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On the Chemistry of Pyrrole Pigments, XCV [1]: 1,4-*bis*-(Dipyrrinone-9-ylidene)-butene-2 – A Novel *b-homo*-Verdin Chromophore

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Summary. 1,4-*bis*-(Dipyrrinone-9-ylidene)-butene-2, a verdinoid system extended at C-10, was synthesized by condensing a dipyrrinone unsubstituted in position 9 with 2,5-dihydro-2,5-dimethoxyfuran or 2,5-dimethoxy-tetrahydrofuran. The chemical and spectroscopic properties of this novel chromophoric system are discussed.

Keywords. 1,4-*bis*-(Dipyrrinone-9-ylidene)-1,3-butene; Dipyrrinone; *b-homo*-Verdin; Synthesis; Spectroscopy; Protonation.

Zur Chemie von Pyrrolpigmenten, 95. Mitt. [1]: **1,4-*bis*-(Dipyrrinon-9-yliden)-buten-2 – ein neuer *b-homo*-Verdinchromophor**

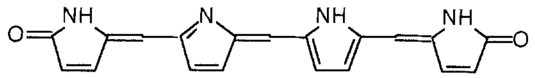
Zusammenfassung. 1,4-*bis*-(Dipyrrinon-9-yliden)-buten-2, ein verdinoides, in Position 10 extendiertes System, wurde durch Kondensation eines in Position 9 unsubstituierten Dipyrrinons mit 2,5-Dihydro-2,5-dimethoxy-furan oder 2,5-Dimethoxy-tetrahydrofuran synthetisiert. Die chemischen und spektroskopischen Eigenschaften dieses neuen chromophoren Systems werden diskutiert.

Introduction

Most natural bile pigments are characterized by the verdin chromophore **I** [2]. It has been shown that this chromophore can be transformed into systems with shortened [3] or lengthened conjugation paths [1, 4, 5]. In the case of the latter, insertion of one carbon atom led to the two interesting novel *b-homo*-verdins **1** and **2** [4, 5], which are of chromophore types **II** and **III**. The two chromophores **II** and **III** differ in their oxidation state. However, in **II** the two dipyrrinone "halves" are identical and the chromophoric system is related to that of the rubins. The type **III** chromophore has been found to be unique because of its two pyrroleninic nitrogen atoms, which render the molecule formally mirror symmetric. Compounds of type **IV** are true *b-homo*-verdins as has been demonstrated recently by a synthesis of **3** [1].

Following a systematic study of these chromophores, we were intrigued by the *b-homo*-verdin system of type **V**, in which two dipyrrinone moieties are separated by four carbon atoms. Extended conjugated systems, such as **4a**–**4d**, had been prepared previously. In the pentapyrrin system **4a** [6], a 3,4-dimethyl-pyrrole-2,5-diyl moiety

I



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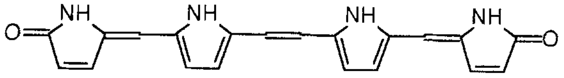

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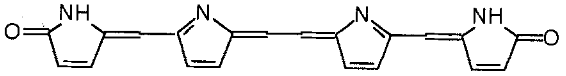

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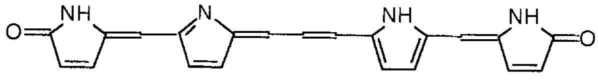
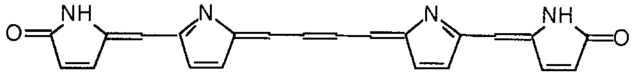
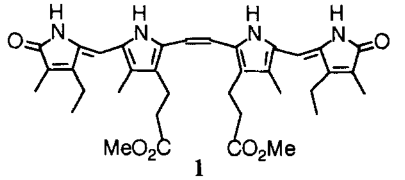


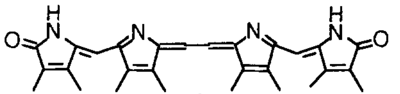
V



has been inserted between two dipyrrinone chromophores yielding a system, which corresponds to the oxidation state of the chromophore type **III**. Its analogs **4b**–**4d** and a *b-homo*-rubin derivative, the latter corresponding to the *meso*-hydrogenated system **II**, have been recently prepared by *Lightner*'s group [7, 8]. However, compounds with the fundamental chromophoric system **V** could not be prepared up to now. Thus, condensation of *o*-phthalicdialdehyde with a dipyrrinone unsubstituted in position 9 was unsuccessful [7]. Therefore, a rational synthesis of



1



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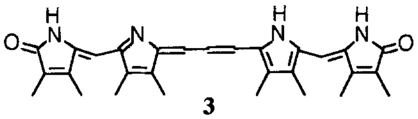

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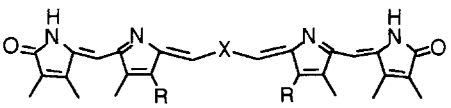


4

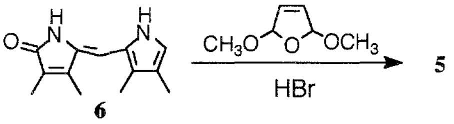
	X	R
4a	3,4-dimethyl-2,5-pyrrole-diyl-	CH_3
4b	3,4-dimethyl-2,5-pyrrole-diyl-	$CH_2CH_2COOCH_3$
4c	1,4-phenyl-diyl-	$CH_2CH_2COOCH_3$
4d	1,3-phenyl-diyl-	$CH_2CH_2COOCH_3$
5	–CH=CH–	CH_3

a compound like **5**, which is of chromophore type **V**, was investigated and is reported in this paper.

Results and Discussion

Synthesis and mechanistic aspects

To prepare a compound of chromophore type **V**, the most obvious acceptor synthon to provide a bridge with a length of four carbon atoms between the two dipyrrinone halves is 2,5-dihydro-2,5-dimethoxylfuran. Thus, this derivative was condensed with dipyrrinone **6**, which was unsubstituted in position 9, to yield **5**. This condensation reaction proceeded rather slowly and provided a yield of 20%. It was interesting to note that the yield of this reaction was critically dependent on the solvent and the kind of acid used to catalyze the reaction. The most appropriate parameters for the formation of the *b-homo*-verdin **5** were found to involve a mixture of dichloromethane and methanol as the solvent, two mole equivalents of 2,5-dimethoxy-2,5-dihydrofuran, and 33% hydrogen bromide in acetic acid. The latter had to catalyze the hydrolysis of 2,5-dimethoxy-2,5-dihydrofuran on the one hand and the condensation reaction on the other hand. Using 9-butoxycarbonyl-2,3,7,8-tetramethyl-dipyrrin-1-one instead of **6** as the substrate resulted in about the same yield of **5**.



Interestingly enough it was found that condensation of **6** with 2,5-methoxy-tetrahydrofuran also gave **5**. This result indicated that the product was formed *via* aerial oxidation of the corresponding partially saturated linear tetrapyrrolic intermediate.

With respect to mechanistic implications, the formation of **5** could be envisaged in a straightforward manner. Thus, 2,5-dimethoxy-2,5-dihydrofuran underwent an acid catalyzed cleavage of its ring to yield buten-1-dial-1,4 *in situ*. Upon protonation of the latter, **6** was attacked in an electrophilic substitution. The remaining carbonyl group was then involved in the same reaction type with a second molecule of the dipyrrinone as discussed recently [1, 4, 5]. Similarly, the condensation of **6** with 2,5-dimethoxy-tetrahydrofuran followed the same type of mechanism. Obviously, the intermediate dihydro-**V** chromophoric system was prone to be easily oxidized to the completely unsaturated derivative **5**.

Structural assignments

The constitutional, tautomeric, and configurational aspects [2] of **5** could be derived from its NMR, IR, and mass spectra. Thus, the molecular ion peak of **5** appeared in its mass spectrum at $m/e = 480$, and the peaks at $m/e = 358$, 277, and 214 corresponded to the characteristic fragments shown in Fig. 1. Accordingly, the constitution of **5** followed unequivocally from this fragmentation pattern. The NMR data were

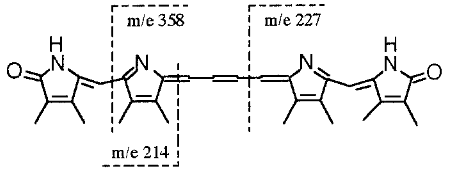


Fig. 1. Mass fragmentation of **5**

characteristic of a symmetrical constitution with the chemical shifts of the –CH= groups at 5.30 ($CDCl_3$), 6.15 ($CDCl_3$ + 1 drop *TFA*-d), and 5.76 (*DMSO*-d_6) ppm, pointing to (*Z*) configurations at the two lactam ring exocyclic double bonds. A broad singlet for the =CH–CH=CH–CH= protons was observed at 5.88 ($CDCl_3$), 7.25 ($CDCl_3$ + *TFA*-d), and 7.95 (*DMSO*-d_6) ppm. Of course, the configurations at the double bonds of this fragment could not be assigned. The ^{13}C NMR spectrum displayed a C=O signal at about 172 ppm, which is typical for the *bis*-lactam tautomer [2]. Moreover, the number of carbon signals corresponded to the proposed constitution. The IR spectra of **2** contained the typical lactam vibration at 1699 cm^{-1} [2] and thus confirmed the presence of the *bis*-lactam tautomer.

Electronic absorption spectra, conformation, protonation and complexation of 5

The electronic absorption spectra of **5** in two different solvents are illustrated in Fig. 2. The long wavelength absorption was found at 844 nm in dichloromethane and 650 nm in dimethyl sulfoxide. Judged from the standpoint of the electron-in-a-box model [2] the three band pattern with the long wavelength band being the less intense one corresponds to a more or less circular or coiled chromophore with pronounced extensions in all three dimensions. Indeed, it could be derived by means of PCMODEL [10] calculations that there was no stable planar arrangement possible for this molecule. Thus, the (5*Z*,9*Z*,11*E*,13*E*,18*Z*) and (5*Z*,9*Z*,11*E*,13*Z*,18*Z*) diastereomers were derived to be the most stable ones from the 32 diastereomers possible. The dihedral angles at the C10–C11 and C12–C13 single bonds of these diastereomers were found to be 26° and 5° for the first one, and 31° and 3° for the second one.

Interestingly enough, the absorption spectrum of **5** displayed a pronounced solvatochromic effect which was similar to that of the *b*-*homo*-verdin **3** [1]. The long

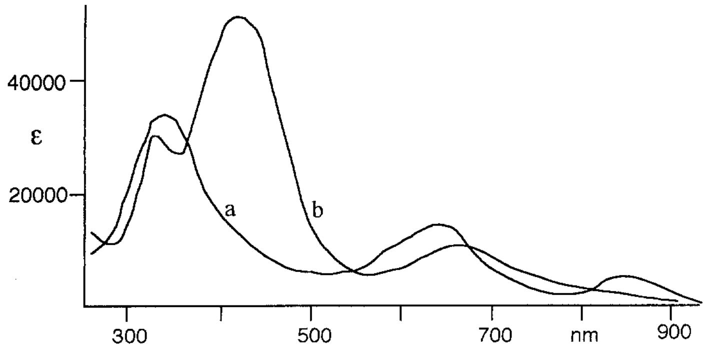


Fig. 2. UV/Vis spectra of **5** in dichloromethane (a) and dimethyl sulfoxide (b)

wavelength band was shifted from 844 nm in dichloromethane as the solvent *via* 746 nm in methanol and 650 nm in dimethyl sulfoxide to 624 nm in acetone. Accordingly, the solvent could stabilize various different configurational and conformational ground states of **5** as discussed recently [1]. As observed for **3** [1], the spectroscopic solvent shifts of **5** did not correlate with solvent polarity parameters like E_T [9].

Protonation pK_a values of 4.1 and 2.9 were measured for **5**. The first one corresponded to the normal protonation of verdins [2]. The second one at 2.9 was significantly higher than the second one found for **2** (pK_a values of 4.0 and 0.1 [5]). Obviously, the two basic pyrrolenine nitrogen atoms became more independent in **5** from each other upon lengthening the bridge between the dipyrrinone halves. Thus, the pK_a difference between the two equal basic centers of **5** approached the statistical limit. Unlike the *b-homo*-verdin compound **3**, the electronic absorption spectrum of **5** did not severely change upon protonation, however. The rather small shifts starting from 844 nm of the free base to 820 and finally 826 nm in dichloromethane suggested that the conformational situation of the conjugation path did not change seriously upon the introduction of one and two positive charges.

Transition metal ions, such as Zn(II), Co(II), Cd(II), Ni(II), and Cu(II), were observed to form complexes with the pigment **5** in dichloromethane, methanol, acetone, 1,2-dichloromethane, and dimethyl sulfoxide. This behavior could perhaps be used to create a novel agent for facilitated transport of metal ions [2].

Experimental

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker-AC 200 instrument. UV/Vis and IR spectra were run on Hitachi-U-3210 and Biorad-FT-IR-45 spectrophotometers. Mass spectra were measured on a MAT 95 instrument, and melting points were determined by means of a Kofler hot stage microscope (Reichert, Vienna). Aluminum oxide (active, type 90, neutral) and silica GF_{254} were used for column chromatography. The dipyrrinone **6** was prepared according to Ref. [11]. Spectrophotometric pK_a estimates were derived using sulfuric acid and trifluoroacetic acid dilution series in dichloromethane as described in Ref. [12]. Complex formation of **5** was observed by UV/Vis spectra recorded after addition of 10 mg of the Zn(II), Co(II), Cd(II), Ni(II), and Cu(II) acetates to the respective 3.10^{-5} molar solutions of **5** (used before to record the UV/Vis spectra) and equilibration in dichloromethane, methanol, dimethyl sulfoxide, acetone, and dichloroethane.

(5Z,18Z)-1,4-bis-(2,3,7,8-Tetramethyl-dipyrrinone-9-ylidene)-but-2-ene (**5**; $C_{30}H_{32}N_4O_2$)

Method A

In a round-bottom flask, 100 mg 2,3,7,8-tetramethyl-9*H*-dipyrrinone (**6**, 0.46 mmol), 60 mg 2,5-dihydro-2,5-dimethoxy-furan (0.46 mol, 2.0 mole equivalents; Aldrich), 100 ml methanol, and 50 ml CH_2Cl_2 were combined, and 2 ml of a solution of hydrogen bromide (33%) in acetic acid was added. The reaction was monitored by periodically quenching an aqliquot of the reaction mixture with aqueous saturated sodium bicarbonate solution and following the disappearance of **6** and the appearance of the product **5** by thin layer chromatography and UV/Vis spectroscopy. After one week, the reaction was obviously complete. Then, 20 ml CH_2Cl_2 and 20 ml of a solution of aqueous ammonia (10%) were added dropwise over 10 min to neutralize the acid. The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 × 50 ml). The combined organic phase was washed with water (50 ml) and brine (30 ml). After drying over anhydrous sodium sulfate and removing the solvent, the residue was purified by means of flash chromatography over aluminum oxide (type 90, neutral) using CH_2Cl_2/ethyl acetate (v/v, 6/4) as the eluent. The blue-green band was further purified by silica gel column chromatography using CH_2Cl_2/ethyl acetate/CCl_4 (v/v/v, 2/2/1). To further purify **5**, the solid was dissolved in the minimum amount CH_2Cl_2; then, hexane was added until **5** started to precipitate. The mixture was kept for 4 h, the solid was filtered off and washed with little methanol (−10 °C). The solid was again dissolved in CH_2Cl_2 and passed through a short aluminium oxide (active, type 90, neutral) chromatographic column (3 × 5 cm). Finally, **2** was purified by crystallization from CH_2Cl_2/hexane, yielding 22 mg (20%).

Method B

Using the procedure described above, the condensation of **6** with 2,5-dimethoxy-tetrahydrofuran (Aldrich) afforded **5** in 15% yield.

Method C

100 mg 9-Butoxylcarbonyl-2,3,7,8-tetramethyl-dipyrrin-1-one (0.32 mmol, [4]) were carefully dissolved in 3 ml trifluoroacetic acid under an argon atmosphere at 25 °C. After stirring for 25 min, a solution of 41 mg 2,5-dihydro-2,5-dimethoxy-furan (0.32 mmol) in 50 ml CH_2Cl_2 chloromethane and 20 ml MeOH was added. After one week, 20 ml aqueous ammonia (15%) were added to quench the reaction. Workup and purification were as described for method *A*. The yield was 14 mg **5** (18%).

M.p.: 270 °C (dec.); ^{1}H NMR (200 MHz, δ, *DMSO*-d_6): 2.73 (s, 4 CH_3), 2.89 (s, 4 CH_3), 5.76 (s, 2 -CH=), 7.95 (br s, =CH–CH=CH–CH=) ppm; ^{1}H NMR (200 MHz, δ, $CDCl_3$): 1.98 (s, C CH_3-2,21), 2.05 (s, 2 CH_3), 2.11 (s, 2 CH_3), 2.15 (s, 2 CH_3), 5.30 (s, –CH=), 5.88 (br s, =CH–CH=CH–CH=), 7.88 (br s, 2 NH) ppm; ^{1}H NMR (200 MHz, δ, $CDCl_3$ + *TFA*-d): 1.84 (s, 4 CH_3), 1.96 (s, 4 CH_3), 6.15 (s, –CH=), 7.25 (br s, =CH–CH=CH–CH=) ppm; ^{13}C NMR (90 MHz, δ, $CDCl_3$ + *TFA*-d), 8.58 (CH_3), 9.52 (CH_3), 9.59 (CH_3), 19.82 (CH_3), 77.22, 96.54, 114.56, 127.56, 128.99, 134.96, 140.69, 140.88, 141.88, 149.82, 172.57 (C=O) ppm; IR (KBr): $\nu = 3334, 2960, 2920, 1703, 1620, 1600, 1541, 1343, 1327, 1174, 1064, 1054, 967\,cm^{-1}$; UV/Vis ($CH_2Cl_2$): $\lambda_{max} = 368$ (34000), 644 (8800), 844 (2700) nm (ε); UV/Vis (CH_2Cl_2 + *TFA*): $\lambda_{max} = 356$ (35500), 654 (13300), 826 (3300) nm (ε); UV/Vis ($CH_2Cl_2 + Zn^{2+}$): $\lambda_{max} = 356$ (36200), 408 (18100), 656 (12800), 699 (11400) nm (ε); UV/Vis ($CH_2Cl_2 + Ni^{2+}$): $\lambda_{max} = 360$ (74600), 604 (22700), 814 (4500 nm) (ε); UV/Vis ($CH_2Cl_2 + Co^{2+}$): $\lambda_{max} = 352$ (50000), 660 (22800), 696 (21300) nm (ε); UV/Vis ($CH_2Cl_2 + Cu^{2+}$): $\lambda_{max} = 319$ (28400), 400 (19700), 703 (6700), 817 (3400) nm (ε); UV/Vis ($CH_2Cl_2 + Cd^{2+}$): $\lambda_{max} = 368$ (35000), 640 (8300) nm (ε); UV/Vis (MeOH): $\lambda_{max} = 369$ (11900), 424 (10800), 632 (3000), 764 (3000) nm (ε); UV/Vis (MeOH + Zn^{2+}): $\lambda_{max} = 373$ (114600), 633 (7200), 681 (9700), 841 (3400) nm (ε); UV/Vis (MeOH + Ni^{2+}): $\lambda_{max} = 368$ (12500), 408 (12200), 648 (3800), 760 (3000) nm (ε); UV/Vis (MeOH + Cu^{2+}): $\lambda_{max} = 402$ (11400), 786 (3160) nm (ε); UV/Vis (MeOH + Co^{2+}): $\lambda_{max} = 332$ (9500), 384 (11100), 648 (3800) nm (ε); UV/Vis (*DMSO*): $\lambda_{max} = 364$ (31000), 486 (50500), 650 (4600) nm (ε); UV/Vis (*DMSO* + *TFA*): $\lambda_{max} = 356$ (62800), 696 (8400) nm (ε); UV/Vis (*DMSO* + Zn^{2+}): $\lambda_{max} = 370$ (35900), 422 (44600), 654 (5300) nm (ε); UV/Vis (*DMSO* + Ni^{2+}): $\lambda_{max} = 368$ (30100), 426 (58300), 678 (5100, 806 (3000) nm (ε). UV/Vis (*DMSO* + Cu^{2+}): $\lambda_{max} = 349$ (48000), 441 (41300), 557 (31000), 801 (3000) nm (ε); UV/Vis (*DMSO* + Co^{2+}): $\lambda_{max} = 428$ (61600), 612 (9300), 680 (10200) nm (ε); UV/Vis (*DMSO* + Cd^{2+}): $\lambda_{max} = 371$ (59000), 477 (27400), 709 (4700), 849 (2200) nm (ε); UV/Vis (acetone): $\lambda_{max} = 364$ (17200), 624 (6300) nm (ε); UV/Vis (acetone + *TFA*): $\lambda_{max} = 357$ (17000), 604 (9000) nm (ε); UV/Vis (acetone + Zn^{2+}): $\lambda_{max} = 369$ (15440), 633 (8000), 685 (10700) nm (ε); UV/Vis (acetone + Ni^{2+}): $\lambda_{max} = 365$ (17400), 406 (9800), 642 (6600) nm (ε); UV/Vis (actone + Cu^{2+}): $\lambda_{max} = 336$ (12700), 412 (3400), 800 (3400) nm (ε); UV/Vis (acetone + Co^{2+}): $\lambda_{max} = 344$ (9900), 372 (12200), 664 (8800) nm (ε); UV/Vis (acetone + Cd^{2+}): $\lambda_{max} = 340$ (22200), 376 (22700), 620 (6900), 668 (8600), 724 (6700) nm (ε); UV/Vis (1,2-dichloroethane): $\lambda_{max} = 364$ (43200), 636 (10200), 840 (2300) nm (ε); UV/Vis (1,2-dichloroethane + *TFA*): $\lambda_{max} = 356$ (46600), 649 (19000), 705 (16300), 825 (4700) nm (ε); UV/Vis

(1,2-dichloroethane + Zn^{2+}): λ_{max} = 356 (44300), 406 (22500), 654 (17000), 698 (15400), 846 (2200) nm (ε); UV/Vis (1,2-dichloroethane + Ni^{2+}): λ_{max} = 356 (47500), 404 (23900), 652 (18900), 692 (15800), 852 (2900) nm (ε); UV/Vis (1,2-dichloroethane + Cu^{2+}): λ_{max} = 342 (28200), 402 (23500), 650 (7900), 734 (7700), 850 (3700) nm (ε); UV/Vis (1,2- dichloroethane + Co^{2+}): λ_{max} = 354 (46600), 410 (25400), 653 (22200), 697 (18600), 849 (2100) nm (ε); UV/Vis (1,2-dichloroethane + Cd^{2+}): λ_{max} = 366 (43900), 650 (10800), 730 (6500), 854 (1600) nm (ε). The pK_a values were estimated from a spectrophotometric titration to amount to 4.1 ± 0.2 and 2.9 ± 0.2. The corresponding **5**, **5**$\cdot H^+$ and **5**$\cdot 2H^+$ species were characterized by long wavelength absorption bands at 844 (1.0), 820 (2.0), and 826 (1.2) nm (relative intensity). MS (70 eV): *m/e* (%) = 480 (2; M^+), 418 (5), 371 (5), 369 (23), 358 (5), 324 (5), 292 (10), 230 (23), 227 (15), 214 (22), 180 (100), 143 (18), 122 (12), 143 (18), 109 (5).

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References

[1] Part XCIV: Chen Q-Q, Falk H (1995) Monatsh Chem **126**: 1233
[2] Falk H (1989) The chemistry of linear oligopyrroles and bile pigments. Springer, Wien New York
[3] Falk H, Flödl H, Wagner UG (1988) Monatsh Chem **119**: 739; Falk H, Flödl H (1988) Monatsh Chem **119**: 1155
[4] Chen Q-Q, Ma J-S, Wang C-Q, Liu Y-Y, Yan F, Cheng L-J, Jin S, Falk H (1995) Monatsh Chem **126**: 983
[5] Chen Q-Q, Falk H (1995) Monatsh Chem **126**: 1097
[6] Falk H, Flödl H (1985) Monatsh Chem **116**: 1177
[7] Nogales DF, Anstine TD, Lightner DA (1994) Tetrahedron **50**: 8579
[8] Pfeiffer PW, Lightner DA (1994) Tetrahedron Lett **35**: 9673
[9] Reichardt C (1988) Solvent effects in organic chemistry. Verlag Chemie, Weinheim
[10] PCMODEL v 5.0 (1994) Serena software, Bloomington, USA
[11] Dobeneck H, Graf W, Ettel W (1962) Hoppe Seyler's Z Physiol Chem **329**: 168; Shrout DP, Puzicha G, Lightner DA (1992) Synthesis **1992**: 328
[12] Albert A, Serjeant EP (1984) The determination of ionization constants. Chapman & Hall, London

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