# Isomerisation of benzopyran-2-imines in [$^2H_6$]dimethyl sulfoxide

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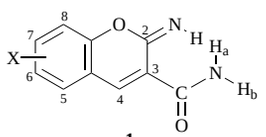
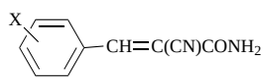
**When 2-imino-2*H*-benzopyran-3-carboxamide 1 (X = H) is dissolved in [$^2H_6$]dimethyl sulfoxide, NMR spectra show that a mixture of 1 and the isomeric 2-cyano-3-(2-hydroxyphenyl)prop-2-ene-1-carboxamide 3 (X = H) is present. Other benzopyran-2-imines behave similarly; the degree of isomerisation varies considerably, depending on the nature and position of the substituents present.**

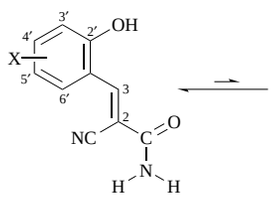
2-Imino-2*H*-benzopyran-3-carboxamide **1** (X = H) was first



**1**

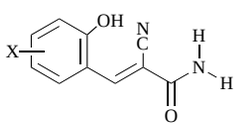


**2**

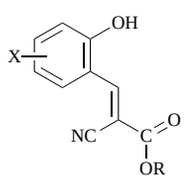


s-*trans*

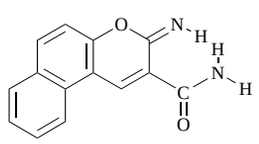
**3**



s-*cis*



**4**



**5**

prepared and correctly formulated in 1962,[1] and since then it and related compounds have been used as starting materials for the synthesis of tricyclic products (see *e.g.* refs. 2–4), some of which have interesting biological activity.[5,6] More significantly, perhaps, compounds of type **1** have been recognised as constrained mimetics of an important group of protein tyrosine kinase (PTK) inhibitors which have valuable potential for the treatment of disease states involving excess cell proliferation.[7] The non-constrained members of the group are essentially aryl-substituted derivatives of 2-cyano-cinnamamide (*e.g.* **2**, X ≠ H).[8]

In the pre-IR era, the compound **1** (X = H) was synthesised and incorrectly formulated as the open-chain derivative **3** (X = H),[9] but IR spectral data of the solid show clearly that the compound is correctly the imine **1** (X = H). The open-chain compound **3** (X = H) would be expected to feature a (highly characteristic) nitrile absorption, and there is no trace of this.

No NMR spectral data have previously been recorded for **1** (X = H), and we now report that its NMR spectra present a much more complex picture than anticipated. This is due to the presence in solution not only of **1** (X = H) but also of the isomeric compound **3** (X = H) which results from the opening of the pyran ring. {Solution IR data [obtained from the compound **1** (X = H) dissolved in dimethyl sulfoxide] confirm the presence of a nitrile band at 2260 cm$^{-1}$}. In the $^1$H NMR spectra of **1** (X = H) and **3** (X = H), the evident differences in integration make it relatively easy to distinguish between the two sets of signals. The application of CH COSY, difference NOE, TOCSY and COLOC NMR techniques has made it possible to assign all the signals in the mixture.

The $^{13}$C spectrum of **3** (X = H) differs significantly from that of **1** (X = H). The main difference, of course, is the replacement of the imino C-2 signal in **1** (X = H) ($\delta_C$ 158.1) by the carbonitrile signal in **3** (X = H) ($\delta_C$ 116.9). The presence in **3** (X = H) of free carbonitrile and hydroxy groups affects in turn the shifts of the neighbouring carbon signals. Thus, the C-3 signal in **1** (X = H) ($\delta_C$ 118.5) appears upfield as C-2 in **3** (X = H) ($\delta_C$ 104.5) due to the presence of the neighbouring carbonitrile group. Likewise, the vinylic C-4 in compound **1** (X = H) ($\delta_C$ 141.0) occurs downfield as C-3 in **3** (X = H) ($\delta_C$ 146.0). Another interesting consequence of ring-opening is the significant change undergone by the C-6 signal in **1** (X = H) ($\delta_C$ 124.0); this appears upfield as C-5′ in the open-chain compound **3** (X = H) ($\delta_C$ 119.1), presumably because of the presence of the free *para*-OH group. Other, less striking changes accompany this.

NOE experiments on **1** (X = H) demonstrate the spatial contiguity of H-4 to H-5. Strong negative NOEs show that $H_a$ is sited close to both $H_b$ and =NH, thus establishing the conformation of the carbamoyl group relative to the pyran ring. Hydrogen bonding between =NH and $NH_2$ must be responsible for the stability of the s-*cis* conformation of the C=O bond relative to the C3–C4 double bond.

The open-chain derivative **3** (X = H) cannot be isolated from solution, but the s-*trans* conformation of the C3–C2 bond (relative to OH) corresponds to the known conformation of the related ester derivative **4** (X = 3′-$OCH_3$, R = $C_2H_5$) (the molecular structure of which has been determined by X-ray crystallography[10]). However, in solution the s-*cis* conformer is also present to a slight extent (*ca.* 5%), in equilibrium with s-*trans*, as evidenced by a very weak effect linking H-3 to H-6′. Only one set of signals is present for the two conformers **3**; this is due either to rapid exchange between the latter, with the NMR signals representing an average, or else to the fact that the percentage of *cis*-isomer is so small that the signals are not visible. [This is similar to the much stronger effect which links H-4 to H-5 in **1** (X = H).] Related compounds, obtained by the Knoevenagel condensation of aromatic aldehydes with alkyl cyanoacetates[11] and malonitrile[12] have shown similar s-*trans* conformations.

The amide protons in compound **3** (X = H) [and also in many related compounds **3** (X ≠ H)] are largely concealed by other signals, but it is clear that the C1–C2 bond can also be s-*trans* or s-*cis* relative to the C2–C3 double bond. We believe that the preferred conformation for this bond is s-*cis* by analogy with the conformation of the related bond in the corresponding ester **4** (X = 3′-$OCH_3$, R = $C_2H_5$). This conformation may arise from repulsions between the C≡N and C=O dipoles.

The ring-unsubstituted compound **1** (X = H) undergoes 35% ring-opening at 21 °C. Isomerisation to this extent is evident immediately on dissolution (after 90 s), and at constant temperature there is no subsequent change in the percentage isomerisation. Measurements at higher temperatures, however (*cf.* Table 1) show that the extent of isomerisation is temperature-dependent, and that this dependence is reversible (prolonged heating at higher temperatures, however, causes decomposition). These findings indicate that the two isomers are in equilibrium in dimethyl sulfoxide.

In other solvents ([$^2H_6$]acetone and [$^2$H]chloroform), isomerisation does not occur, only the starting material **1** (X = H) being present.

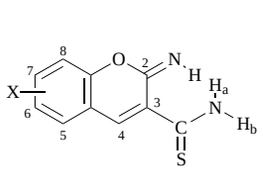
A series of substituted compounds **1** (X ≠ H) displays isomerism similar to **1** (X = H) in dimethyl sulfoxide and provides an interesting set of comparative data, where the extent of isomerisation (measured after 24 h at 20 °C) is clearly related to the nature and position of the substituent.

The only compound of general type **1** which fails to undergo isomerisation is the tricyclic compound **5**, the conformation of which is identical with that of **1** (X = H). At the opposite end of the scale, the nitro derivative **1** (X = 6-$NO_2$) undergoes 86% ring-opening. In contrast to this, only 46% isomerisation takes place in the case of the chloro derivative **1** (X = 6-Cl).

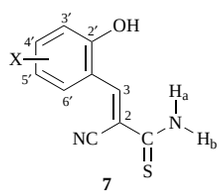
Apart from the nature of the substituent group, the position of the group relative to C-8a in the bicyclic compounds **1** is also significant. This is well illustrated by the derivatives of **1** where X is a methoxy group. Thus, the 6-OMe (*para*-) and 8-OMe (*ortho*-) derivatives of **1** undergo 23 and 30% isomerisation, respectively, but the 7-OMe (*meta*-) derivative displays 55% isomerisation.

The pattern shown by hydroxy derivatives of **1** (6-, 8- and 7-OH derivatives isomerise to the extent of 20, 28 and 41% respectively) closely resembles that of the methoxy derivatives. $^1$H NMR data (in [$^2H_6$]dimethyl sulfoxide) have recently been reported for these compounds, but only one set of signals was reported in each case.[7] There was no mention of the mixtures of signals which we consistently obtain. As the biochemical assays of these compounds were carried out using solutions which had been made up in dimethyl sulfoxide, the occurrence of the isomerisation **1** ⟶ **3** is a factor of some significance, and obviously should be taken into account in evaluating the results. The categorisation of these compounds as 'constrained' mimetics of PTK inhibitors **2** may need to be reconsidered.

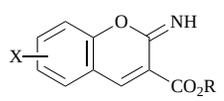
Apart from the 3-carbamoyl derivatives of **1**, the spectra of some other, related, benzopyran-2-imines have also been examined. When the 3-carbamoyl group is replaced by a thiocarbamoyl group (as in **6**) isomerisation to monocyclic compounds



**6**



**7**



**8**

(**7**) again takes place, and the degree of isomerisation follows a pattern very similar to that shown by the 3-carbamoyl compounds **1** (*cf*. Table 2). The exchangeable proton signals (NH, OH) of these thiocarbamoyl derivatives are more clearly separated than those of the corresponding carbamoyl compounds,

**Table 1** Degree of isomerisation of compounds **1** (to **3**) at 20 °C

| X | Degree of isomerisation (%) | X | Degree of isomerisation (%) |
|---|---|---|---|
| H[a] | 34[g] | 7-OH[b] | 47 |
| 6-OMe[b] | 23 | 8-OH[d] | 28 |
| 7-OMe[b] | 55 | 6-Cl[e] | 46 |
| 8-OMe[c] | 30 | 6-$NO_2$[b] | 86 |
| 6-OH[d] | 20 | 5,6-CH=CH=CH=CH[f] | 0 |

[a] Ref. 1. [b] Ref. 5. [c] Ref. 14. [d] Ref. 7. [e] Ref. 15. [f] Ref. 16. [g] At 21 °C, 35%; at 30 °C, 38%; at 50 °C, 40%; at 70 °C, 43%; cooled to 30 °C, 38%; cooled to 21 °C, 35%.

**Table 2** Degree of isomerisation of compounds **6** (to **7**) and **8** (to **4**)

| Compound | Degree of isomerisation (%) | Compound | Degree of isomerisation (%) |
|---|---|---|---|
| **6** X = H[a] | 37 | **6** X = 8-OMe | 30 |
| **6** X = 6-OMe[a] | 18 | **8** X = 7-OH R = Et[b] | 66 |
| **6** X = 7-OMe | 48 | **8** X = 6-Cl R = Me[b] | 89 |

[a] Ref. 17. [b] Ref. 18.

**Table 3** $^1$H NMR spectra ($\delta_H$) of compounds **1**. *J*/Hz values are listed under shifts.

| Substituent (X) | H-4 | H-5 | H-6 | H-7 | H-8 | =NH | NH | NH |
|---|---|---|---|---|---|---|---|---|
| H | 8.42 | 7.76dd (1.3, 7.5) | 7.26t (7.5) | 7.58dt (1.3, 7.5) | 7.22d (7.5) | 8.9 | 7.81 (br s) | 9.59 (br s) |
| 6-OMe[a] | 8.43 | 7.36d (3.0) | | 7.13dd (3.0, 8.9) | 7.16d (8.9) | 9.01 | 8.03 (br s) | 9.87 (br s) |
| 7-OMe[b] | 8.38 | 7.75d (8.7) | 6.85dd (2.3, 8.5) | | 6.75d (2.3) | 8.75 | 7.7 (br s) | 9.60 (br s) |
| 8-OMe[c] | 8.38 | 7.25d (7.9) | 7.32t (7.9) | 7.30dd (1.0, 7.9) | | 9.01 | 7.90 (br s) | 9.61 (br s) |
| 6-OH[d] | 8.34 | 7.066d (2.7) | | 6.98dd (2.7, 8.8) | 7.067d (8.8) | 8.66 | 7.73 | 9.65 |
| 7-OH[e] | 8.27 | 7.51d (8.6) | 6.66dd (2.4, 8.6) | | 6.54d (2.4) | 8.55 | 7.50 | 9.44 |
| 8-OH[f] | 8.13 | 6.88d (8.0) | 6.84t (7.9) | 6.87d (8.0) | | 8.46 | 7.50 | 9.38 |
| 6-Cl | 8.40 | 7.81d (2.5) | | 7.55dd (2.5, 8.8) | 7.23d (8.8) | 9.02 | 7.80 | 9.51 |
| 6-$NO_2$ | 8.41 | 8.71d (2.8) | | 8.34dd (2.8, 9.0) | 7.39d (9.0) | 9.20 | 7.87 (br s) | 7.98 (br s) |

[a] OMe, 3.80. [b] OMe, 3.87. [c] OMe, 3.89. [d] OH, 9.55. [e] OH, 10.35. [f] OH, 9.65.

**Table 4** $^{13}C$ NMR spectra ($\delta_C$) of compounds **1**

| Substituent (X) | C-2 | C-3 | C-4 | C-4a | C-5 | C-6 | C-7 | C-8 | C-8a | C=O |
|---|---|---|---|---|---|---|---|---|---|---|
| H | 155.5 | 120.9 | 141.0 | 118.5 | 129.8 | 124.0 | 132.9 | 114.8 | 153.6 | 162.9 |
| 6-OMe[a] | 156.2 | 121.4 | 119.1 | 119.1 | 152.5 | 155.5 | 120.1 | 116.1 | 148.3 | 163.3 |
| 7-OMe[b] | 155.7 | 117.7 | 141.5 | 112.2 | 131.4 | 111.7 | 163.7 | 100.1 | 155.9 | 163.7 |
| 8-OMe[c] | 155.1 | 128.3 | 141.1 | 119.0 | 123.8 | 121.0 | 115.4 | 145.8 | 145.7 | 162.9 |
| 6-OH | 156.1 | 120.8 | 141.2 | 118.9 | 114.2 | 153.3 | 120.2 | 115.5 | 147.0 | 163.1 |
| 7-OH | 156.9 | 111.2 | 141.6 | 110.9 | 131.5 | 113.0 | 160.9 | 101.6 | 155.9 | 164.0 |
| 8-OH | 155.8 | 120.6 | 142.1 | 117.9 | 123.8 | 119.8 | 119.4 | 145.4 | 143.9 | 163.2 |
| 6-Cl | 157.1 | 122.7 | 142.1 | 122.3 | 129.1 | 130.4 | 134.5 | 119.0 | 154.6 | 164.7 |

[a] $CH_3$, 56.1. [b] $CH_3$, 55.8. [c] $CH_3$, 55.9.

**Table 5** $^1H$ NMR spectra ($\delta_H$) of compounds **3**. *J*/Hz values are listed under shifts.

| Substituent (X) | H-3 | H-6′ | H-5′ | H-4′ | H-3′ | 2′-OH | NH | NH |
|---|---|---|---|---|---|---|---|---|
| H | 8.47 | 8.03dd (1.5, 7.8) | 6.95dt (1.5, 7.8) | 7.42dt (1.5, 7.8) | 7.00dd (1.5, 7.8) | 10.44 (br s) | 7.7 | 7.8 |
| 5′-OMe[a] | 8.44 | 7.61d (2.9) | | 7.13dd (2.9, 8.8) | 6.96d (8.8) | 10.18 (br s) | 7.68 | 7.85 |
| 4′-OMe[b] | 8.42 | 8.10d (9.0) | 6.61d (2.3, 9.0) | | 8.52d (2.3) | 10.44 (br s) | 7.60 | 7.63 |
| 3′-OMe[c] | 8.48 | 7.62 (8.0) | 6.95t (8.1) | 7.15d (8.0) | | 10.5 (br s) | 7.75 | 7.95 |
| 5′-OH[d] | 8.41 | 7.45d (2.7) | | 6.88dd (2.7, 8.8) | 6.85d (8.8) | 9.6 (br s) | 7.55 (br s) | 7.80 |
| 4-OH[e] | 8.40 | 8.02d (8.8) | 6.41dd (2.4, 8.8) | | 6.43d (2.4) | 10.5 (br s) | 7.5 | 7.65 |
| 3′-OH[f] | 8.28 | 7.30d (8.0) | 6.55t (8.0) | 6.77dd (1.0, 8.0) | | 10.0 (br s) | 7.43 | 8.0 |
| 5′-Cl | 8.36 | 7.96d (2.6) | | 7.45dd (2.6, 8.8) | 7.17d (8.8) | 10.4 (br s) | 7.75 | 7.80 |
| 5′-$NO_2$ | 8.40 | 8.93d (2.8) | | 8.23dd (2.8, 9.0) | 7.04d (9.0) | 12.10 (br s) | 7.79 | 7.94 |

[a] $CH_3$, 3.77. [b] $CH_3$, 3.81. [c] $CH_3$, 3.86. [d] OH, 9.3. [e] OH, 10.5. [f] OH, 9.7.

**Table 6** $^{13}C$ NMR spectra ($\delta_C$) of compounds **3**

| Substituent (X) | C≡N | C-2 | C-3 | C-1′ | C-6′ | C-5′ | C-4′ | C-3′ | C-2′ | C=O |
|---|---|---|---|---|---|---|---|---|---|---|
| H | 116.9 | 104.5 | 146.0 | 119.0 | 128.0 | 119.1 | 134.1 | 116.4 | 158.1 | 162.9 |
| 5′-OMe[a] | 117.6 | 105.0 | 146.0 | 117.6 | 111.5 | 155.5 | 120.1 | 116.1 | 152.0 | 163.2 |
| 4′-OMe[b] | 118.1 | 100.5 | 145.4 | 112.5 | 129.6 | 107.1 | 164.6 | 100.2 | 160.7 | 163.6 |
| 3′-OMe[c] | 115.1 | 104.5 | 145.8 | 117.0 | 119.2 | 118.8 | 115.3 | 148.2 | 148.0 | 162.9 |
| 5′-OH | 116.9 | 103.9 | 147.0 | 120.4 | 112.3 | 149.7 | 122.3 | 117.2 | 151.0 | 163.1 |
| 4′-OH | 118.4 | 98.7 | 145.7 | 113.1 | 129.7 | 108.7 | 163.2 | 103.0 | 157.1 | 164.0 |
| 3′-OH | 117.2 | 103.7 | 146.3 | 119.6 | 119.3 | 118.7 | 118.4 | 146.1 | 147.9 | 163.1 |
| 5′-Cl | 118.7 | 108.6 | 146.7 | 125.0 | 129.4 | 129.8 | 135.7 | 120.3 | 158.9 | 164.9 |
| 5′-$NO_2$ | 116.4 | 106.5 | 144.5 | 119.3 | 124.7 | 137.8 | 128.9 | 117.7 | 162.5 | 165.6 |

[a] $CH_3$, 55.8. [b] $CH_3$, 55.2. [c] $CH_3$, 55.9.

**Table 7** $^1H$ NMR spectra ($\delta_H$) of compounds **6**. *J*/Hz values are listed under shifts.

| Substituent (X) | H-4 | H-5 | H-6 | H-7 | H-8 | =NH | NH | NH |
|---|---|---|---|---|---|---|---|---|
| H | 8.94 | 7.81d (7.8) | 7.29dt (1.0, 7.8) | 7.61dt (1.0, 7.8) | 7.26d (7.8) | 11.76 (br s) | 9.16 | 10.36 |
| 6-OMe[a] | 8.90 | 7.41d (1.5) | | 7.17dd (1.5, 8.9) | 7.18d (8.9) | 11.8 (br s) | 9.01 | 10.38 |
| 7-OMe[b] | 8.96 | 7.76d (8.4) | 6.90dd (2.2, 8.4) | | 6.81d (2.2) | 11.76 (br s) | 9.0 | 10.81 |
| 8-OMe[c] | 8.89 | 7.31d (8.0) | 7.21t (8.0) | 7.36d (8.0) | | 11.77 (br s) | 9.22 | 10.33 |

[a] OMe, 3.77. [b] OMe, 3.82. The compound, prepared according to the standard method,[17] had mp 180–182 °C (Found: C, 56.5; H, 4.5; N, 11.8. $C_{11}H_{10}N_2O_2S$ requires C, 56.4; H, 4.4; N, 12.0%), $\nu_{max}/cm^{-1}$ 3305 (=NH), 3230, 3185 ($NH_2$), 1626, 1611, 1592, 1563. [c] OMe, 3.91. The compound, prepared according to the standard method, had mp 185–187 °C (Found: C, 56.6; H, 4.4; N, 11.9. $C_{11}H_{10}N_2O_2S$ requires C, 56.4; H, 4.4; N, 12.0%), $\nu_{max}/cm^{-1}$ 3310 (=NH), 3225, 3180 ($NH_2$), 1624, 1609, 1590, 1561.

and are fully identifiable. NOE experiments on the bicyclic compound **6** (X = 8-OMe) show the spatial proximity of NH to =NH (and also of H-4 to H-5), thus establishing the s-*cis* orientation of the thiocarbonyl group C=S relative to the double bond C3–C4. In the case of the open-chain isomer **7** (X = 3′-OMe), where the s-*trans* conformer predominates, NOE shows the contiguity of $H_a$ to H-3 and also to OH. The explanations used in the case of the carbamoyl compounds **1** and **3** are equally relevant for the thiocarbamoyl compounds.

Ester derivatives of type **8** undergo isomerisation similar to that shown by the carbamoyl and thiocarbamoyl derivatives **1** and **6**. The ring-unsubstituted structure **8** (X = H, R = Et) has

**Table 8** $^{13}C$ NMR spectra ($\delta_C$) of compounds **6**

| Substituent (X) | C-2 | C-3 | C-4 | C-4a | C-5 | C-6 | C-7 | C-8 | C-8a | C=S |
|---|---|---|---|---|---|---|---|---|---|---|
| H | 155.6br | 122.9br | 145.1br | 118.5 | 130.3 | 124.2 | 133.5 | 114.9 | 153.3 | 192.7br |
| 6-OMe[a] | 155.6br | 123.1br | 145.3br | 120.3 | 113.1 | 155.4 | 121.1 | 116.2 | 147.7 | 192.6br |
| 7-OMe[b] | 155.8br | 119.3br | 146.2br | 112.1 | 131.7 | 112.2 | 164.0 | 100.8 | 155.9 | 192.6br |
| 8-OMe[c] | 155.3br | 123.1br | 145.4br | 119.4 | 121.5 | 124.1 | 116.0 | 145.8 | 142.5 | 192.6br |

[a] $CH_3$, 55.8. [b] $CH_3$, 55.0. [c] $CH_3$, 56.06.

**Table 9** $^{1}H$ NMR spectra ($\delta_H$) of compounds **7**. *J*/Hz values are listed under shifts.

| Substituent (X) | H-3 | H-6′ | H-5′ | H-4′ | H-3′ | 2′-OH | NH | NH |
|---|---|---|---|---|---|---|---|---|
| H | 8.43 | 8.01dd (1.2, 7.8) | 6.97t (7.8) | 7.43dt (1.2, 7.8) | 7.01d (7.8) | 10.7 | 9.82 | 10.05 |
| 5′-OMe[a] | 8.40 | 7.62d (1.5) | | 7.06dd (1.5, 8.9) | 6.94d (8.9) | 10.22 | 9.48 | 10.01 |
| 4′-OMe[b] | 8.49 | 8.11d (8.9) | 6.62dd (2.4, 8.9) | | 6.54d (2.4) | 10.18 | 9.31 | 9.87 |
| 3′-OMe[c] | 8.47 | 7.62d (8.0) | 6.95t (8.0) | 7.18d (8.0) | | 9.88 | 9.53 | 10.19 |

[a] $CH_3$, 3.76. [b] $CH_3$, 3.89. [c] Me, 3.88.

**Table 10** $^{13}C$ NMR spectra ($\delta_C$) of compounds **7**

| Substituent (X) | C≡N | C-2 | C-3 | C-1′ | C-6′ | C-5′ | C-4′ | C-3′ | C-2′ | C=S |
|---|---|---|---|---|---|---|---|---|---|---|
| H | 116.6 | 111.0 | 143.8 | 118.5 | 128.1 | 119.4 | 134.1 | 116.6 | 158.0 | 193.1 |
| 5′-OMe[a] | 116.7 | 110.8 | 143.9 | 118.9 | 111.7 | 152.4 | 121.8 | 117.7 | 151.8 | 192.6 |
| 4′-OMe[b] | 117.3 | 106.9 | 144.1 | 111.8 | 129.4 | 106.9 | 164.5 | 99.7 | 160.5 | 194.0 |
| 3′-OMe[c] | 116.0 | 111.2 | 147.6 | 116.5 | 119.3 | 119.0 | 115.5 | 148.0 | 147.6 | 192.5 |

[a] Me, 55.5. [b] Me, 56.0. [c] Me, 55.11.

**Table 11** $^{1}H$ NMR spectra ($\delta_H$) of compounds **8**. *J*/Hz values are listed under shifts.

| Substituents | H-4 | H-5 | H-6 | H-7 | H-8 | =NH | OH | $CH_3$ | $CH_2$ |
|---|---|---|---|---|---|---|---|---|---|
| X = 7-OH | 8.24 | 7.54d | 6.61dd | | 6.44d | 10.75 | 10.75 | 1.2t | 4.29q |
| R = Et | | (8.5) | (2.1, 8.5) | | (2.1) | | | (7) | (7) |
| X = 6-Cl | 8.26 | 8.06 | | 7.65dd | 7.29d | 8.56 | | 3.87 | |
| R = Me | | (2.6) | | (2.6, 8.8) | (8.8) | | | | |

**Table 12** $^{13}C$ NMR spectra ($\delta_C$) of compounds **8**

| X = 7-OH | C-2 | C-3 | C-4 | C-4a | C-5 | C-6 | C-7 | C-8 | C-8a | C=O |
|---|---|---|---|---|---|---|---|---|---|---|
| R = Et | 156.3 | 115.2 | 142.5 | 109.7 | 132.0 | 108.7 | 164.5 | 102.3 | 161.7 | 165.2 |

**Table 13** $^{1}H$ NMR spectra ($\delta_H$) of compounds **4**. *J*/Hz values are listed under shifts.

| Substituents | H-3 | H-6′ | H-5′ | H-4′ | H-3′ | OH-2′ | OH-4′ | $CH_3$ | $CH_2$ |
|---|---|---|---|---|---|---|---|---|---|
| X = 4′-OH | 8.58 | 8.15d | 6.45dd | | 6.44d | 10.75 | 10.75 | 1.31t | 4.30 |
| R = Et | | (9.1) | (2.1, 9.1) | | (2.1) | (br s) | (br s) | (7.0) | (7.0) |
| X = 5′-Cl | 8.54 | 8.10d | | 7.53dd | 7.06d | 10.9 | | 3.88 | |
| R = Me | | (2.6) | | (2.6, 8.8) | (8.8) | (br s) | | | |

been reported in the literature (without NMR data),[13] but we have been unable to repeat this synthesis. (In our hands, the product formed is the 1 : 2 adduct obtained from the reaction of salicylaldehyde with ethyl cyanoacetate in 1 : 2 ratio.[12]) However, at least two authentic substituted ester derivatives are available (**8**, X = 7-OH, R = Et and **8**, X = 6-Cl, R = Me), and NMR data show that in [$^2H_6$]dimethyl sulfoxide these partially isomerise to the hydroxy derivatives **4**.

It is clear that benzopyran-2-imines have a strong tendency to isomerise in dimethyl sulfoxide solution by ring-opening, and this should be borne in mind when assessing relevant literature. The characterisation of compounds of this type should include full NMR spectral data, with interpretation.

## Experimental

NMR spectra were recorded in ppm on a Bruker MSL 400 instrument, using [$^2H_6$]dimethyl sulfoxide as solvent. *J* values are given in Hz. In Tables 3, 5, 7, 9, 11 and 13, signals are singlets unless otherwise stated.

NMR spectra of 3-imino-3*H*-naphtho[2,1-*b*]pyran-2-carboxamide **5**: $\delta_H$ 7.42 (1H, d, *J* 8.9, H-5), 7.59 (1H, t, *J* 7.5, H-8), 7.73 (1H, t, *J* 7.5, H-9), 7.89 (1H, br s, NH), 8.02 (1H, d, *J* 8.1, H-7), 8.16 (1H, d, *J* 8.9, H-6), 8.43 (1H, d, *J* 8.3, H-10), 8.9 (1H, br s, =NH), 9.1 (1H, br s, H-1), 9.6 (1H, br s, NH); $\delta_C$ 112.2 (C-2), 116.2 (C-5), 120.4 (C-10b), 122.1 (C-10), 126.1 (C-8), 129.0 (C-9), 129.3 (C-7), 129.7 (C-6a), 130.1 (C-10a),

**Table 14** $^{13}C$ NMR spectra ($\delta_C$) of compounds **4**

| Substituents | C≡N | C-2 | C-3 | C-1′ | C-6′ | C-5′ | C-4′ | C-3′ | C-2′ | C=O |
|---|---|---|---|---|---|---|---|---|---|---|
| X = 4′-OH R = Et | 117.1 | 93.9 | 148.1 | 110.7 | 130.3 | 109.5 | 161.6 | 102.7 | 163.3 | 165.0 |
| X = 5′-Cl R = Me | 115.6 | 101.8 | 147.7 | 119.6 | 127.5 | 123.0 | 135.2 | 118.4 | 157.4 | 162.4 |

134.5 (C-6), 136.7 (C-1), 153.9 (C-4a), 155.9 (C-3), 163.5 (C=O).

The NMR spectra of all other compounds are recorded in the Tables as follows. Tables 3, 4: 2-Imino-2*H*-benzopyran-3-carboxamides. Tables 5, 6: 2-Cyano-3-(2-hydroxyphenyl)prop-2-ene-1-carboxamides. Tables 7, 8: 2-Imino-2*H*-benzopyran-3-carbothiamides. Tables 9, 10: 2-Cyano-3-(2-hydroxyphenyl)-prop-2-ene-1-carbothiamides. Tables 11, 12: Alkyl 2-imino-2*H*-benzopyran-3-carboxylates. Tables 13, 14: Alkyl 2-cyano-3-(2-hydroxyphenyl)prop-2-enoates.

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