An Unusual Ring Transformation: Reaction of Phenyl 4-Chromone-3-sulfonate with Methyl 3-Aminocrotonate

Werner Löwe*, Peter Jeske and Anneliese Kradepohl [1]

Institut für Pharmazie, Freie Universität Berlin, Königin-Luise-Str. 2+4, D-1000 Berlin 33, West Germany

Received May 18, 1987

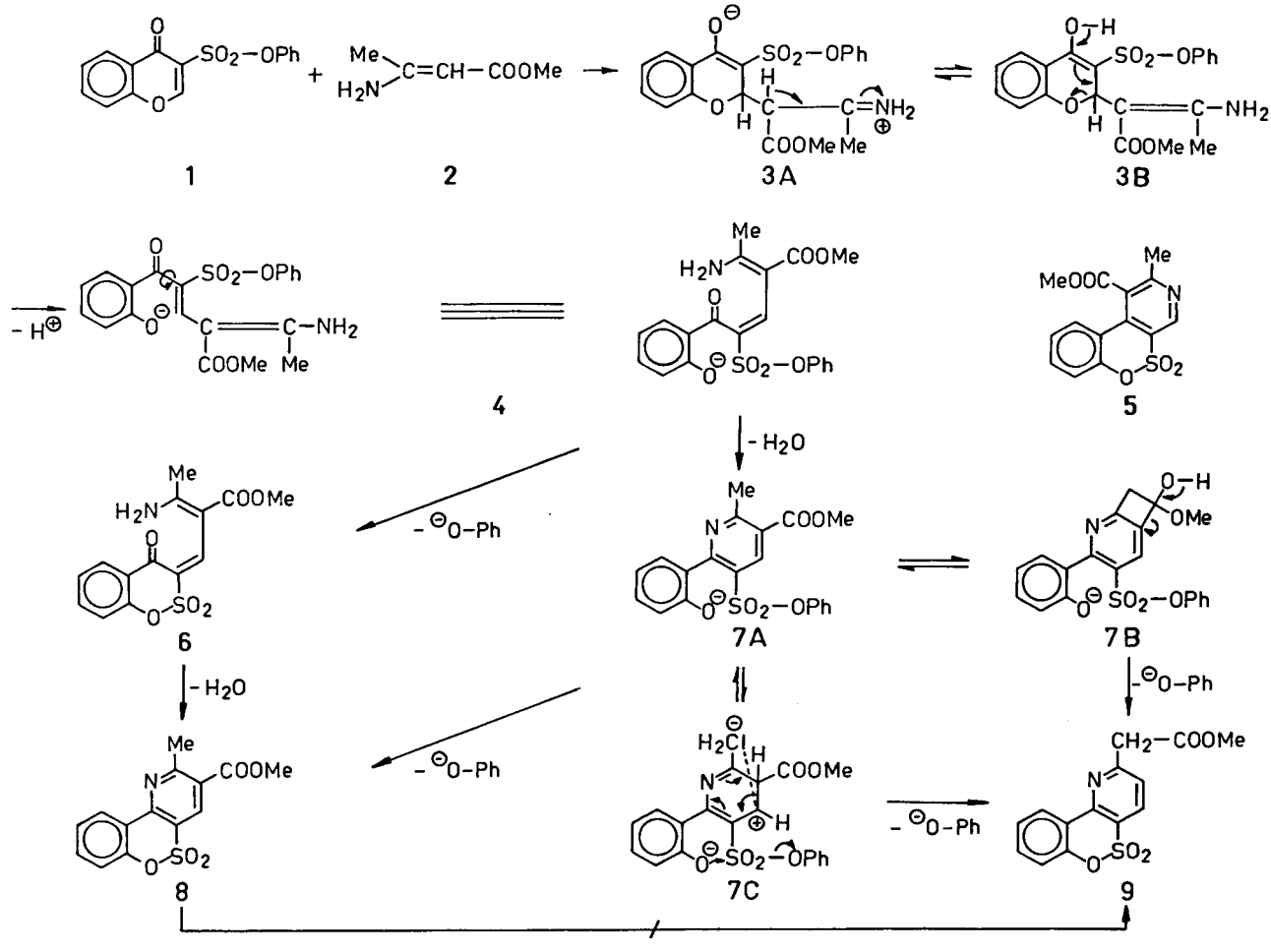
The novel benzoxathiinopyridines **8** and **9** were synthesized by ring transformation of phenyl 4-chromone-3-sulfonate (**1**) with methyl 3-aminocrotonate (**2**). The structures of **8** and **9** were determined by spectroscopic methods and the reaction courses for the formation of these compounds are discussed.

J. Heterocyclic Chem., **25**, 699 (1988).

Recently, phenyl 4-chromone-3-sulfonate (**1**) has been found to be an useful synthon for the synthesis of various heterocycles *via* ring transformation reactions [2,3].

In order to test the further applicability of these types of reactions, **1** was treated with methyl 3-aminocrotonate (**2**) in a one step melting reaction in the presence of sodium acetate. In this case a mixture of **8** and **9** in a ratio of about 1:5 (nmr) was obtained, from which **8** and **9** could be isolated by thin layer chromatography.

Structural assignments of the products formed were mainly based on ir, ^{1}H-nmr and ^{13}C-nmr studies. The compounds **8** and **9** show an infrared absorption at 1730 cm^{-1}, which indicates an ester carbonyl group. The SO_2-absorptions of **8** and **9** at 1390, 1185 cm^{-1} and 1375, 1185 cm^{-1} are produced by the cyclic sultone structure. In the ^{1}H-nmr spectrum (DMSO-d_6) of **8** the H-4 appears at 8.74 ppm. The H-10 doublet is downfield shifted to 8.54 ppm. The AB-pattern of **9** (H-3: 7.78, d, J = 8.1 Hz; H-4: 8.59, d,



Scheme I

J = 8.1 Hz), measured in DMSO-d_6 is typical in position and distribution for an 3,4-unsubstituted pyridine ring. The resonance of the CH_2-group is observed at 4.18 ppm and the H-10 shows signals at 8.44 ppm. None of the four downfield shifted carbon atoms of **8** and **9** shows any doublet in the off-resonance spectrum (^{13}C-nmr).

Hence structure **5** can be excluded. In this case, the first step of the ring transformation must be a nucleophilic attack of the amino group of **2** at C-2 of **1**.

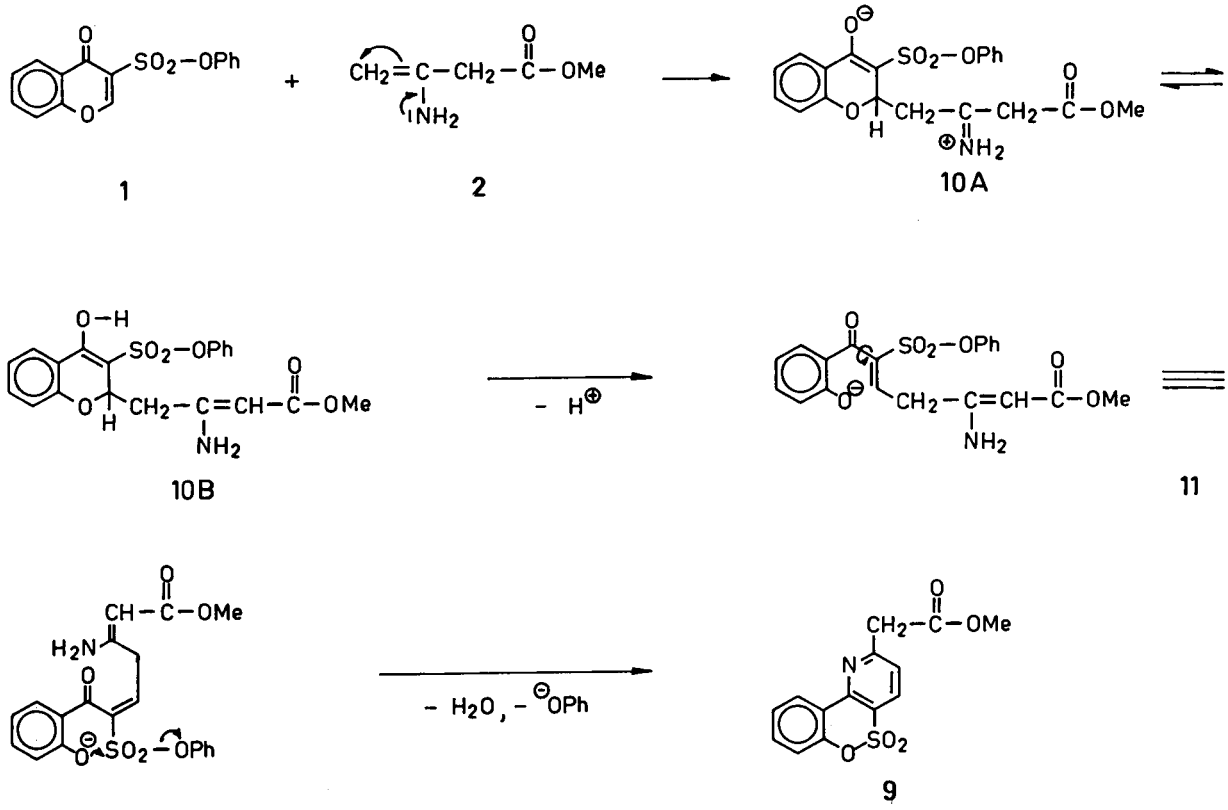
The mechanism for the preparation of **8** and **9** is suggested as follows (Scheme I):

The initial Michael addition of the electron rich C-2 of the enamine **2** at C-2 of the chromone **1** leads to a zwitterionic intermediate **3A**, which forms an equilibrium (**3A** ⇌ **3B**) in the melting reaction. This step is comparable with the addition of ethyl 3-aminocrotonate to an activated double bond of *p*-quinone in the Nenitzescu reaction [4].

Compound **3B** is then deprotonated to an anion **4** under the influence of acetate. From **4** there are two ways possible to afford the benzoxathiinopyridine **8**: Phenolate elimination to **6** and subsequent dehydration to **8** or first pyridine ring closure to **7A** and subsequent sultone annelation.

Compound **9** differs from **8** by the position of the ester group. Whereas in **8** this group is directly connected with the pyridine ring, the pyridine ring in formula **9** seems to stabilize itself by a hitherto unknown migration of the ester group from C-3 to the exocyclic methyl group. We believe, that the carbonyl moiety of the ester group in **7A** is activated by the sulfonyl group to give the four-membered intermediate **7B** after attack of a carbanion formed by the exocyclic methyl group. From **7B** compound **9** is obtained by ring opening and phenolate elimination. This way does not preclude the possibility that the formation of **9** from **7A** may occur *via* an intermediate **7C**. In this case the pyridine ring possesses a highly electron deficient C-4, which is activated in addition by the adjacent ester and sulfonyl groups. Hence the formation of **9** *via* **7C** could involve a bond cleavage between C-3 and C-4 in **7C**, followed by a recyclization under participation of the methylen carbanion.

An alternative to yield compound **9** from **1** and methyl 3-aminocrotonate without an acyl-migration is shown in scheme II. This mechanism is similar to what happens in scheme I. But in this case, it is the methyl group of methyl 3-aminocrotonate that reacts with the C-2 position of **1** in a Michael addition to give formulae (**10A** ⇌ **10B**). Deprotonation, followed by ring opening leads to the intermediate **11**, from which subsequent ring closure results in compound **9**. This reaction can happen since methyl 3-dimethylaminocrotonate has been found to react with iminium salts under participation of the methyl group [5].



Scheme II

The formation of **9** could be possible from compound **8** in similar ways, too. But all our attempts to convert **8** into **9** by treatment with sodiumacetate or sodiumacetate/-phenol failed.

EXPERIMENTAL

General Methods.

Melting points were determined on a Linström apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 297 spectrometer. The ^{1}H-nmr (250 MHz) and ^{13}C-nmr spectra were recorded on a Bruker WM-250 spectrometer. Mass spectra were obtained on a Finnigan MAT Bremen CH-7A spectrometer. The exact analyses by mass spectrometry were carried out at the Institut für Organische Chemie Mass Spectrometry Centre. Elemental analyses were performed by the Institut für Pharmazie Analytical Service Laboratory.

General Procedure for the Synthesis of **8** and **9**.

A mixture of **1** (1.0 g, 3.3 mmoles), **2** (1.0 g, 8.7 mmoles) and sodiumacetate (1.0 g) was heated at 120° for 3 hours. After cooling to room temperature, 50% aqueous ethanol (120 ml) was added. The resulting mixture was stirred for 4-5 hours. The compounds **8** and **9** separated out under these conditions as a yellow solid. The crude product was recrystallized from ethanol/water to give 400 mg (40%) of **8** and **9** (1:5, nmr) as colorless needles. The crystals were dissolved in 2 ml of chloroform and chromatographed by preparative thin layer chromatography (silica gel, chloroform) to give pure **7** and **9** as colorless crystals.

Methyl 2-methyl-1,2-benzoxathiino[4,3-*b*]pyridine-3-carboxylate 5,5 Dioxide (**8**).

This compound had mp 171° (methanol), Rf 0.57 (silica gel/chloroform); ir (potassium bromide): 1730 (C=O, ester), 1390, 1185 (SO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 2.97 (s, 3H), 3.95 (s, 3H), 7.58-7.83 (m, 3H), 8.54 (d, 1H), 8.74 (s, 1H); ms: m/z 305 (M^+, 100%); exact mass spectrum for $C_{14}H_{11}NO_5S$. Calcd: 305.0357. Found: 305.0356.

Anal. Calcd. for $C_{14}H_{11}NO_5S$: C, 55.08; H, 3.63; N, 4.59. Found: C, 55.09; H, 3.64; N, 4.26.

Methyl 1,2-benzoxathiino[4,3-*b*]pyridine-2-acetate 5,5 Dioxide (**9**).

This compound had mp 132° (methanol), Rf 0.33 (silica gel/chloroform); ir (potassium bromide): 1730 (C=O, ester), 1375, 1185 (SO_2) cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.70 (s, 3H), 4.18 (s, 2H), 7.58-7.84 (m, 3H), 7.78 (d, 1H, J = 8.1 Hz), 8.44 (d, 1H), 8.59 (d, 1H, J = 8.1 Hz); ms: m/z 305 (M^+, 100%); exact mass spectrum for $C_{14}H_{11}NO_5S$. Calcd: 305.0357. Found: 305.0359.

Anal. Calcd. for $C_{14}H_{11}NO_5S$: C, 55.08; H, 3.63; N, 4.59. Found: C, 55.13; H, 3.54; N, 4.62.

The ^{13}C-nmr spectrum (DMSO-d_6) of the mixture of **8** and **9** showed two sets of peaks, data are given for the four downfield shifted peaks and the CH_3- and CH_2-signals: **8**: 25.6 (q), 53.8 (q), 150.4 (s), 152.4 (s), 166.4 (s), 166.8 (s); **9**: 44.0 (t), 52.8 (q), 148.8 (s), 151.8 (s), 162.8 (s), 172.0 (s).

REFERENCES AND NOTES

[1] Part of the planned dissertation, P. Jeske and A. Kradepohl, FU Berlin.

[2] W. Löwe and P. Jeske, *Ann. Chem.*, 1124 (1986).

[3] W. Löwe and P. Jeske, *Ann. Chem.*, in press.

[4a] C. D. Nenitzescu, *Bull. Soc. Chim. Rom.*, **11**, 37 (1929). [b] G. R. Allen, Jr., C. D. Pidacks and M. J. Weiss, *J. Am. Chem. Soc.*, **88**, 2536 (1966).

[5] H. Möhrle and H. W. Reinhardt, *Arch. Pharm.* (Weinheim), **317**, 1017, (1984).