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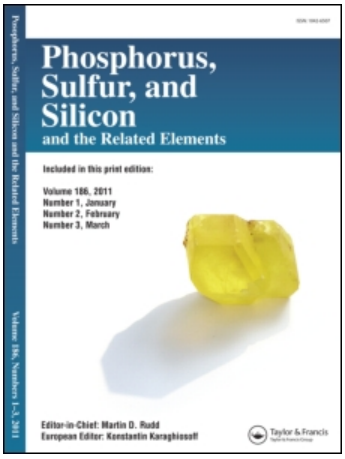

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AMINOPHOSPHONIC DERIVATIVES OF CHROMONE. SYNTHESIS OF NOVEL CHROMONE-3-(α-AMINO) METHANEPHOSPHONIC ACIDS

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AMINOPHOSPHONIC DERIVATIVES OF CHROMONE. SYNTHESIS OF NOVEL CHROMONE-3-(α-AMINO) METHANEPHOSPHONIC ACIDS

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Reactions of 3-formylchromones with benzyl carbamate and triphenyl phosphite in acetic acid lead to the corresponding diphenyl chromone-3-[α(-N-benzyloxycarbonyl)amino]-methanephosphonates **2** in high yields. Deprotection of the Z-substituted diphenyl esters **2** by means of acetic hydrogen bromide solution and the subsequent hydrolysis by means of 20% aq. HCl, lead to the final chromone-3-(α-amino)methanephosphonic acids **4**. Attempts of synthesis of the corresponding chromone-2- aminophosphonic derivatives by this way, have failed. On the other hand, chromone-2-(α-amino)methanephosphonic acid (**6**) was successfully obtained by an addition of tris(trimethylsilyl) phosphite to the aldimine, which was formed from the 2-formylchromone.

Keywords: 3-Formylchromones; amidoalkylation reaction; diphenyl chromone-3-(α-amino) -methanephosphonates; chromone-2-[α-(N-benzyl)amino]methanephosphonic acid

INTRODUCTION

The oxygen heterocyclic systems have a widespread occurrence amongst the vegetable kingdom. Two groups of oxygen heterocycles, being derivatives of chromone, i.e. the hydroxyflavones and the anthocyanins are the main colouring components of flowers, trees and fruits.

* Correspondance Authors.

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Biological and pharmacological activities of some chromone derivatives are well documented[1]. An example of the pharmaceutical agent, derived from chromone, used in medicine, is the *intal,* which is applied for bronchitis asthma disease.

The aim of this work is the synthesis of the novel chromone derivatives of aminomethanephosphonic acid. As it is widely known, the derivatives of aminophosphonic acids are substances of great interest, because of their biological activity. Therefore, it seems that, the combination in one molecule of the chromone system with aminophosphonate would result in some new products with potential biological activity.

Chromone derivatives of aminomethanephosphonic acid are not described in the literature, according to our knowledge. Synthesis of some chromone derivatives of methanephosphonic acid and hydroxymethanephosphonic acid, was reported a few years ago[2]. These products were obtained by an addition reaction of dialkyl phosphites to the corresponding formylchromones. Reduction of the formed hydroxyphosphonates with hydrogen iodide in the presence of red phosphorus led to the chromone-3-methanephosphonic acids[2].

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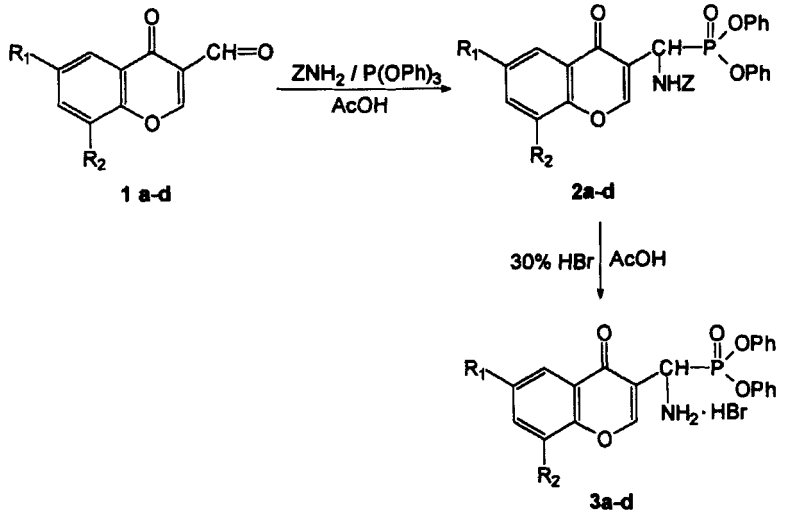
RESULTS AND DISCUSSION

3-Formylchromones **1a-d**, which are commercially available agents, react easily with benzyl carbamate and triphenyl phosphite in acetic acid solution to form the Z- substituted diphenyl aminophosphonates **2a-d** in considerably high yield.

Reaction of aldehydes with carbamates and esters of phosphorous acid is known as the amidoalkylation reaction of trivalent phosphorus compounds[3]. This reaction has a wide application in the preparation of a large number of aminophosphonates, especially the diphenyl esters of various aminophosphonic acids.

In our case, following the literature method, we obtained the phosphonates **2a-d**, as it is shown in scheme 1.

The basic physicochemical data of the obtained compounds **2a-d** are given in the table I. The N-carbobenzyloxy aminophosphonates **2a-d** were easily deprotected by the action of hydrogen bromide solution in acetic acid (scheme 1). After reaction, the aminophosphonates with unsubstituted amino group were obtained in high yield, as hydrobromides **3a-d.** However, when the diphenyl esters **2a** and **2b** were treated with 30% HBr/AcOH, the corresponding monophenyl esters were obtained. In this



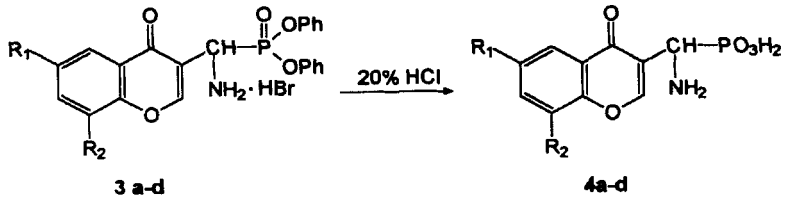
a: $R_1=R_2=H$, **b:** $R_1=Me$, $R_2=H$, **c:** $R_1=Cl$, $R_2=H$, **d:** $R_1=R_2=Cl$

Z=$PhCH_2OCO$

SCHEME 1

case, one phenyl group has also been removed from the diphenyl phosphonate **3** during treatment of it with HBr/AcOH solution.

The aminophosphonic esters **3a-d** were easily hydrolysed to the corresponding aminophosphonic acids **4a-d,** by means aq. 20% HCl (scheme 2).



SCHEME 2

The chromone-3-(α-amino)methanephosphonic acids (**4**) are stable, white solids. The physicochemical data of the obtained acids are given in table II.

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TABLE I Physicochemical Properties of Chromone-3-[α-(N-Benzyloxycarbonyl)amino]methanephosphonates **2**

No.	R^1	R^2	*Yield %*	*M. p. °C*	*^{1}H-NMR ($CDCl_3$), ppm*	*^{13}C-NMR, ppm*	*^{31}P-NMR, ppm*
2a	H	H	58	159–160	8.22 (d, 1H, arom.), 8.12 (d, 1H, arom.), 7.67 (m, 1H, arom.), 7.43–7.11 (m, 17H, arom.), 6.88 (d, 1H, NH, J=9.6 Hz), 5.70 (dd, 1H, CH-P, J_1=21.7 Hz, J_2=9.8 Hz), 5.10 (dd, 2H, CH_2O)	176.4 (C=O), 156.1, 155.7, 155.36, 155.23, 150.42, 150.25, 150.12, 136.01, 134.15, 129.72, 129.61, 128.50, 128.20, 128.14, 125.99, 125.63, 125.35, 125.28, 123.93, 120.50, 120.44, 118.15, 117.94, 67.45 (CH_2), 47.36 (d, CH-P, J=165 Hz)	13.127 (s)
2b	Me	H	61	179–180	8.11 (d, 1H, arom.), 7.97 (s, 1H, arom.), 7.46 (d, 1H, arom.), 7.32–7.11 (m, 16H, arom.), 6.94 (d, 1H, NH, J=9.6 Hz), 5.68 (dd, 1H, CH-P, J_1=21.6 Hz, J_2=9.7 Hz), 5.11 (dd, 2H, CH_2O), 2.43 (s, 3H, CH_3)	176.48 (C=O), 155.73, 155.29, 155.17, 154.37, 150.43, 150.26, 150.13, 136.04, 135.65, 135.37, 129.69, 128.48, 128.16, 128.10, 125.31, 125.23, 123.58, 120.60, 120.55, 120.50, 120.45, 117.88, 117.66, 67.40 (CH_2O), 47.32 (d, CH-P, J=165 Hz), 20.95 (CH_3)	13.292 (s)
2c	Cl	H	63	175–176	8.14 (m, 1H, arom), 7.58 (m, 1H, arom), 7.36–7.10 (m, 17H, arom), 6.88 (d, 1H, NH, J=9.66 Hz), 5.72 (dd, 1H, CH-P, J_1=21.9 Hz, J_2=9.7 Hz), 5.12 (dd, 2H, CH_2O)	175.17 (C=O), 155.61, 155.49, 154.36, 150.34, 150.21, 150.18, 150.05, 135.94, 134.34, 131.60, 129.70, 129.36, 128.49, 128.21 128.11, 125.39, 125.34, 124.76, 120.53, 120.45, 120.39, 119.88, 118.29, 67.49 (CH_2O), 46.84 (d, CH-P, J=165 Hz)	12.923 (s)
2d	Cl	Cl	60	167–168	8.18 (d, 1H, arom.), 8.05 (s, 1H, arom.), 7.70 (s, 1H, arom.), 7.30–7.10 (m, 15H, arom), 6.83 (d, 1H, NH, J=9.2 Hz), 5.74 (dd, 1H, CH-P, J_1=22.2 Hz, J_2=9.7 Hz), 5.12 (dd, 2H, CH_2O)	174.36(C=O), 155.57, 155.45, 150.43, 150.30, 150.17, 150.12, 149.99, 135.89, 134.17, 131.28, 129.75, 128.48, 128.19, 128.03, 125.54, 124.43, 124.10, 120.46, 120.42, 120.36, 119.05, 67.50 (CH_2O), 46.23 (d, CH-P, J=165 Hz)	12.545 (s)

TABLE II Physicochemical Properties of Chromone-3-(α-Amino)-Methanephosphonic Acids **4**

No.	R^1	R^2	*Yield %*	*M.p. °C*	*^{1}H-NMR, ppm*	*^{31}P-NMR, ppm*
4a	H	H	51	202–207 (dec)	[D_2O]: 8.29 (bs, 1H, arom.) 7.76 (d, 1H, arom., J=7.6 Hz) 7.62 (bs, 1H, arom.) 7.41–7.22 (m, 2H, arom.) 4.66 (d, 1H, CH-P, J= 18.2 Hz)	12.356 (s)
4b	Me	H	95	210–215 (dec)	[DMSO]: 8.82 (bs, 1H, arom.) 7.84 (bs, 1H, arom.) 7.60 (bs, 1H, arom.) 7.51 (bs, 1H, arom.) 4.52 (d, 1H CH-P, J= 16.1 Hz) 2.39 (s, 3H, CH_3)	8.981 (s)
4c	Cl	H	96	255–257 (dec)	[DMSO + D_2SO_4]: 8.76 (bs, 3H, NH_3^+) 8.62 (bs, 1H, arom.) 8.05 (bs, 1H, arom.) 7.92 (bs, 1H, arom.) 7.82 (bs, 1H, arom.) 4.70 (d, 1H CH-P, J = 16.2 Hz)	12.734 (s)
4d	Cl	Cl	94	249–251 (dec)	[DMSO + D_2SO_4]: 8.81 (bs, 3H, NH_3^+) 8.68 (bs, 1H, arom.) 8.21 (bs, 1H, arom.) 8.02 (bs, 1H, arom.) 4.69 (d, 1H CH-P, J = 16.3 Hz)	12.445 (s)

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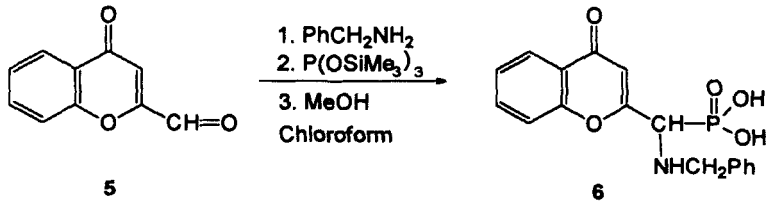
In continuation of our work, we have tried to apply the amidoalkylation reaction [3] for 2-formylchromone (**5**), in hope to obtain the corresponding chromone-2 phosphonic derivatives. After several experiments we found that, in the case of 2-formylchromone, such a reaction does not take place. No phosphonic products were obtained in these experiments, and instead of that, decompositions of the reaction mixtures were observed.

Next, we tried the Kabachnik-Fields method, which uses the addition of diethyl phosphite to aldimine, formed from 2-formylchromone and benzylamine. The expected diethyl chromone-2-[α-(N-benzyl)amino]methanephosphonate was also not obtained, and decomposition of the reaction mixture was observed in this case, too.

Finally, the one example of phosphonic acid, derived from 2-formylchromone, was obtained by the action of tris(trimethylsilyl) phosphite on aldimine, formed *in situ* from **5** and benzylamine, and subsequent methanolysis of the silylated product. The reaction was carried out without isolation of the intermediates, and the final yield of chromone-2-[α-(N-benzyl)amino]-methanephosphonic acid (**6**) was 31%. The acid **6** was a stable, white amorphous solid. The synthesis of **6** is illustrated in scheme 3.

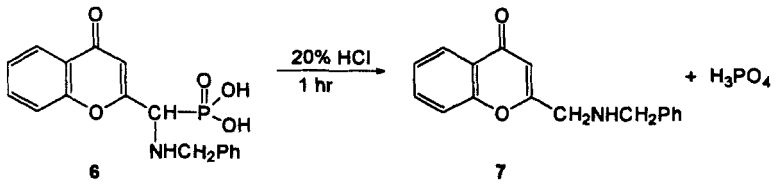


5 **6**

SCHEME 3

An interesting and unexpected reaction was observed in the case of the synthesized chromone-2-[α-(N-benzyl)amino]-methanephosphonic acid (**6**).

The acid **6**, contrary to the chromone-3-phosphonic acids **4**, is unstable in acidic aqueous solutions. During heating of **6** in aqueous HCl or other strong mineral acids, the acid **6** undergoes a decomposition, combined with a C-P bond cleavage in the molecule and with formation of N-(Chromone-2-yl-methyl)-benzylamine (**7**) and phosphoric acid. The cleavage of the **6** is shown in scheme 4.



6 **7**

SCHEME 4

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The presented cleavage is a new example of a C-P bond splitting observed on heterocyclic aminophosphonates in acidic conditions. Similar phenomena were reported in the case of 2- and 4-pyridylmethyl(amino)phosphonates[4,5].

The unusual cleavage of chromone-2 phosphonic derivatives is now investigated in our group and will be the subject of a separate publication.

CONCLUSIONS

The chromone-3 derivatives of aminomethanephosphonic acid **2** were easily obtained in *one-pot* reactions from the corresponding aldehyde, benzyl carbamate and triphenyl phosphite in high yield. However, the corresponding chromone-2 phosphonic derivatives cannot be obtained in this way. This is probably due to the fact, that these compounds are unstable in acidic conditions. This was proved by the independent synthesis of chromone-2 phosphonic derivative **6** by the Fields method, and by studying the behaviour of **6** in acidic solutions. It has been found, that the chromone-2 phosphonic derivative undergoes a cleavage during treatment with acid, combined with the formation of the corresponding amine and phosphoric acid. The observed reaction is a new example of a C-P bond cleavage in aminophosphonates caused by a strong mineral acid.

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EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in $CDCl_3$, DMSO-d_6 or D_2O solutions respectively, using 300.13 MHz for ^1H NMR, 75.477 MHz for ^{13}C NMR and 121.51 MHz for ^{31}P NMR spectra. G.C.-M.S. analyses were carried out with a Hewlett Packard HP 5971A apparatus, at an ionization potential of 70 eV, equipped with HP-1 capillary column, and also the M.S. analyses were performed on a Finnigan TSQ 700 instrument (electrospray ionization, on mode: ESI±Q1MS). Elemental analyses were done in the laboratory of Instrumental Analysis, in the Institute. Melting points were measured on a Digital Melting Point Apparatus Electrothermal 9200, and were uncorrected.

All commercially available reagents were used as received from the supplier (Aldrich Company). 2-Formylchromone was prepared from methyl chromone-2-carboxylate, according to the published method[6].

Synthesis of Diphenyl Chromone-3-[α-(N-Benzylaxycarbonyl)amino]-Methanephosphonates (2)

3-Formylchromone (**1a-d**) (20 mmol), benzyl carbamate (3.1g, 20 mmol) and triphenyl phosphite (6.4g, 20 mmol) were dissolved in 45 mL acetic acid and the solution heated at 90–100 °C for 1.5 hr. The vent was removed by evaporation under reduced pressure and the obtained oil was treated with 50 mL methanol and cooled. The precipitated crystalline product (**2a-d**) was collected by filtration, washed twice with 20 mL cold methanol and dried. The data of **2** are given in table I.

Elemental Anal. for **2a**: Calc. C 66.54, H 4.47, N 2.59, P 5.72; Found: C 66.30, H 4.50, N 2.59, P 5.86.

Elemental Anal. for **2b**: Calc. C 67.02, H 4.72, N 2.52, P 5.58; Found: C 66.90, H 4.48, N 2.70, P 5.71.

Elemental Anal. for **2c**: Calc. C 62.56, H 4.03, N 2.43, P 5.38, Cl 6.16; Found: C 62.42, H 4.18, N 2.45, P 5.39, Cl 6.46.

Elemental Anal. for **2d**: Calc. C 59.03, H 3.63, N 2.29, P 5.07, Cl 11.62; Found: C 58.90, H 3.82, N 2.31, P 5.28, Cl 11.79.

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Removing of Benzylaxycarbonyl Group from Phosphonates 2. Formation of Hydrobromides of Phosphonates 3

Phosphonate **2a-d** (5 mmol) was mixed with 30% HBr /AcOH solution (6 mL) and protected against moisture. The mixture was stirred for 1 hr, and then mixed with dry diethyl ether (100 mL). The precipitated material was collected by filtration, washed several times with dry diethyl ether and dried, to give the almost pure products **3a-d**, as pale yellow powders.

Monophenyl ester, hydrobromide **3a**: Yield 84%. M.p. 215–218 °C (dec.). ^{1}H NMR (DMSO): 8.67(bs, 3H, NH_3^+), 8.60(s, 1H), 8.11(d, 1H, J=7.68 Hz), 7.88(t, 1H, J=8.70 Hz), 7.72(d, 1H, J=8.16 Hz), 7.55(t, 1H, J=7.68 Hz), 7.14(t, 2H, Ph), 6.75(d, 3H, Ph), 4.64(d, 1H, CH-P, J=16.83 Hz). ^{31}P NMR: 12.665 (s), ppm.

Monophenyl ester, hydrobromide **3b**: Yield 92%. M.p. 175–178 °C (dec.). ^{1}H NMR (DMSO): 8.67(bs, 3H, NH_3^+), 8.57(d, 1H, J=2.43 Hz),

7.89(s, 1H), 7.63(m, 2H), 7.14(m, 2H), 6.75(m, 3H), 4.63(d, 1H, CH-P, J=16.80 Hz),2.439(s, 3H, CH_3). ^{31}P NMR: 12.783 (s), ppm.

Diphenyl ester, hydrobromide **3c**: Yield 91%. M.p. 239–242 °C (dec.). ^{1}H NMR (DMSO): 9.35(bs, 3H, NH_3^+), 8.92(d, 1H, J=2.4 Hz), 8.04(s, 1H), 7.95(d, 1H, J=8.64 Hz), 7.83(d, 1H, J=8.64 Hz), 7.44–7.12(m, 10H, Ph), 5.53(d, 1H, CH-P, J=18.72 Hz). ^{31}P NMR: 10.905(s), ppm.

Diphenyl ester, hydrobromide **3d**: Yield 89%. M.p. 150–151 °C (dec.) ^{1}H NMR (DMSO): 9.37(bs, 3H, NH_3^+), 8.99(d, 1H, J=2.88 Hz), 8.29(d, 1H, J=2.40 Hz), 8.02(s, 1H), 7.45–7.13(m, 10H, Ph), 5.54(d, 1H, CH-P, J=18.72 Hz). ^{31}P NMR: 10.642(s), ppm.

Hydrolysis of Esters 3a-d to Phosphonic Acids 4a-d

Hydrobromide **3a-d** (3 mmol) was treated with 20% HCl (50 mL) and refluxed for 6 hrs. After evaporation of solvent under reduced pressure, the remaining residue was treated with 40 mL water and 10 mL ethanol. The undissolved material was filtered off and dried, to give the product **4a-d**. Data of obtained products are given in the table II.

Elemental Anal. for **4a** × H_2O: Calc. C 43.96, H 4.43, N 5.13, P 11.34; Found: C 44.19, H 4.42, N 4.59, P 11.11.

Elemental Anal. for **4b**: Calc. C 49.08, H 4.49, N 5.20, P 11.51; Found: C 48.63, H 4.89, N 5.01, P 11.62.

Elemental Anal. for **4c:** Calc. C 41.47, H 3.13, N 4.84, P 10.70, Cl 12.24; Found: C 40.98, H 3.10, N 4.66, P 10.57, Cl 12.21.

Elemental Anal. for **4d**: Calc. C 37.06, H 2.49, N 4.32, P 9.56, Cl 21.88; Found: C 36.88, H 2.56, N 4.11, P 9.52, Cl 21.91.

Synthesis of Chromone-2-[α-(N-Benzyl)amino]Methanephosphonic Acid (6)

2-Formylchromone[6] (0.63g, 3.6 mmol) was dissolved in dry chloroform (50 mL) and then benzylamine (0.38g, 3.6 mmol) was added. The solution was stirred for 24 hrs in the presence of anh. sodium carbonate (1g). Next day the sodium carbonate was filtered off, and to such a prepared solution of aldimine in chloroform, the fresh by prepared solution of $P(OSiMe_3)_3$ in chloroform was added. [The silylated phosphite was obtained by dissolving $P(OMe)_3$ (0.49g, 3.9 mmol) and Me_3SiBr (1.9g, 12.4 mmol) in dry chloroform (50 mL), and the mixture was left for 24 hrs]. The final mix-

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ture was kept for 24 hrs at room temperature and the solvent was evaporated. The obtained oil was treated with methanol (10 mL) and the solution was diluted with diethyl ether (10 mL). After several hours, the precipitated product **6** was collected by filtration, washed with diethyl ether and dried.

Yield 0.38g (31%). M.p. 157–160 °C (dec.).

Elemental Anal. for **6**: Calc. C 59.13, H 4.67, N 4.06, P 8.97; Found: C 58.81, H 4.75, N 3.92, P 9.15.

^{1}H NMR (DMSO): 7.68(d, 1H, arom., J=7.8 Hz), 7.74(t, 1H, arom., J=7.0 Hz), 7.60(d, 1H, arom., J=8.0 Hz), 7.46(m, 3H, arom.), 7.22bs, 3H, arom.), 6.48(s, 1H, arom.), 4.21(bs, 2H, CH_2N), 4.09(d, 1H, CH-P, J_{P-H}=17.6 Hz). ^{31}P NMR: 5.667 (s).

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The Cleavage of the Acid 6 in aqueous HCl. Formation of the Amine 7

A sample of chromone-2-[α-(N-benzyl)amino]-methanephosphonic acid (**6**) (90 mg, 0.26 mmol) was dissolved in 20% aq. HCl (50 mL) and the solution was refluxed for 1 hr. The mixture was evaporated to dryness under reduced pressure, and the semi-solid residue (0.12g) was dissolved in D_2O (1.5 mL). The ^{1}H and ^{31}P NMR spectra of this solution were recorded. The ^{31}P NMR spectrum of this showed a singlet attributed to the phosphoric acid (H_3PO_4) at 0.74 ppm. The singlet at 5.67 ppm (starting material) was not observed. An addition of some H_3PO_4 to this solution increased the amplitude of the signal, but the value of chemical shift of it was not changed. The ^{1}H NMR spectrum showed a remarkable difference, in comparison with the ^{1}H NMR spectrum of the original material **6**.

The formed amine **7** was isolated and characterized by the following method: The analyzed D_2O solution, containing the products of a cleavage (1.5 mL) was neutralized with aq. 10% sodium carbonate solution (3 mL), and the mixture was extracted with 10 mL chloroform. The $CHCl_3$ layer was dried (anh. Na_2CO_3) filtered and evaporated to give a yellow thick oil (65mg), which was shown to be the amine **7**.

Yield of **7**: 94%. ^{1}H NMR ($CDCl_3$) 8.11(dd, 1H, J_1=7.94 Hz, J_2=1.59 Hz), 7.57(t, 1H, J=8.64 Hz), 7.37–7.16(m, 7H, arom.), 6.34(s, 1H, H_3), 3.80(s, 2H, CH_2N), 3.69(s, 2H, NCH_2). G.C.-M.S.: 264 (M-1, 6.0%), 174 (15.9%), 160 (100%), 131(37.4%), 121(10.2%), 120 (16.8%), 106 (68.1%), 92 (24.9%), 91 (76.9%), 77 (20.4%), 65 (12.3%).

The amine **7** was also characterized as the oxalate salt. The free amine (50 mg) was dissolved in acetone (1 mL) and oxalic acid (100mg) dissolved in acetone (1 mL) was added. This caused the precipitation of a white solid, which was collected by filtration, washed with acetone and dried.

Yield: 45 mg. M.p. 209–211 °C (dec.). ^{1}H NMR (DMSO): 8.02(d, 1H, J=7.75 Hz), 7.81(t, 1H, J=7,15 Hz), 7.62(d, 1H, J=8.30 Hz), 7.51–7.28(m, 7H, arom.), 6.47(s, 1H, H_3), 4.03(s, 2H, CH_2N), 3.98(s, 2H, NCH_2).

Acknowledgements

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