A NEW PATHWAY IN THE REACTIONS OF CHROMONES AND HYDROXYL-AMINE IN ANHYDROUS SOLUTIONS

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Summary. In the nucleophilic reaction of chromone (1) with NH₂OH·HCl in anhydrous methanol a new compound 2-methoxychromanone (6) appeared as an intermediate in the formation of chromone oxime (8) and 2-methoxychromanone oxime (7).

In earlier reports¹⁻⁵ we have shown that nucleophilic reagents (OH⁻, EtO⁻, NH₂OH, H₂NNHR) attack the chromone ring (<u>1</u>) at the C-2 atom.

An attack of NH₂OH·HCl at the C-4 atom, which results in the formation of chromone oxime was described by Beugelmans and Morin⁶. They hypothesized that the pyrylium cation (2) was formed early in this reaction and the C_4 -OH group was the "leaving group".

Having repeated the experiments of Beugelmans and Morin⁶ (0.25 M NH₂OH+HCl in MeOH) indeed, <u>8</u> (m.p. 130° C, lit. 127^{7}), <u>5</u> (m.p. 186° C, lit. 181^{7} , $185-187^{9}$) and <u>10</u> [oil: ¹H-NMR data: (δ , DMSO-d₆, DSS): H-vinyl 6.74 <u>d</u> and 8.45 <u>d</u> lit. 6.7 <u>d</u> and 8.4 <u>d</u>⁶] were isolated. Separation by chromatography a new compound <u>9</u> [N_{calc}: 7.82 %, N_{found}: 7.98 %, m.p.: 87.0-87.5 °C, ¹H-NMR data: (δ , acetone-d₆, TMS): H-4 3.49 <u>q</u> and 3.65 <u>q</u>, H-5 5.68 <u>m</u>, C₅-OCH₃ 3.47 <u>s</u>, C₂,-OH 9.86 <u>s</u>]was also obtained.

In these reaction mixtures it was always possible to detect a fluorescent spot on t.l.c. (R_f : 0.62 in ClCH₂CH₂Cl:CH₃COC₂H₅=95:5) above that of the chromone. This component was also observed in the reaction mixtures of chromone (<u>1</u>) or various substituted chromones when boiled with 0.25 M HCl in anhydrous methanol. In the ¹H-NMR spectra of the compounds obtained from evaporated MeOH solutions signals characteristic of chromone, a methoxy group and an ABX system appeared, identical with those of 2-hydroxychromanone⁸.

The ratio of <u>6</u> and <u>1</u> (Table 1) was the same independently of whether <u>1</u> or <u>11</u> was boiled in 0.25 M HCl-containing anhydrous MeOH, although the reaction is somewhat faster starting with <u>11</u>.

In other alcohols (EtOH, n-BuOH) the formation of compounds of 6-type was observed.

The <u>6:1</u> ratio depends on the substituent of the starting chromone derivative. Electron attracting groups stabilize <u>6</u>.



Scheme 1

Starting chromone deriv.	Vinyl protons	с ₂ -осн ₃	ABX system	<u><u>6</u>** <u>1</u></u>
Chromone (<u>la</u>)	н-2 8.15 <u>d</u> н-3 6.30 <u>d</u>	3.40 <u>s</u>	H-2 (X) 5.63 m H-3 (A) 2.56 q H-3 (B) 3.35 q	0.06
6-Chlorochromone (<u>1b</u>)	H-2 8.26 <u>d</u> H-3 6.30 <u>d</u>	3.45 <u>s</u>	H-2 (X) 5.65 <u>m</u> H-3 (A) 2.61 <u>g</u> H-3 (B) 3.40 <u>g</u>	0.13
6-Nitrochromone (<u>lc</u>)	H-2 7.65 <u>d</u> H-3 6.26 <u>d</u>	3.50 <u>s</u>	H-2 (X) 5.85 <u>m</u> H-3 (A) 2.77 <u>q</u> H-3 (B) 3.53 <u>q</u>	1.66
2-Hydroxychromanone (<u>11</u>) ⁸	-	-	H-2 (X) 5.85 <u>m</u> H-3 (A) 2.70 <u>q</u> H-3 (B) 3.08 <u>q</u>	

Table 1. ¹H-NMR data of the product obtained from chromones in HC1-containing boiling anhydrous methanol (δ , acetone-d₆, TMS)^{*}

*s: singulet, d: doublet, q: quartet, m: multiplet

** The <u>6:1</u> ratio was calculated using the integrated ¹H-NMR signal intensities of H-2 atoms.

The chromones show no change in HCl-containing anhydrous dioxane, dimethoxyethane, or diisopropylether. In these solvents chromones give 5 with $NH_2OH \cdot HCl$. The compound obtained by Beugelmans and Morin (8) was not observed, although protonation of 1 to 2 can be expected in these systems.

¹H-NMR study of the reaction mixture of 1 and NH₂OH·HCl in anhydrous



Fig.1. ¹H-NMR spectrum of reaction mixture of <u>la</u> and NH₂OH·HCl (δ , acetone-d₆, TMS)

MeOH shows the presence of 5, 6, 8, 9 and a new component, 7 (2-methoxy-chromanone oxime).

These data show that attack at C-2 results in the formation of 5. Attack at C-4 <u>(6)</u>gives rise to <u>7</u>, <u>8</u> and <u>9</u>. Upon prolonged treatment <u>10</u> is obtained. C-2 and C-4 reactivity ratio of <u>1</u> and <u>6</u> was calculated from ¹H-NMR integral intensities (Table 2). From these data it can also be seen that electron attracting substituents reduce the reactivity at C-4 in <u>1</u> and <u>6</u>.

Compound	H-2	н-	3	с2-осн3	C-4/C-2	
<u>7a</u>	5.32 <u>m</u>	2.80	3.25 <u>q</u>	3.42 <u>s</u>	32	
<u>7b</u>	5.38 <u>m</u>	2.85	3.30 <u>q</u>	3.40 <u>s</u>	7	
<u>7c</u>	5.80 <u>m</u>	3.58	3.82 <u>q</u>	3.25 <u>s</u>	0.4	

Table 2. ¹H-NMR data^{*} of <u>7a-7c</u> and ratio of C-4/C-2 attack^{**}

* (δ , acetone-d₆, TMS)

****** calculated as the $(\underline{7}+\underline{8}+\underline{9})/\underline{5}$ ratio

The order of appearance $\underline{8}$ and $\underline{9}$ in the reaction mixture, as well as the change of the ratio of $\underline{8}$ to $\underline{9}$ during the course of the reaction showed that the formation of $\underline{8}$ was kinetically, while that of $\underline{9}$ thermodynamically controlled.

On the basis of our experiments the sensitivity of C-4 in $\underline{2}$ towards nucleophilic reagents is questionable. It seems that the C₄-OH of $\underline{2}$ is not a good leaving group in the case of this condensed delocalized-electron system.

The formation of <u>8</u> is most probably the result of an acid catalyzed MeOH addition of <u>1 via 6</u> and <u>7</u> (Scheme 1).

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