	5.1	9.6	$C_{15}H_{14}N_2O_4$	62.9	4.9	9.8

hydroxylamine hydrochloride (139 mg), and the solution was immediately cooled to 20 °C and stored for 30 min. The yellow *oxime* (164 mg) which quickly separated had m.p. >300 °C (dimethylformamide); $\nu_{max.}$ 3 180—3 200w, 1 650, and 1 620 cm^{-1} (Found: C, 63.3; H, 4.5; N, 11.7. $C_{13}H_{10}N_2O_3 \cdot 0.25H_2O$ requires C, 63.3; H, 4.3; N, 11.4%). Other new oximes are listed in Table 4.

When the reaction mixture was heated for 30 min after addition of hydroxylamine hydrochloride, only the dioxo-compound (3; R = R′ = H) was obtained. Similar results were obtained with other imines; in some cases a mixture of the insoluble yellow oxime and the soluble colourless dioxo-compound was produced.

Condensation of the Imine (1; R = H) *with Ethyl Acetoacetate*.—A solution of the imine (1.88 g) and ethyl acetoacetate (5 ml) in ethanol (50 ml) containing piperidine (0.2 ml) was refluxed for 9 h. The solvent was then removed *in vacuo*, leaving a sticky residue which was extracted with chloroform. The chloroform extract yielded 1-*ethoxycarbonyl*-2-*methyl*-1-*benzopyrano*[3,4-c]*pyridine*-4(3H),5-*dione* (3; R = H, R′ = CO_2Et) m.p. 296—299 °C (MeOH); $\nu_{max.}$ 1 755 (lactone), 1 720 (CO_2Et), and 1 640 cm^{-1}; δ 2.36 (s, 5-Me) (Found: C, 63.9; H, 4.2; N, 5.0. $C_{16}H_{13}NO$ requires C, 64.2; H, 4.3; N, 4.7%). The chloroform-insoluble residue was 1-*cyano*-2-*hydroxy*-4-*methyl*-1-*benzopyrano*[3,4-c]-*pyridin*-5-*one* (11), m.p. >300 °C (dimethylformamide–ethanol); $\nu_{max.}$ 2 225 (C≡N), 1 745 (lactone), and 1 650br cm^{-1} (Found: C, 66.3; H, 3.2; N, 10.9. $C_{14}H_8N_2O_3$ requires C, 66.7; H, 3.2; N, 11.1%).

1-*Acetyl*-2-*methyl*-1-*benzopyrano*[3,4-c]-*pyridin*-4(3H),5-*dione* (3; R = H, R′ = COMe).—This was obtained as the only *product* from the condensation of the imine (1; R = H) with pentane-2,4-dione under similar conditions; m.p. 293—295 °C; $\nu_{max.}$ 1 755 (lactone), 1 690 (COMe), 1 635 cm^{-1}; δ 2.35 (s, 5-Me), 2.28 (s, COMe) (Found: C, 66.8; H, 4.1; N, 5.4. $C_{15}H_{11}NO_4$ requires C, 66.9; H, 4.1; N, 5.2%).

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