Michael Additions with an Enaminoester: Reaction of Phenyl 4-Chromone-3-sulfonate with Methyl 3-Amino-2-pentenoate

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The novel benzoxathiinopyridines **5** and **8** and the hitherto unknown oxathiinobenzopyran **17** were synthesized by ring transformations of phenyl 4-chromone-3-sulfonate (**1**) with methyl 3-amino-2-pentenoate (**2**). The structures of **5**, **8** and **17** were determined by spectroscopic methods and the reaction pathways for the formation of these compounds are discussed.

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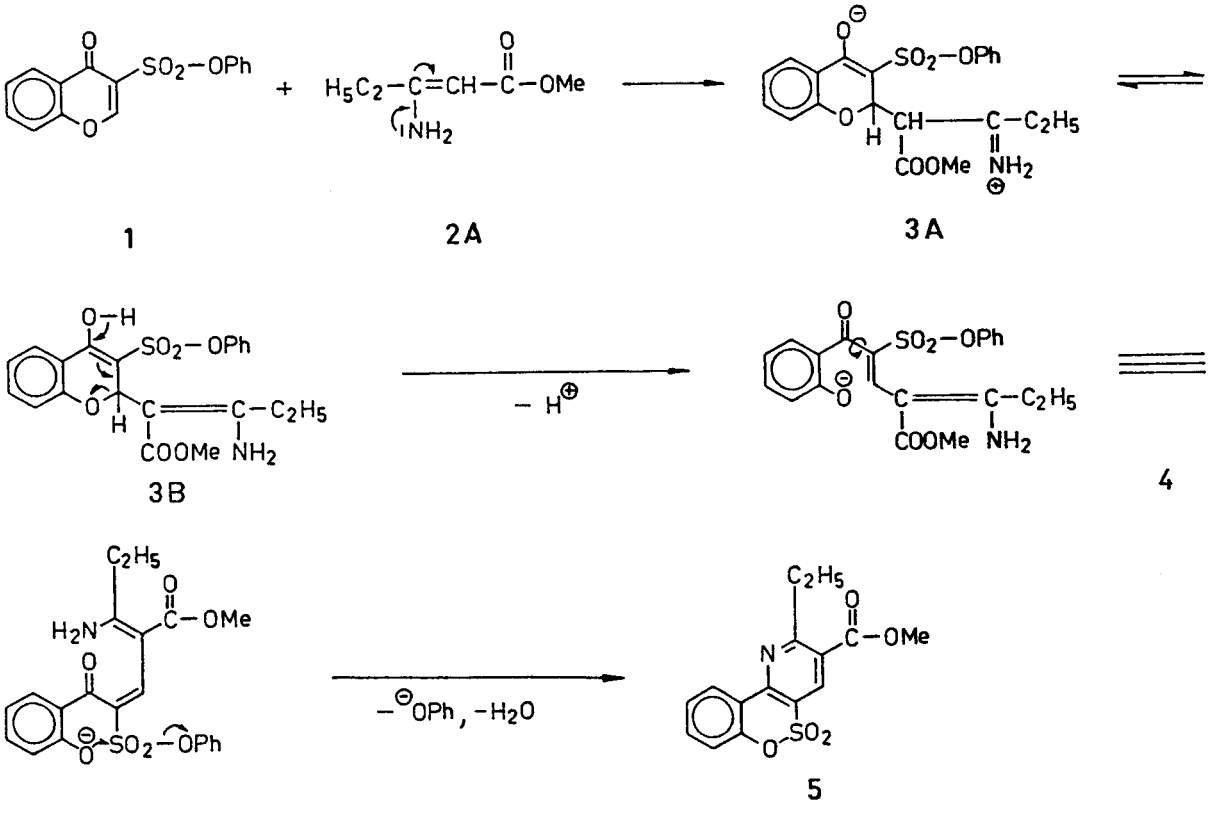
Methyl 3-aminocrotonate has been discussed to be an intermediate in the synthetic procedures of 1,4-dihydropyridines [2,3]. These compounds have received increasing attention because of their ability to regulate calcium concentrations in cardiovascular cells [4]. In spite of this renewed interest in this Hantzsch reaction there are remarkably few reports of an unexpected reactivity of enaminoesters [5].

In a previous paper [6] we reported a facile preparation of fused benzoxathiinopyridine derivatives, in which additions of the negative charged C-2 or C-4 atoms of methyl 3-aminocrotonate to the C-2 atom of phenyl 4-chromone-3-sulfonate (**1**) could be involved. This paper describes the reaction of methyl 3-amino-2-pentenoate (**2**) [7] with **1** in the presence of sodium acetate. In this case a mixture of **5**, **8** and **17** in a ratio of about 1:1:1 (nmr) was obtained, from which **5**, **8** and **17** have been separated by silica gel chromatography. The structures of all these compounds were confirmed by their spectra.

Thus the ν (C=O) occurred characteristically for the esters **5** and **8** near 1725 cm^{-1}. The SO_2 absorptions of **5** and **8** at 1375, 1175 cm^{-1} and 1370, 1170 cm^{-1} could be attributed to a cyclic sultone structure. In the ^1H nmr spectra (DMSO-d_6) of **5** the H-4 appears at 8.72 ppm and the

Scheme I



signals of the H-10 are shown to be a doublet at 8.53 ppm. The H-4 of **8** is observed as a singlet at 8.43 ppm. The resonance of the CH_2 group appears at 4.16 ppm and the ester methyl group shows a signal at 3.70 ppm. The singlet of the pyridine methyl is observed at 2.45 ppm. The compounds **5** and **8** gave a molecular ion at m/z 319 and elemental analyses confirmed the molecular formulae as $C_{15}H_{13}NO_5S$.

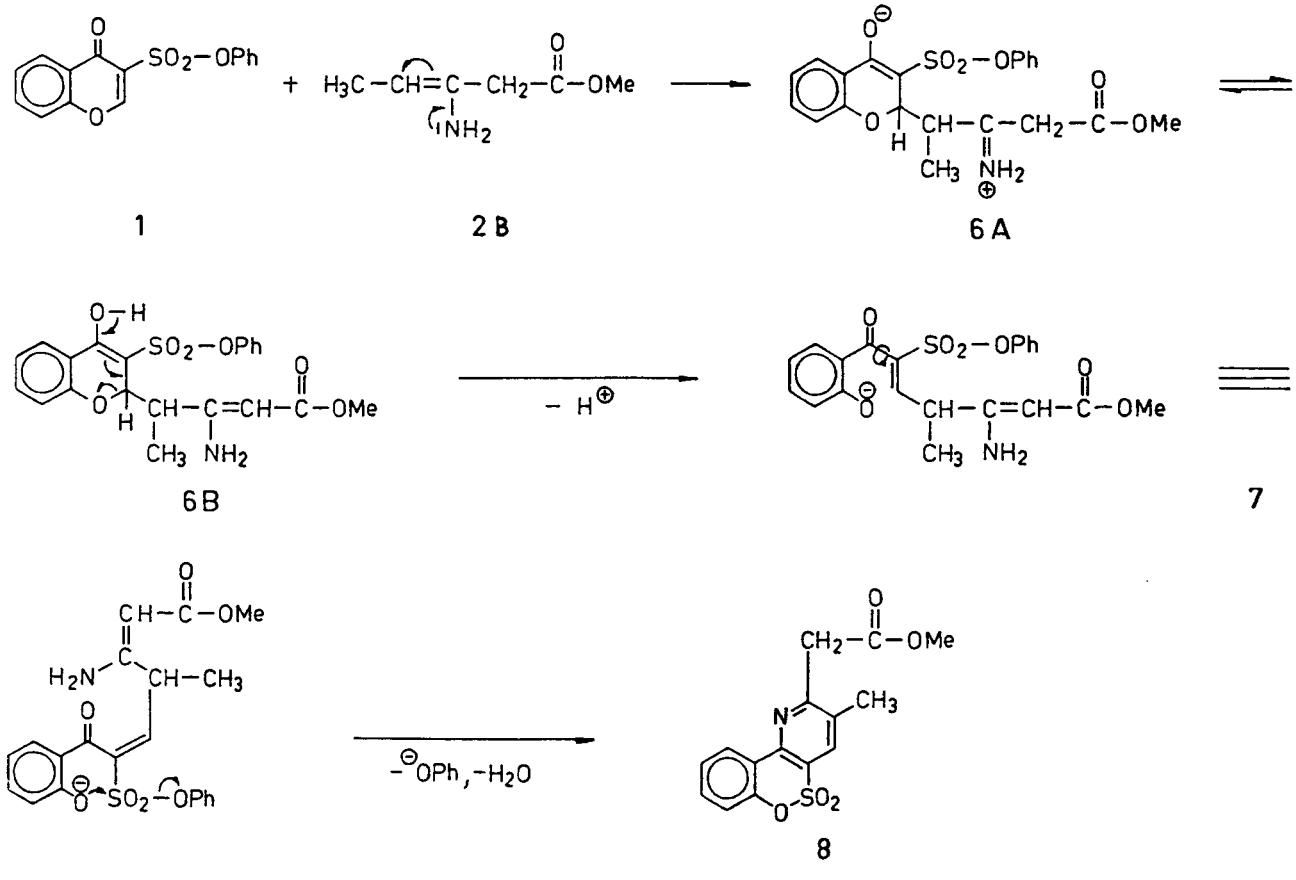
The olefinic CH peak of compound **17** is found at 6.50 ppm in DMSO-d_6 solution. The benzene ring CH signals form a multiplet at 7.59-8.05 ppm, which is diagnostically not very helpful, but the aliphatic CH_2 and CH_3 signals are clearly identificable at 2.81 ppm and 1.26 ppm. The ^{13}C nmr spectra of **17** shows the expected eleven resonances and the infrared spectra demonstrates the lactone carbonyl stretching band as a peak centered at 1750 cm^{-1}. The SO_2 absorptions at 1380 and 1175 cm^{-1} are produced by the cyclic sultone structure. The mass spectra shows a molecular ion peak (M^+) at m/z 278, which confirmed the structure of the product as **17**.

It is interesting to see that the addition of methyl 3-amino-2-pentenoate (**2**) to the chromone **1** gave equal amounts of **5**, **8** and **17** even though the only isomer **2A** exists in the starting enaminoester (nmr, DMSO-d_6). These results clearly indicate that different mechanisms operate for the three compounds. Thus, a reasonable pathway for the transformation of phenyl 4-chromone-3-sulfonate (**1**) and methyl 3-amino-2-pentenoate (**2A**) to compound **5** (Scheme I) involves formation of the intermediate **3A** ⇌ **3B** by the addition of the negative charged C-2 of **2A** to the C-2 of **1**. Compound **3B** is then deprotonated to an anion **4** under the influence of acetate. The subsequent phenolate elimination and dehydration afforded the benzoxathiinopyridine derivative **5**.

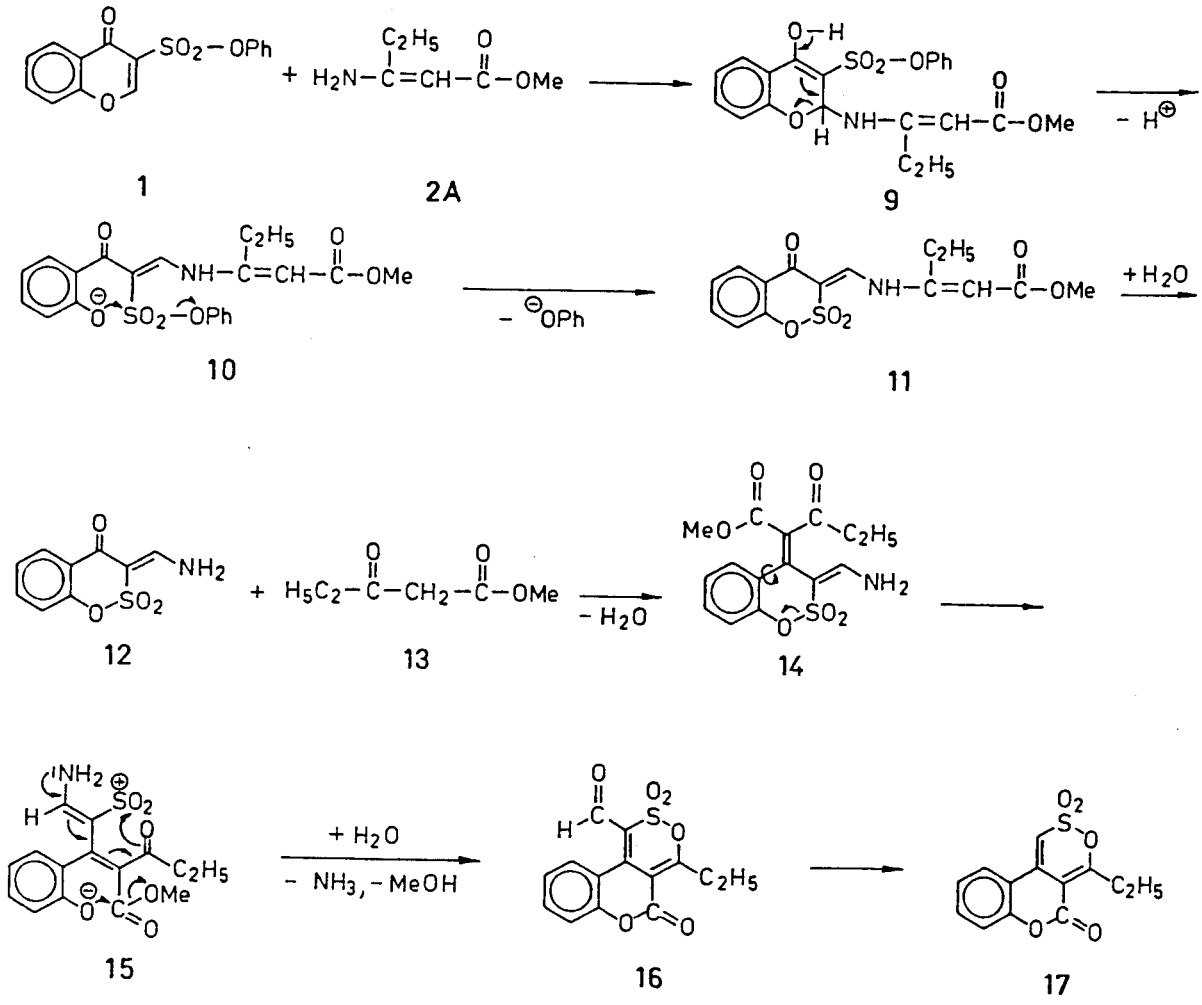
The mechanism for the preparation of **8** is suggested as follows (Scheme II). This route is similar to what happens in Scheme I. But in this case, it is the C-4 of **2B** that reacts with C-2 of **1** in a Michael addition to give formulae **6A** ⇌ **6B**. Deprotonation followed by ring opening leads to the intermediate **7**, from which subsequent ring closure results in compound **8**.

The formation of the nitrogen-free compound **17** can be explained as follows (Scheme III): under the reaction con-

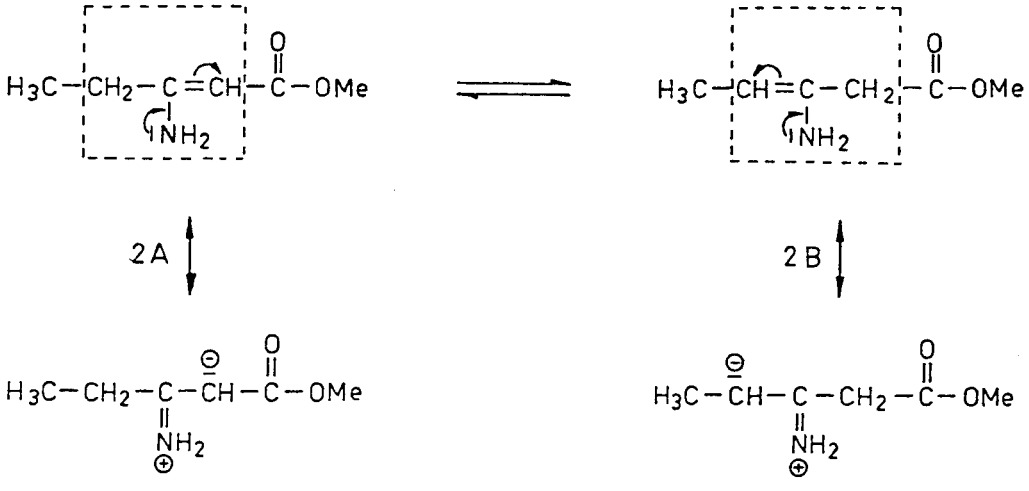
Scheme II



Scheme III



Scheme IV



ditions the amino group of **2A** would attack the C-2 of **1** to give formula **9**. The intermediate **9** is then deprotonated to an anion **10**. Subsequent ring closure to the sulton **11** is facilitated by the presence of a suitable phenolate leaving group. It is noteworthy that in this case no pyridine ring closure has been observed. We believe that the enaminoester group of **11** is hydrolyzed to compound **12** [8] and methyl 3-oxopentanoate (**13**). The enaminone group of **12** reacts with the acidic CH_2 of **13** to give the intermediate **14** in an 1,2-addition. Compound **14** is not stable and a bond cleavage between oxygen and sulfur leads to **15**, from which the oxathiinobenzopyran **16** is produced by a lactone ring closure under participation of the ester group and sultone annelation. This step involves hydrolysis of a suggested imine intermediate to the aldehyde **16**. Subsequent hydrolysis of the formyl group afforded compound **17**. The strongest evidence for the proposed pathway stems from the fact that **12**, which has been synthesized by another route [8], and **13** give rise to product **17** in the presence of sodium acetate. This way does not preclude the possibility that the formation of **12** arises directly from **1** by reaction with ammonia, which could be produced from **2A** by hydrolysis.

In conclusion, reaction of phenyl 4-chromone-3-sulfonate (**1**) with methyl 3-amino-2-pentenoate (**2**) in the presence of sodiumacetate yielded the novel benzoxathiinopyridines **5** and **8** and the hitherto unknown oxathiinobenzopyran **17**, respectively, by processes involving a guanidine-like reactivity of **2** (Scheme IV). Thus, it is apparent that 2-position, 4-position and the amino group of compound **2** are highly reactive to electrophilic attack.

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 ^1H 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. Elemental analyses were performed by the Institute für Pharmazie Analytical Service Laboratory.

General Procedure for the Synthesis of **5**, **8** and **17**.

A mixture of **1** (0.5 g, 1.66 mmoles), **2** (0.5 g, 3.88 mmoles) and sodiumacetate (0.5 g) was heated at 120° for one hour. After cooling to room temperature, 50% aqueous ethanol (10 ml) was added. After standing overnight 200 mg of compounds **5**, **8** and **17** (1:1:1, nmr) separated out as a pale yellow solid. 80 mg of the crude product **5**, **8** and **17** were dissolved in 5 ml of chloroform and chromatographed by preparative thin layer chromatography (silica gel, benzine/ethyl acetate 9:1). Subsequent eluation with 30 ml chloroform afforded pure **5**, **8** and **17** as colorless crystals.

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

This compound had mp 159° (ethanol), Rf 0.61 (silica gel, benzine/ethyl acetate 9:1); ir (potassium bromide): 1725 (C=O, ester), 1375, 1175 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.35 (t, 3H), 3.29 (q, 2H), 3.93 (s, 3H), 7.62-7.83 (m, 3H), 8.53 (d, 1H), 8.72 (s, 1H); ^{13}C nmr (DMSO-d_6): data are given for the CH_3 and CH_2 signals and the four downfield shifted peaks δ 12.7 (q), 29.7 (t), 52.9 (q), 148.5 (s), 150.4 (s), 164.5 (s), 168.6 (s); ms: m/z 319 (M^+, 73%).

Anal. Calcd. for $C_{15}H_{13}NO_5S$: C, 56.42; H, 4.10; N, 4.39. Found: C, 56.33; H, 4.05; N, 4.49.

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

This compound had mp 169° (ethanol); Rf 0.13 (silica gel, benzine/ethyl acetate 9:1); ir (potassium bromide): 1725 (C=O, ester), 1370, 1170 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.45 (s, 3H), 3.70 (s, 3H), 4.16 (s, 2H), 7.57-7.73 (m, 3H), 8.36 (d, 1H), 8.43 (s, 1H); ^{13}C nmr (DMSO-d_6): data are given for the CH_3 and CH_2 signals and the four downfield shifted peaks δ 17.8 (q), 41.6 (t), 52.0 (q), 143.9 (s), 149.6 (s), 159.9 (s), 169.6 (s); ms: m/z 319 (M^+, 100%).

Anal. Calcd. for $C_{15}H_{13}NO_5S$: C, 56.42; H, 4.10; N, 4.39. Found: C, 56.68; H, 3.96; N, 4.48.

4-Ethyl-5*H*-2,3-oxathiino[5,4-*c*][1]benzopyran-5-one 2,2 Dioxide (**17**).

This compound had mp 188° (ethanol); Rf 0.26 (silica gel, benzine/ethyl acetate 9:1); ir (potassium bromide): 3070 (CH, olefinic), 1750 (C=O, lactone), 1380, 1175 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.26 (t, 3H), 2.81 (q, 2H), 6.50 (s, 1H), 7.59-8.05 (m, 4H); ^{13}C nmr (DMSO-d_6): data are given for the CH_3 and CH_2 signals, the olefinic CH and the four downfield shifted peaks δ 12.3 (q), 25.6 (t), 112.9 (d), 148.5 (s), 154.7 (s), 155.8 (s), 157.4 (s); ms: m/z 278 (M^+, 82%).

Anal. Calcd. for $C_{13}H_{10}O_5S$: C, 56.11; H, 3.62. Found: C, 56.08; H, 3.43.

Compound **17** arises from the enaminone **12** as follows:

A mixture of **12** [8] (0.1 g, 0.44 mmole) methyl 3-oxopentanoate (**13**) (0.1 g, 0.77 mmole) and sodium acetate (0.1 g) was heated at 160° for 15 minutes. After cooling to room temperature, 4 ml of 50% aqueous ethanol was added. The residue was recrystallized from ethanol to yield 60 mg (49%) of compound **17**. This compound had mp 188° (ethanol).

Methyl 3-Amino-2-pentenoate (**2**) [7].

This compound had ^1H nmr (DMSO-d_6): δ 1.03 (t, 3H), 2.08 (q, 2H), 3.49 (s, 3H), 4.34 (s, 1H), 6.97 (s, br, 1H), 7.72 (s, br, 1H).

REFERENCES AND NOTES

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