Reactions of 2-Oxo-2*H*-1-benzopyran-3-carbonitrile

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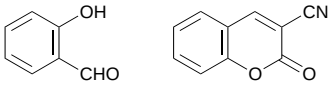
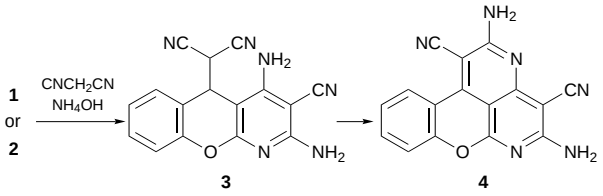
Synthetic reactions of 2-oxo-2*H*-1-benzopyran-3-carbonitrile afford products which establish that partial or complete cleavage of the starting material occurs in the course of reaction.

Benzopyran derivatives are useful starting materials for the preparation of polyheterocyclic compounds,[2–4] but the products vary considerably according to the structure and reactivity of the parent benzopyran. The use in synthesis of the stable compound 2-oxo-2*H*-1-benzopyran-3-carbonitrile **2** (which is formed by reaction of salicylaldehyde **1** with alkyl cyanoacetates[5]) is now described.



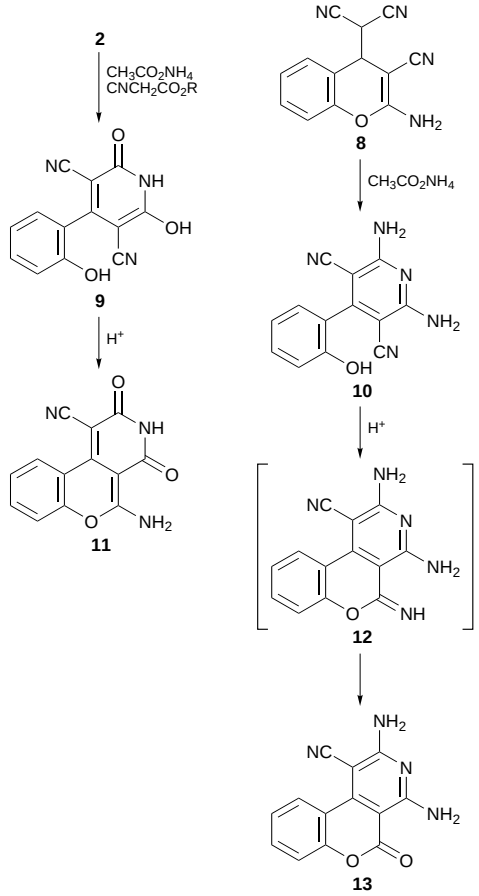
1 **2**

Some synthetic reactions of the bicyclic compound **2** have already been reported in the literature. Most of these reactions were carried out in the pre-NMR era; in some cases it was not possible to formulate the products, while in others the products were formulated incorrectly. It is now clear that the basic mistake was the assumption that, during reaction,the 2-oxo-2*H*-1-benzopyran structure remained essentially intact (as happens, for example, when 2-oxo-2*H*-1-benzopyran-3-carboxamide undergoes reaction[4]). In fact, our results show that the nitrile derivative **2** usually undergoes ring-opening (by fission of the 1,2 bond) and that fission of the 3,4-bond may also occur, resulting in cleavage of the molecule. This is well illustrated by the reaction of 2-oxo-2*H*-1-benzopyran-3-carbonitrile **2** with malononitrile and ammonium acetate. A previous report states that this affords an inseparable mixture of (unformulated) products.[6] The products formed are now identified as the tri- and tetra-cyclic compounds **3** and **4**, both of which have been shown to be formed directly from the reaction of salicylaldehyde with malononitrile.[2]



The reaction of the bicyclic compound **2** with methyl cyanoacetate in the presence of ammonia or ammonium acetate affords the tricyclic product **11**. (This product is also obtained from the reaction of **2** with ammonia or ammonium acetate alone, when the mechanism must involve disproportionation of **2**.) Prior to purification of **11**, when the crude product is first obtained, the ^{1}H NMR spectrum shows that a monocyclic impurity is also present. This is presumed to be the pyridine derivative **9** but it is not isolable; in [$^2H_6$]dimethyl sulfoxide solution it slowly changes into the tricyclic product **11** (a change which takes place more rapidly in the presence of mineral acid).

In the course of examining the reaction **2**→**9**→**11**, we studied also the related reaction of ammonium acetate with the benzopyran derivative **8** (which represents the first isolable product formed by reaction of salicylaldehyde with malononitrile in 1:2 ratio). This reaction follows a similar pathway **8**→**10**→**12**→**13**, but in this case it is possible to isolate the monocyclic pyridine intermediate **10**. This is also converted, in the presence of acid, into a tricyclic product **13**; presumably the imino group in the postulated intermediate **12** is hydrolysed during formation of **13**.



The reaction of **2** with 2-aminoprop-1-ene-1,1,4-tricarbonitrile **14** in the presence of ammonia has been reported to afford the simple addition compound **15**,[11] but the NMR spectrum is not reconcilable with the structure, and in fact the correct formulation of the product is **16**.

In a different type of reaction, the benzopyran **2** reacts with ketones and ammonium acetate to afford the bridged structure **20**. Thus, with 3-oxobutanamide **17** (R = H, R′ = $CONH_2$) and ammonium acetate, the amide derivative **20** (R = H, R′ = $CONH_2$) is formed. In a related reaction, when the benzopyran **2** reacts with methyl acetoacetate and ammonium acetate, the main product is the ester derivative **20** (R = CO_2Me, R′ = H). The molecular structure of this compound, as determined by X-ray diffraction, is shown in Fig. 1. This appears to be the first published example of an X-ray determination of a bridged structure of this general type.

Crystal Structure Determination of **20** (R = CO_2Me, R′ = H).—Data were collected on an Enraf-Nonius CAD-4

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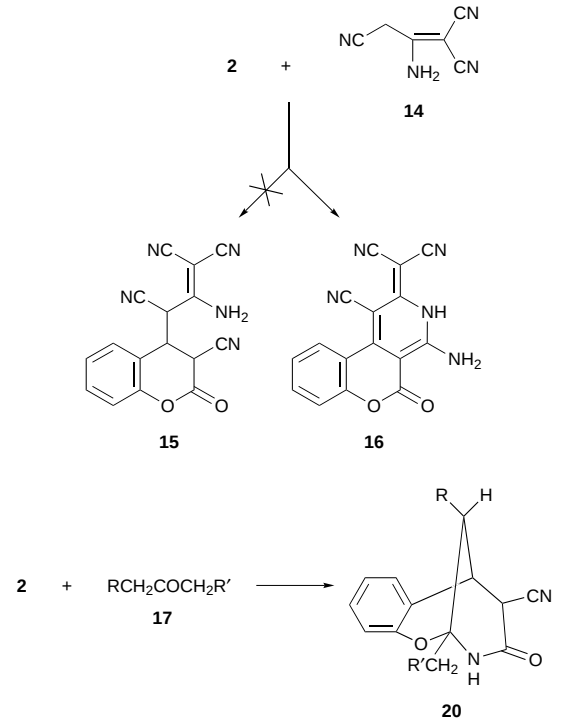

diffractometer (Mo radiation, graphite monochromator, ω–2θ scans) at 20 °C. The crystal data and experimental parameters are given in Table 1. The final cell parameters were determined using the Celdim routine. It was not found necessary to apply decay or absorption corrections to the data. The data were reduced to give the number of unique reflections and those with $|F| \geq 4\sigma|F|$ were used in structure solution and refinement.

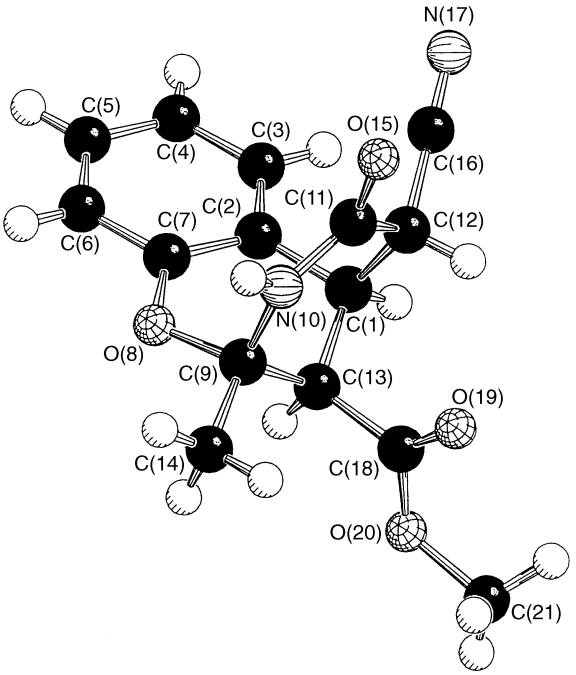

Fig. 1 Molecular structure of methyl 12-cyano-9-methyl-11-oxo-8-oxa-10-azatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylate **20** (R = CO_2Me, R′ = H), showing the crystallographic numbering system

Table 1 Crystal data and structure refinement for **20** (R = CO_2Me, R′ = H)

Empirical formula	$C_{15}H_{14}N_2O_4$
Formula weight	286.28
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 13.445(2) Å α = 90°
	b = 12.449(2) Å β = 108.57°
	c = 8.918(3) Å γ = 90°
Volume	1415.0(5) Å
Z	4
Density (calculated)	1.344 g cm^{-3}
Absorption coefficient	0.099 mm^{-1}
F(000)	600
Crystal size	0.3 × 0.5 × 0.4 mm
Theta range for data collection	1.60–21.98°
Index ranges	$-13<h<13$, $0<k<13$, $0<l<9$
Reflections collected	1866
Independent reflections	1728 [R(int) = 0.0189]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1728/0/246
Goodness-of-fit on F^2	1.219
Final R indices [$I>2\sigma(I)$]	R_1 = 0.0444, wR_2 = 0.1074
R indices (all data)	R_1 = 0.0600, wR_2 = 0.1132
Largest diff. peak and hole	0.198 and −0.205 e Å^{-3}

The structure was solved by automatic direct methods using SHELXS-86.[15] The structure was refined by full-matrix least-squares analysis on F^2 with SHELXL.[16] The non-hydrogen atoms were refined anisotropically and all the hydrogen atoms were located from subsequent difference Fourier maps and refined with individual temperature factors to a final R value of 4.4%.

Techniques used: IR, ^{1}H NMR, ^{13}C NMR, X-ray crystallography, elemental analysis

References: 17

Appendix: Tables of atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates and isotropic displacement parameters for **20** (R = CO_2Me, R′ = H)

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