Chemistry of Heterocyclic Compounds, Vol. 34, No. 3, 1998

USE OF LANTHANIDE SHIFT REAGENTS FOR STUDYING PYRIDINE ANALOGS OF ISOFLAVONES

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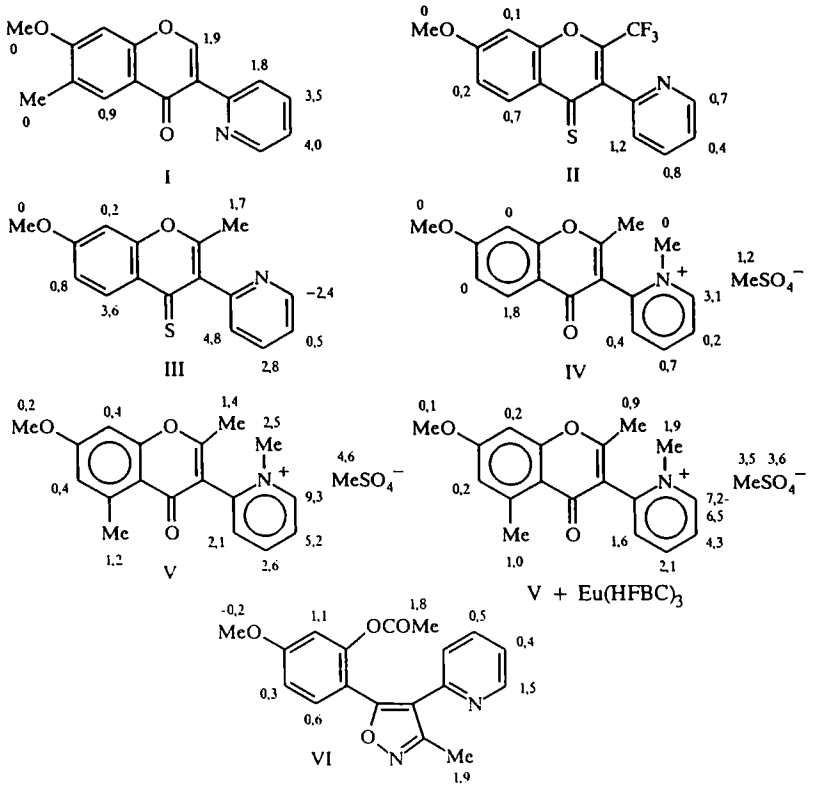
The interaction of lanthanide shift reagents (LSR) with pyridine analogs of isoflavone and their derivatives has been studied. It was found that the pyridine nitrogen atom can increase the coordinating ability of electron donor groups in the molecule, in particular the sulfur atom in chromone thiones. It has been shown that LSR interact actively with pyridinium methylsulfate salts containing the 3-chromone substituent. The efficiency of the coordination is influenced by the occurrence of steric hindrance around the chromone carbonyl. The structure of the adducts of these salts with LSR is discussed.

Heterocyclic analogs of isoflavones react efficiently with LSR allowing the determination of their conformation and structural features and establishment of their chirality [1-3]. Using this method we have studied benzofurans [4, 5], thiazoles [6], benzodioxanes and their analogs [7], as well as native isoflavonoids [8]. Even though pyridine analogs of isoflavone and their many derivatives have been synthesized some time ago [9, 10] they have not been studied by the indicated method. In addition, such an investigation is of interest because of the high biological activity of the pyridine chromone series.



Taras Shevchenko University, Kiev 252033, Ukraine. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 342-345, March, 1998. Original article submitted June 19, 1997; revision submitted November 10, 1997.

 0009-3122/98/3403-0308$20.00

In this work we present the results of our primary investigation of various chromones containing the 2-pyridyl substitutent in position 3 (I-V) and of an isoxazole derivative (VI). The values of the specific lanthanide induced shifts (LIS) are given in parts per million for the corresponding protons in the presence of $Eu(FOD)_3$ and also in the presence of europium heptafluorobutyrylcamphorate ($Eu(HFBC)_3$) in the case of compound V. Chromones I and II were synthesized by analogy to the known chromones III-V [9]. The former was prepared from 7-hydroxy-6-methyl-3-(2-pyridyl)chromone (VII) and the latter by thionylation of 2-trifluoromethyl-3-(2-pyridyl)-7-methoxychromone (VIII) using P_2S_5. The ability of 3-hetarylchromones to undergo recyclization with nucleophilic reagents [11-15] was used to prepare the isoxazole VI from 2-methyl-3-(2-pyridyl)-7-methoxychromone.

A pyridine nitrogen atom is an efficient coordinating center for LSR [16] hence large specific lanthanide induced shifts might be expected for the compounds studied. However, it was found that this coordinating center is sterically hindered in 3-(2-pyridyl)chromones and the observed LIS values are comparatively small. For the interaction of $Eu(FOD)_3$ with compound I the maximum observed LIS for one of the pyridine ring β-protons is 4 whereas for pyridine itself it can reach 30-40 ppm. In the spectrum, the pyridine α-proton signal is not observed and this relates to a strong broadening due to a chelation effect (cf. [6]).

Interaction of $Eu(FOD)_3$ with the thione derivatives II and III is of great interest. As a rule LSR either do not coordinate with the C=S group or the LIS values prove to be very small, but marked LIS were found for thiones with the pyridine fragment. They were particularly large in the case of compound III. The most powerfully downfield shifted signals were those of the thiochromone ring 5-H proton and one of the β-protons in the pyridine ring. A significant upfield shift was noted for the α-proton of the pyridine ring. Based on the dipolar nature of the LIS, the observed shifts arise because the LSR coordinates with the thione sulfur atom which approaches the pyridine nitrogen atom in space. Hence, in the given case, we observed a strong effect of the pyridine ring on the coordinating ability of the sulfur atom. This effect may find use in coordination chemistry.

Introduction of an electron acceptor substituent into the 2 position of the thiochromone ring leads to a sharp weakening of the coordination of the LSR with the sulfur atom. Hence in the trifluoromethyl derivative II there is almost no coordination of the LSR with the thione group and here the LIS is mainly due to coordination to the pyridine nitrogen atom.

The interaction of $Eu(FOD)_3$ with the pyridinium salts IV and V also proved of interest. In these cases, coordination of the LSR can occur both at the oxygen atom of the carbonyl group and at the anion (coordination of simpler pyridinium salts with LSR at the anion has been reported in detail [17]). The LIS values found for salt IV show that the most active coordination center is the carbonyl oxygen atom. This is indicated since the most marked shift is for the chromone 5-H and not the methyl group of the anion. By contrast in V, where the chromone carbonyl is sterically hindered by the 5-CH_3 substituent, coordination occurs at the anion. Here the signal for the methyl group of the anion has an LIS of 4.6 whereas the 5-CH_3 is only 1.2 ppm. The pyridine α-proton signal in V is shifted more strongly than the anion proton signal even though LSR coordination occurs at the latter. This may be due to a specific structure for the LSR-salt adduct (cf. [18]) in which the cation and anion are placed on different sides of the LSR molecule (as an unusual "sandwich"). Its formation may be because the anion coordinated with the anion proves to be sterically unavailable for the cation whereas, on the other side of the LSR molecule, there are electron donor groups effectively solvating the cation and favoring its positioning not too far from the anion.

We have studied the reaction of salt V with the optically active LSR $Eu(HFBC)_3$. The latter forms an adduct with the anion of salt V just as efficiently as with $Eu(FOD)_3$. As shown by examining steric models, in compound V rotation of the pyridine fragment relative to the chromone ring is impossible hence there is a chirality axis which coincides with the chemical bond joining the heterocyclic fragments. Splitting of a series of signals in the presence of $Eu(HFBC)_3$ confirms the presence of such chirality (the LIS values for diastereomer adduct protons at 330 K are given on the formula). The fact that the anion methyl group signal is also split points to slow exchange between the adduct anion antipodes of salt V with $Eu(HFBC)_3$ on the NMR time scale. Lowering of the temperature caused an additional significant splitting of the signals for the 2- and 5-methyl groups.

Hence the reaction of LSR with pyridine analogs of isoflavone leads to further important information about them.

Recyclization of 3-(2-pyridyl)chromones [9] gives compounds with a structure like VI containing several possible centers for reaction with LSR, hence their coordination characteristics are difficult to predict. It was found that the LIS values for the signals of the synthesized isoxazole VI were small but that, basically, the LSR interacts with the pyridine nitrogen atom. Hence $Eu(FOD)_3$ can be used to define more accurately the structure of compounds of this type.

EXPERIMENTAL

PMR Spectra were measured on a Bruker WP-100SY spectrometer at 100.13 MHz and with TMS internal standard. LSR were used for this work without additional treatment. Specific LIS were calculated as mean values for a series of spectra with stepwise increasing amounts of LSR.

2,4-Dihydroxy-5-methyl-α-(2-pyridyl)acetophenone was prepared from 2-cyanomethylpyridine and 1,3-dihydroxy-4-methylbenzene in the presence of boron trifluoride etherate by a known method [9] in 73% yield with mp 241°C with decomposition (from propanol). Found, %: N 5.8. $C_{14}H_{13}NO_3$. Calculated, %: N 5.8. PMR Spectrum (DMSO-D_6, here and further pyridine ring protons are assigned dashes): 4.51 (2H, s, CH_2); 12.21 (1H, s, 2-OH); 6.40 (1H, s, 3-H); 10.68 (1H, s, 4-OH); 2.15 (3H, s, 5-CH_3); 7.33 (2H, m, 3′ and 5′-H); 7.78 (1H, t, ^3J = 8 Hz, 4′-H); 8.46 ppm (1H, d, ^3J = 5 Hz, 6′-H).

7-Hydroxy-6-methyl-3-(2-pyridyl)chromone (VII) was prepared from acetophenone using ethyl orthoformate by method [9] in 90% yield with mp 265°C. Found, %: N 5.6. $C_{15}H_{11}NO_3$. Calculated, %: N 5.5. PMR Spectrum (DMSO-D_6): 8.64 (1H, s, 2-H); 7.77 (1H, s, 5-H); 2.30 (3H, s, 6-CH_3); 10.63 (1H, s, 7-OH); 6.86 (1H, s, 8-H); 7.28 (3H, m, 3′ to 5′-H); 8.45 ppm (1H, d, ^3J = 4 Hz, 6′-H).

6-Methyl-7-methoxy-3-(2-pyridyl)chromone (I) was prepared by a known method from the hydroxychromone VII in 88% yield with mp 160°C. Found, %: N 5.2. $C_{16}H_{13}NO_3$. Calculated, %: N 5.24. PMR Spectrum ($CDCl_3$): 8.61 (1H, s, 2-H); 7.91 (1H, s, 5-H); 2.35 (3H, s, 6-CH_3); 3.98 (3H, s, 7-OCH_3); 6.77 (1H, s, 8-H); 7.7 (3H, m, 3′ to 5′-H); 8.44 ppm (1H, d, ^3J = 4 Hz, 2′-H).

2-Trifluoromethyl-3-(2-pyridyl)-7-methoxy-4-thiochromone (II) was prepared from chromone VIII and P_2S_5 according to method [9] in 70% yield with mp 130-132°C. Found, %: S 9.8. $C_{16}H_{10}F_3NO_2S$. Calculated, %: S 9.5. PMR Spectrum ($CDCl_3$): 8.47 (1H, d, ^3J = 8 Hz, 5-H); 7.04 (1H, dd, ^3J = 8, ^4J = 2 Hz, 6-H); 3.97 (3H, s, 7-OCH_3); 6.95 (1H, d, 8-H); 7.31 (2H, m, 3′ and 5′-H); 7.78 (1H, t, ^3J = 8 Hz, 4′-H); 8.71 ppm (1H, d, ^3J = 4 Hz, 6′-H).

3-Methyl-4-(2-pyridyl)-5-(2-hydroxy-2-methoxyphenyl)isoxazole (IX). A mixture of 2-methyl-3-(2-pyridyl)-7-methoxychromone ([9], 2 mmole) and hydroxylamine hydrochloride (6 mmole) in dry pyridine (4 ml) was held at 100-115°C for 2 h and the hot solution was added to water (150 ml). The oil produced gradually solidified and the precipitate obtained was crystallized from aqueous alcohol in 71% yield with mp 145°C. Found, %: N 9.8. $C_{16}H_{14}N_2O_3$. Calculated %: N 9.9. PMR Spectrum ($CDCl_3$): 12.81 (1H, s, 2-OH); 6.68 (1H, d, ^4J = 2 Hz, 3-H); 3.92 (3H, s, 4-OCH_3); 6.58 (1H, dd, ^3J = 8 Hz, ^4J = 2 Hz, 5-H); 7.34 (1H, d, ^3J = 8 Hz, 6-H); 2.55 (3H, s, 3-CH_3, isoxazole fragment); 7.70 (2H, m, 3′- and 5′-H); 7.8 (1H, t, ^3J = 8 Hz, 4′-H); 8.57 ppm (1H, d, ^3J = 4 Hz, 6′-H).

3-Methyl-4-(2-pyridyl)-5-(2-acetoxy-4-methoxylphenyl)isoxazole (VI). A mixture of product IX (1 mmole) and acetic anhydride (3 ml) was refluxed for 1 h and the product poured into a mixture of finely divided ice and water (100 ml). The precipitated oil was triturated and gradually solidified to a precipitate which was filtered, washed with water, and crystallized from alcohol to give VI (76%) with mp 99-100°C. Found, %: N 8.6. $C_{18}H_{16}N_2O_4$. Calculated, %: N 8.64.

The authors thank the INTAS program and the International Sorosovsk ISSEP program (grant N SPU063069) for financial support of this work.

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