2-Hydroxy-2-methyl-2*H*-1-benzopyran-3-carboxamide Derivatives produced by Knoevenagel Condensation

J. Chem. Research (S), 1997, 78–79
J. Chem. Research (M), 1997, 0643–0649

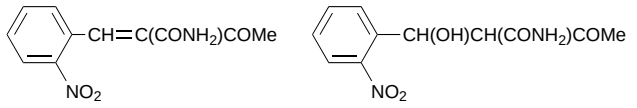
Conor N. O'Callaghan* and T. Brian M. McMurry

University Chemical Laboratory, Trinity College, Dublin 2, Ireland

The reaction of 2-hydroxybenzaldehydes with 3-oxobutanamide affords 2,4-dihydroxy-2-methyl-2*H*-3,4-dihydro-1-benzopyran-3-carboxamides and 2-hydroxy-2-methyl-2*H*-1-benzopyran-3-carboxamides, depending on the particular aldehyde and the experimental conditions used.

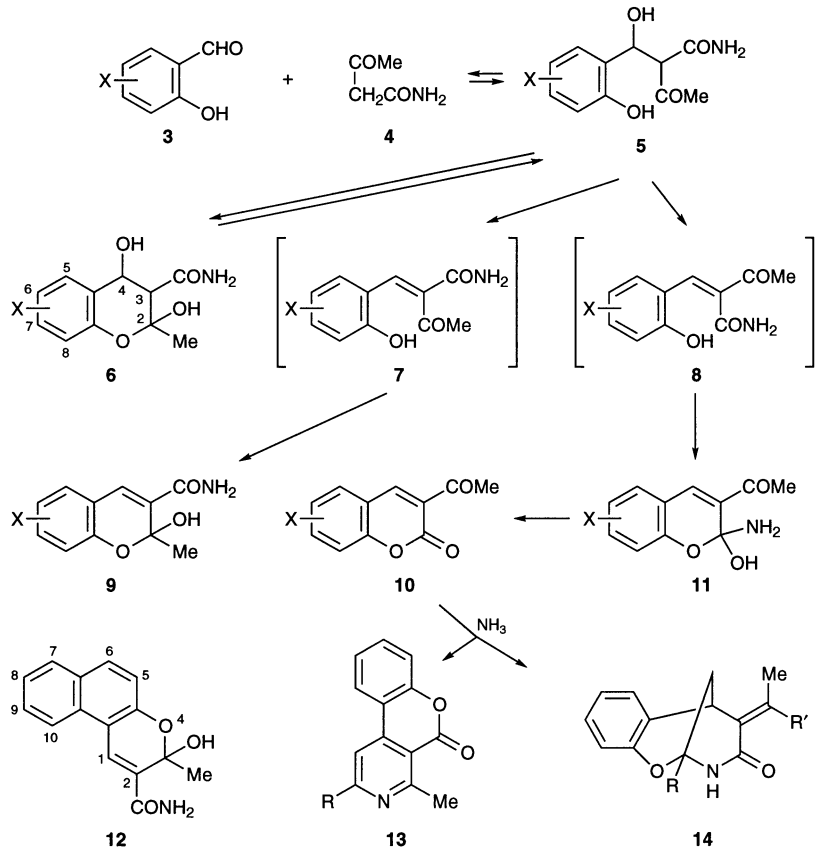
Many benzopyran derivatives occur in nature,[1] and 2,2-disubstituted 2*H*-1-benzopyrans are of considerable biological importance. The tocopherol (vitamin E) compounds have been known for many years,[2] and more recently 7-methoxy-2,2-dimethyl-2*H*-1-benzopyran was shown to inhibit insect hormone activity.[3] At present there is widespread interest in the potassium channel modulatory (antihypertensive) activity of a range of 3-hydroxy-2,2-dimethyl-2*H*-1-benzopyran derivatives,[4] which have been developed following the discovery of cromakalim.[5] New 2,2,3-tri- and 2,2,3,4-tetra-substituted benzopyran derivatives, obtained by the reaction of 2-hydroxybenzaldehydes with 3-oxobutanamide, are now reported.

3-Oxobutanamide has been little studied in the Knoevenagel condensation, but it is clearly less reactive than the classical activated methylene derivatives normally cited,[6] and is more sensitive to alterations in reaction conditions. Thus, for example, reaction with *o*-nitrobenzaldehyde under normal basic conditions affords the expected product **1**, but in mildly acid solution two diastereoisomeric racemates **2** are obtained.



1 **2**

There is a considerable literature describing the Knoevenagel condensations of salicylaldehyde **3a**.[6,7] With methylene compounds activated by, *e.g.*, C≡N and CO_2R groups, the reaction affords, almost invariably, coumarin-type products or products derived from these. Initial examination of the reaction of salicylaldehyde with 3-oxobutanamide **4** indicates that it fits into this pattern. Even under very mild Knoevenagel conditions, the only stable, solid product (obtained in very small yield) is the benzopyranopyridine derivative **13** (R = coumarin-3-yl). Under less mild conditions, a complex solid foam is obtained, the two main components of which are the bridged tricyclic derivatives **14** (R = coumarin-3-yl) where R′ = OH and NH_2 respectively. All three of these products have previously been shown to be obtained from the reaction of 3-acetyl-2*H*-1-benzopyran-2-one **10a** with ammonia.[8]



3 **4** **5** **6** **7** **8** **9** **10** **11** **12** **13** **14**

Scheme 1 **a** X = H; **b** X-6-Cl; **c** X = 8-OMe; **d** X = 7-OMe; **e** X = 6,8-Br_2; **f** X = (5,6)-CH=CH—CH=CH (benzopyran numbering)

*To receive any correspondence.

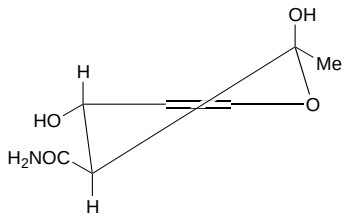


Fig. 1 Probable conformation of the dihydroxy derivative **6a**

In contrast to this, the sole product formed from the reaction of salicylaldehyde with 3-oxobutanamide in ethanol containing acetic acid and minimal piperidine is the crystalline dihydroxy derivative **6a**. The observed vicinal coupling constant, 10.5 Hz, for the pyran ring protons H^3 and H^4 establishes that the latter are *trans*, with H^3 axial and H^4 quasi-axial. It is most likely that the 2-hydroxy group is also axial, as shown in Fig. 1 (*cf*. ref. 9).

The fully saturated compound **6a** is stable in the solid state and is recrystallisable, but when the [$^2H_6$]DMSO NMR solution is stored, it is clear that it undergoes dissociation into the original two components within 48 h. The reaction of 5-chloro-2-hydroxybenzaldehyde **3b** with 3-oxobutanamide under similar conditions affords the analogous dihydroxy compound **6b** as the main product. NMR confirms this formulation, but shows that in solution in [$^2H_6$]DMSO the pyran ring rapidly undergoes ring-opening. Two racemic open-chain compounds **5b** are present in solution, but these intermediate decomposition products are too unstable to be isolated; further decomposition, with liberation of the original aldehyde, is evident within 2 h.

The instability of the compounds **6** in solution is discouraging, but other, substituted *o*-hydroxybenzaldehydes afford products which are considerably more stable. In contrast to salicylaldehyde and 5-chloro-2-hydroxybenzaldehyde, the reaction of 2-hydroxy-3-methoxybenzaldehyde with 3-oxobutanamide (in methanol containing catalytic piperidine) affords the 2,2,3-trisubstituted product **9c** and a little of the coumarin-type product **10c**. The compounds **9** and **10** are much more stable than the saturated structures **6** (which are formed without dehydration), and rapid ring-opening and decomposition reactions are not evident.

2-Hydroxy-1-naphthaldehyde behaves like 2-hydroxy-3-methoxybenzaldehyde, affording the 3,3-disubstituted tricyclic product **12** in moderate yield. Two other aldehydes which afford the same type of product (**9e** and **9d** respectively) but in much smaller yield, are 3,5-dibromo- and 2-hydroxy-4-methoxybenzaldehyde; in the case of the latter, the 2-oxo derivative **10d** is the main product formed. The isolation of the two types of product **9** and **10** shows that the initial condensation can result in the formation of both of the possible stereoisomers **7** and **8**. The sequence of formation of the various products can be summarised as shown in Scheme 1.

Techniques used: IR, mp, ^1H and ^{13}C NMR, elemental analysis

References: 12

Schemes: 1

Figures: 1

Received, 29th October 1996; Accepted, 9th December 1996
Paper E/6/07362J

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