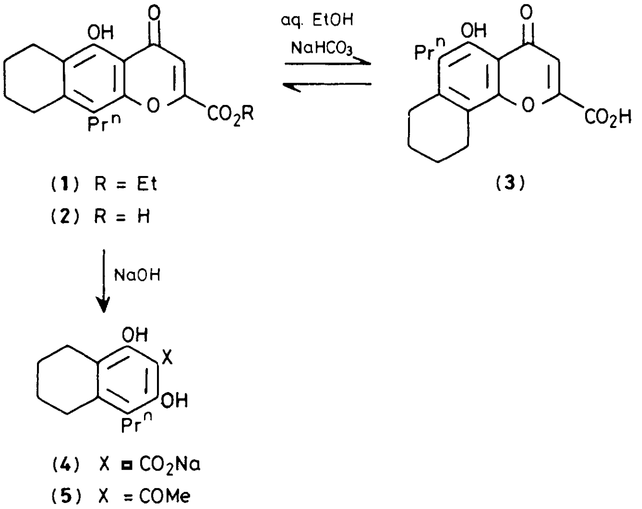
A Novel Irreversible Wessely–Moser Rearrangement of a 5-Mercaptochromone

John L. Suschitzky
Fisons plc, Pharmaceutical Division, Science and Technology Laboratories, Bakewell Road, Loughborough, Leicestershire LE11 0RH, U.K.

The first synthesis of a 5-mercaptochromone is described, which on treatment with aqueous sodium hydroxide undergoes a novel irreversible Wessely–Moser rearrangement to the corresponding 5-hydroxythiochromone.

The Wessely–Moser rearrangement[1] is a reversible isomerisation of 5-hydroxy-4*H*-1-benzopyran-4-ones (5-hydroxychromones) conventionally carried out under strongly acid conditions. Very few examples of base catalysed Wessely–Moser rearrangements have been reported[2,3] but work in our laboratories has shown that 5-hydroxychromone-2-carboxylic esters rearrange under basic conditions. For example, treatment of the ethyl ester (**1**) of the antiallergic tetrahydronaphthopyran [(**2**), proxicromil[4]] with sodium hydrogen carbonate in aqueous ethanol under reflux, gave, after acidification, a 3:1 equilibrium mixture of (**2**):(**3**).[5] In the presence of a stronger base [5% aqueous sodium hydroxide at room temperature (r.t.)], the intermediate β-diketone is cleaved yielding the salicylic acid derivative [(**4**), 68%] and the hydroxyacetophenone [(**5**), 10%].

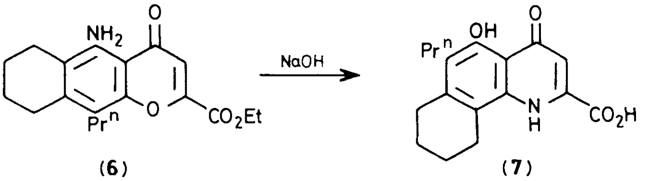


(**1**) R = Et
(**2**) R = H

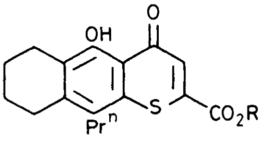
(**3**)

(**4**) X = CO_2Na
(**5**) X = COMe

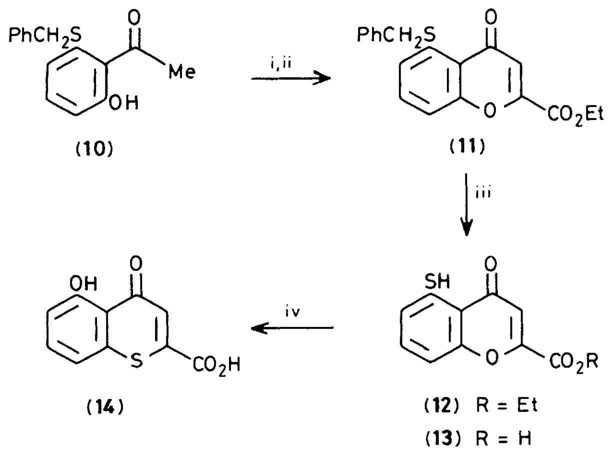
In contrast to 5-hydroxychromones, 5-aminochromones rearrange rapidly and irreversibly in the presence of sodium hydroxide to the corresponding 5-hydroxyquinolin-4-ones. For example, boiling ethanolic NaOH transformed (**6**) into (**7**) in 91% yield.[6]



(**6**) (**7**)



(**8**) R = Et
(**9**) R = H



Scheme 1. i, $(CO_2Et)_2$–NaOEt; ii, HCl (g); iii, $AlBr_3$; iv, NaOH.

The irreversibility (and hence synthetic utility) of this transformation is a consequence of the stability of the product quinolinones toward base. Thiochromones are also considerably more stable than chromones to base. We have found that the thiochromone-2-carboxylic ester (**8**) when treated with 2 M NaOH at 100 °C for two days merely hydrolyses to the corresponding acid [(**9**), 100%]. Simonis and Elias showed that 2,3-dimethylthiochromone could be ring opened with boiling aqueous alkali to yield 2-mercaptobenzoic acid, but the reaction was slow and did not go to completion.[7] The possibility that 5-mercaptochromones may undergo irreversible Wessely–Moser rearrangement was therefore investigated.

Although such compounds have previously not been reported, ethyl 5-mercapto-4-oxo-4*H*-1-benzopyran-2-carboxylate (**12**) was readily prepared from 2-hydroxy-6-phenylmethylthioacetophenone (**10**).[8] Reaction of (**10**) with diethyl oxalate (5 mol) and sodium ethoxide (2.5 mol) in ethanol under reflux for 3 h, followed by treatment of the solution with HCl (g) gave ethyl 4-oxo-5-phenylmethylthio-4*H*-1-benzopyran-2-carboxylate [(**11**), 82%]. Debenzylation of (**11**) [anhydrous aluminium bromide (2.5 mol), benzene, r.t., 4 h] gave (**12**), (92%), which on heating under reflux for 30 min with aqueous ethanolic sodium hydrogen carbonate (1.1 equiv.) gave the corresponding acid [(**13**), 86%]. No products of rearrangement were obtained. However, on heating (**12**) with 2 M NaOH (on a steam bath for 30 min with acid work-up), 5-hydroxy-4-oxo-4*H*-1-benzothiopyran-2-carboxylic acid [(**14**), 92%] was obtained. Compounds (**13**) and (**14**) were readily distinguished by ^{1}H n.m.r. spectroscopy in $[^2H_6]Me_2SO$ as solvent. In particular the protons on the 5-substituents appeared as singlets at δ 6.15 (SH) and 13.78 (OH).

This is the first example of a Wessely–Moser rearrangement involving sulphur and represents a potentially useful synthesis of 5-hydroxythiochromones.

Received, 8th December 1983; Com. 1596

References

1 F. Wessely and G. H. Moser, *Monatsh. Chem.*, 1930, **56**, 97; G. P. Ellis, 'Chromenes, Chromanones, and Chromones,' Wiley, New York, 1977, pp. 703–708.
2 W. Marlow, *Chem. Ind.*, 1969, 1838.
3 J. Varady, *Tetrahedron Lett.*, 1965, 4281.
4 J. Augstein, H. Cairns, D. Hunter, T. B. Lee, J. Suschitzky, R. E. C. Altounyan, D. M. Jackson, J. Mann, T. S. C. Orr, and P. Sheard, *Agents Actions*, 1977, **7**, 443.
5 H. Cairns and D. Hunter, *J. Heterocycl. Chem.*, 1977, **14**, 245.
6 R. C. Brown, H. Cairns, and J. Suschitzky, *Synthesis*, 1977, 276.
7 H. Simonis and A. Elias, *Chem. Ber.*, 1916, **49**, 768.
8 R. Kirchlechner, *Chem. Ber.*, 1982, **115**, 2461.