Unusual Ring Transformations: Reaction of Phenyl 7-Fluoro-4-chromone-3-sulfonate with Methyl 3-Oxopentanoate in the Presence of Ammonium Acetate

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The novel benzoxathiinopyridines **4** and **5**, the hitherto unknown dibenzopyrone **6** and the heterocyclic enaminone **7** have been synthesized by ring transformations of phenyl 7-fluoro-4-chromone-3-sulfonate (**1**) with methyl 3-oxopentanoate (**2**) in the presence of ammonium acetate (**3**). The structures of **4-7** were determinated by spectroscopic methods and the reaction pathways of formation for these compounds are discussed.

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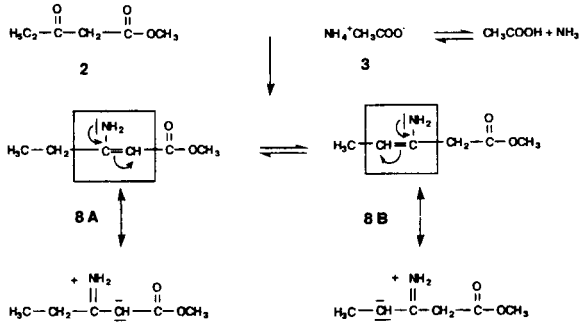
We previously [1] described a facile preparation of fused benzoxathiinopyridine derivatives and a novel oxathiino[5,4-*c*][1]benzopyran-5-one 2,2-dioxide by ring transformation reactions starting with phenyl 4-chromone-3-sulfonate and methyl 3-amino-2-pentenoate in the presence of sodium acetate. In this paper, we would like to report our observations on the title reaction.

Four different substances are produced, when melting phenyl 7-fluoro-4-chromone-3-sulfonate (**1**) [2] with methyl 3-oxopentanoate (**2**) in the presence of ammonium acetate. In this case a mixture of **4-7** in a ratio of about 3:9:1:3 (weight) was obtained. The compounds **4-7** were separated using a Chromatotron. The structures of all these compounds were confirmed by their elemental analyses and spectra.

Structural assignments of the products formed were mainly based on ir and ^{1}H-nmr studies. The benzoxathiinopyridines **4** and **5** show an ir absorption near 1725 cm^{-1}. The SO_2 absorptions of **4** and **5** at 1369, 1178 cm^{-1} and 1380, 1198 cm^{-1} could be attributed to a cyclic sultone structure. In the ^{1}H-nmr spectra (DMSO-d_6) of **4** the H-4 is observed as a singlet at 8.45 ppm. The resonance of the exocyclic CH_2 group appears at 4.16 ppm and the ester methyl group shows a signal at 3.70 ppm. The signal of the pyridine methyl is observed at 2.50 ppm. The H-4 of **5** appears at 8.72 ppm and the signals of the H-10 are shown at 8.57 ppm. Compounds **4** and **5** gave a molecular ion at m/z 337 and elemental analyses confirmed the molecular formulae as $C_{15}H_{12}FNO_5S$. The exocyclic methyl group of the dibenzopyron **6** is found at 2.16 ppm. The benzene ring CH signals form a multiplet at 7.34-7.45 ppm. The H-9 signal is identifiable at 7.78 ppm. One of the N-H signals lies under the aromatic signals, the other one is combined with H-1 at 8.93 ppm. The ir spectra demonstrates the lactone carbonyl stretching band as a peak centered at 1697 cm^{-1}. The SO_2 absorptions at 1338 and 1177 cm^{-1} are produced by the sulfonate ester. The intensive N-H absorptions at 3466 and 3333 cm^{-1} are very typical. The mass spectrum shows a molecular ion peak at m/z 399 and elemental analysis confirmed the molecular formulae as $C_{20}H_{14}FNO_5S$. The ir spectra of the heterocyclic enaminone **7** also shows the typical NH absorptions at 3346 and 3211 cm^{-1}. In the ^{1}H-nmr spectra the NH protons are observed at 9.52 and 9.84 ppm. The mass spectrum shows a molecular ion peak at m/z 243 and elemental analysis confirmed the molecular formulae as $C_9H_6FNO_4S$.

Scheme I

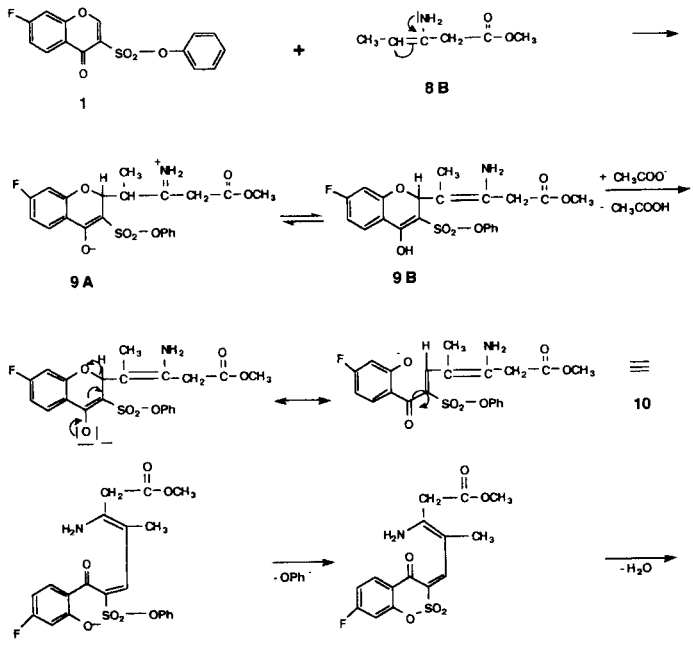


It is indicated that different mechanisms operate for the four compounds. During the syntheses of **4, 5** and **6** the enamino ester **8** is also produced *in situ* from methyl 3-oxopentanoate (**2**) and ammonium acetate (**3**). The former being an enamine with two sites of high electron density either, its C-4 or its C-2 can as a nucleophile attack the chromone **1** (Scheme I).

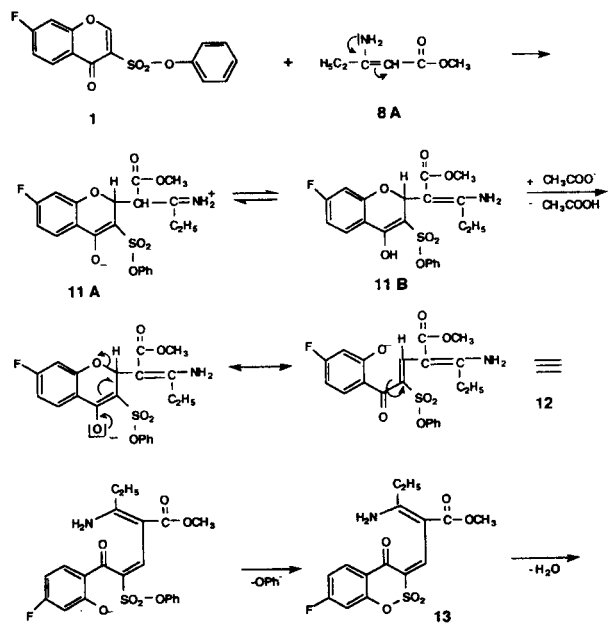
The mechanism for the preparation of **4** is suggested as follows (Scheme II). The initial Michael addition of the electron rich C-4 of the enamine **8B** at C-2 of the chromone **1** leads to a zwitterionic intermediate, which forms an equilibrium with the neutral form (**9A** ⇌ **9B**). The following deprotonation of **9B** with ammonium acetate **3** causes ring opening resulting in the intermediate **10**. Phenolate elimination and subsequent dehydration from **10** yields the end product **4**.

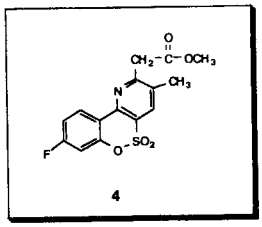
The synthesis of the benzoxathiinopyridine **5** is a similiar process, however it is the C-2 part of the enamine **8A** which reacts (Scheme III). Clearly, the latter pathway

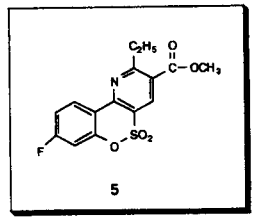
Scheme II



Scheme III







is more likely, which can be seen from the amount of **5** obtained. Again the first step is a Michael addition. The formulae **11A** ⇌ **11B** show that a nucleophilic 1,4-addition has taken place. Deprotonation occurring from **11B**, followed by ring opening to formulae **12** and subsequent sultone ring closure results in the intermediate **13**. Pyridine ring closure yields compounds **5**.

The first step to synthesize dibenzopyrone **6** could be a nucleophilic addition of the enamine **8A** to the chromones **1**, an activated C-4 carbonyl group, forming **14A** ⇌ **14B** (Scheme IV). Formula **14B** shows that a 1,2-addition has happened. A conjugated system has developed after dehydration. Now the 2-position of the chromone has an electron deficit (Formula **15**). The reaction water present and the auxiliary base ammonium acetate **3** cause ring opening to **16A**. A vinylogous iminoenole is developed. The tautomeric intermediate **16B** demonstrates the presence of an aldehyde. The 2-pyrone ring develops due to methanol elimination and the second ring is closed when the electron rich enamine carbon atom attacks at the carbonyl group to form **17A**. This case is remarkable because the primary amino group is not involved in the ring closure. The betaine structure **17A** forms an equilibrium with formula **17B**. Subsequently further dehydration occurs and the transient state **6A** is transformed into dibenzopyrone **6** by imine-enamine-tautomerism. Producing the aromatic and thus energetically most favourable state is the driving force behind the last two steps (Scheme IV).

Ammonia and acetic acid form an equilibrium with ammonium acetate **3**. The former and chromone **1** react to produce formula **18A**. The resulting zwitterionic structure forms an equilibrium with the vinylogous structure of the sulfonate ester (**18A** ⇌ **18B**). From that deprotonation easily occurs **19**. The heterocyclic enaminone **7** originates after phenolate elimination and ring closure (Scheme V).

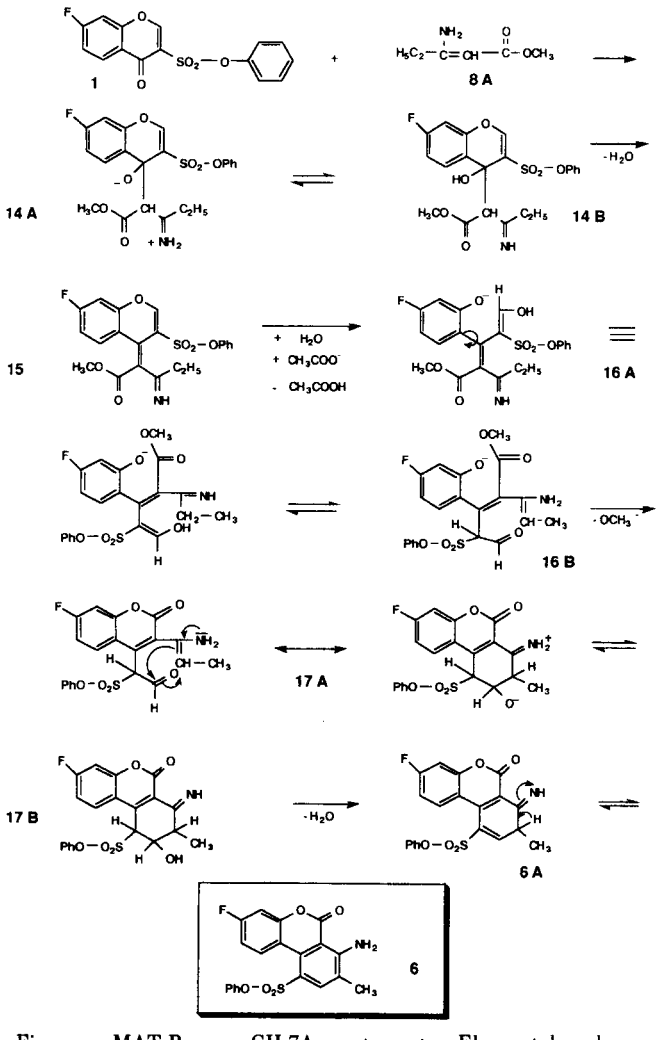
All four ring transformations occur to the definition of van der Plas [3,4].

EXPERIMENTAL

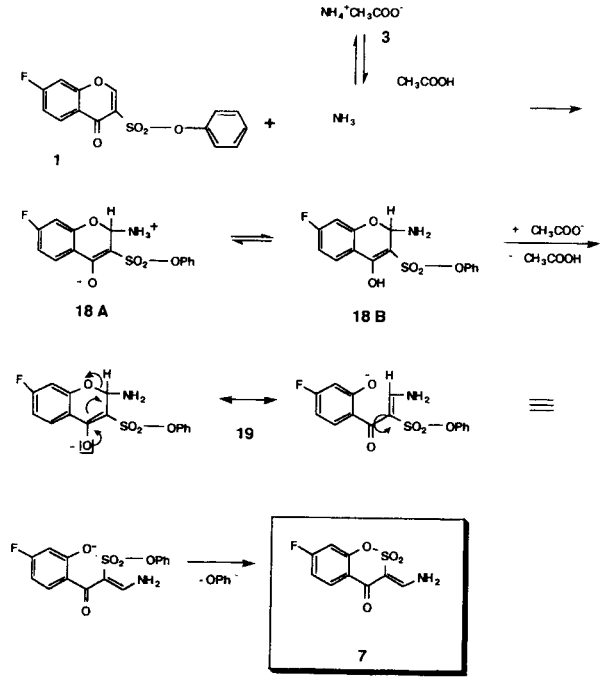
General Methods.

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 spectra were recorded on a Bruker AC 300 spectrometer. Mass spectra were obtained on a

Scheme IV



Scheme V



Finnegan MAT Bremen CH-7A spectrometer. Elemental analyses were performed by the Institute für Pharmazie Analytical Service Laboratory.

General Procedure for the Synthesis of **4-7**.

A mixture of **1** (0.3 g, 0.94 mmoles), **2** (0.2 g, 1.5 mmoles) and ammonium acetate (0.3 g) was heated at 110° for one hour. After cooling to room temperature, 50% aqueous ethanol (15 ml) was added. After standing over night 200 mg of a mixture of compounds **4-7** was separated out as a pale yellow solid. From the mixture (600 mg) the compounds **4-7** were isolated using a Chromatotrone with benzene/ethyl acetate (9:1); silica gel 60 PF 254 (Merck); **4**: rf, 0.60; **5**: rf, 0.82; **6**: rf, 0.58; **7**: rf, 0.33.

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

The colourless crystals had mp 148° (ethanol), yield 51 mg, Rf 0.60; ir (potassium bromide): 3062 cm^{-1} (=CH-), 2956 (CH_2), 1731 (C=O), 1369, 1178 (SO_2); ^{1}H-nmr (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 3.70 (s, 3H, OCH_3), 4.16 (s, 2H, CH_2), 7.48 (m, 1H, H-9), 7.65 (m, 1H, H-7), 8.41 (m, 1H, H-10), 8.45 (s, 1H, H-4); ms: m/z 337 (M^+ 100%).

Anal. Calcd. for $C_{15}H_{12}FNO_5S$: C, 53.41; H, 3.59; N, 4.15. Found: C, 53.14; H, 3.53; N, 4.11.

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

The colourless crystals had mp 135° (ethanol), yield 150 mg, Rf 0.82; ir (potassium bromide): 3068 cm^{-1} (=CH-), 2964, 2942 (CH_2, CH_3), 1725 (C=O), 1380, 1198 (SO_2); ^{1}H-nmr (DMSO-d_6): δ 1.35 (t, J = 7 Hz, 3H, CH_3), 3.26 (q, J = 14/7 Hz, 2H, CH_2), 3.93 (s, 3H, OCH_3), 7.53 (m, 1H, H-9), 7.74 (m, 1H, H-7), 8.57 (m, 1H, H-10), 8.72 (s, 1H, H-4); ms: m/z 337 (M^+ 59%).

Anal. Calcd. for $C_{15}H_{12}FNO_5S$: C, 53.41; H, 3.59; N, 4.15. Found: C, 53.47; H, 3.56; N, 4.13.

Phenyl 7-Amino-3-fluoro-8-methyl-6*H*-6-oxo-dibenz[*b*,*d*]pyran-10-sulfonate (**6**).

The colourless crystals had mp 219° (ethanol), yield 15 mg, Rf 0.58; ir (potassium bromide): 3466 cm^{-1} (NH), 3333 (NH), 3065 (=CH-), 1697 (C=O), 1608 (NH), 1338, 1177 (SO_2); ^{1}H-nmr (DMSO-d_6): δ 2.16 (s, 3H, CH_3), 7.34-7.45 (m, 8H, arom + NH), 7.78 (s, 1H, H-9), 8.93 (m, 2H, H-1 + NH); ms: m/z 399 (M^+ 26%).

Anal. Calcd. for $C_{20}H_{14}FNO_5S$: C, 60.15; H, 3.53; N, 3.51. Found: C, 59.73; H, 3.31; N, 3.59.

3-Aminomethylene-7-fluoro-3,4-dihydro-1,2-benzoxathiin-4-one 2,2-Dioxide (**7**).

The colourless crystals had mp 230° (ethanol), yield 54 mg, Rf 0.33; ir (potassium bromide): 3346 cm^{-1} (NH), 3211 (NH), 1652 (C=O), 1342, 1160 (SO_2); ^{1}H-nmr (DMSO-d_6): δ 7.32-8.07 (m, 3H, arom), 9.52 (s, 1H, NH), 9.84 (s, 1H, NH); ms: m/z 243 (M^+ 86%).

Anal. Calcd. for $C_9H_6FNO_4S$: C, 44.44; H, 2.49; N, 5.76. Found: C, 44.34; H, 2.57; N, 5.52.

REFERENCES AND NOTES

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