NOVEL DIPOLAR AND TRIPOLAR BETAINES: SYNTHESIS, RING-CLEAVAGE, SPECTROSCOPIC FEATURES, AND X-RAY ANALYSIS OF A POSITIVELY CHARGED PYRIMIDIN-4-OLATE

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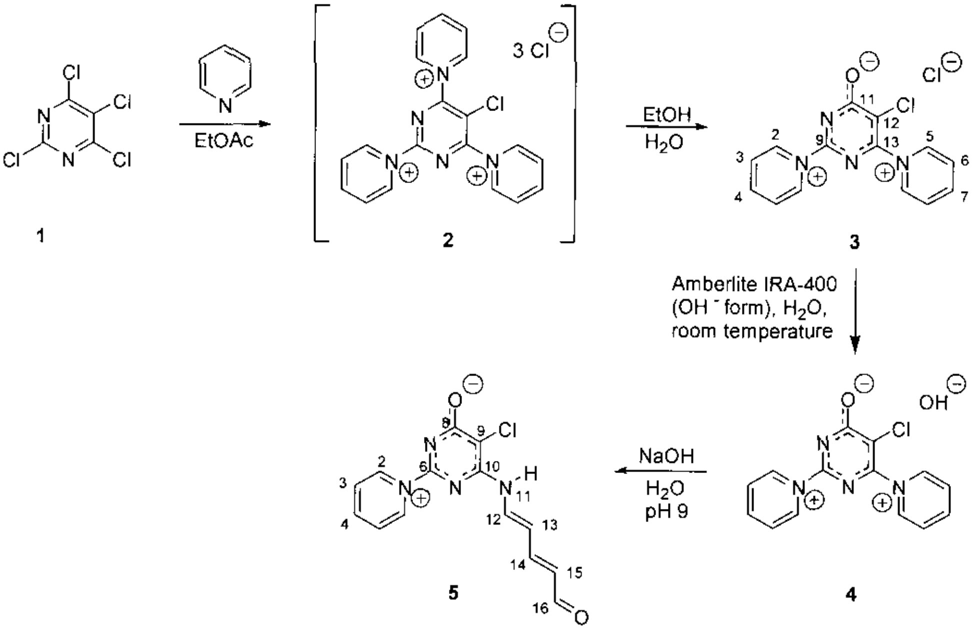
Abstract - Reaction of tetrachloropyrimidine (**1**) with pyridine resulted in the formation of a heteroaromatic tripole, the 2,6-bispyridiniopyrimidin-4-olate chloride (**3**), the structure of which was established by X-Ray crystallography. Amberlite® IRA-400 in its hydroxy form converted **3** into the corresponding stable hydroxide (**4**), which undergoes ring-cleavage on titration with sodium hydroxide to pH 9. Thus, the 5-aminopenta-2,4-dienal appended mesomeric betaine (**5**) formed.

During recent years, both charge-cumulated and charge-separated heteroaromatics have been identified as significant biologically active molecules. Thus, oligocationic alkaloids[1] from natural sources as well as betainic alkaloids[2] have been investigated for drug serendipity. Furthermore, among the betainic nucleobases, 7-methylguanosine plays an important biological role as *cap*-structure of *m*RNA.[3] Modified guanines have been reported as pharmacologically interesting mesomeric betaines.[4] Moreover, the well-known NO donor Molsidomin®, a mesoionic heterocycle, is currently used in coronary therapy.

As part of our work aimed at syntheses of pyrimidine derivatives that combine oligocationic and betainic properties,[5,6] we describe here the preparation of novel heteroaromatic tripoles that are *positively charged pyrimidin-4-olates* with two positive charges and one negative charge delocalised within a common π-electron system. An unusual pentadienal substituted cross-conjugated mesomeric betaine is formed by pericyclic ring-cleavage.

Treatment of tetrachloropyrimidine (**1**) at room temperature with a threefold excess of pyridine in anhydrous ethyl acetate resulted in the formation of a beige hygroscopic precipitate of 1,1′,1′′-(5-chloropyrimidin-2,4,6-triyl)trispyridinium trichloride (**2**) which was filtered off. Substitution of all the nucleofugal chlorine atoms of the starting material (**1**) is due to the additivity of substituent effects, leading to increasing reactivity of the remaining chlorine atoms with proceeding substitution. Our own results reveal that such tricationic pyrimidines are stable, if they are unsubstituted at C(5) of the pyrimidine ring.[7] However, traces of moisture converted the 5-chloro derivative (**2**) into 5-chloro-2,6-bispyridiniopyrimidin-4-olate chloride (**3**) and equimolar amounts of pyridinium chloride. Recrystallization of the crude product from aqueous ethanol formed the tripole (**3**) as a pure, well-defined compound, the structure of which was established by X-Ray crystallography (*vide infra*). Obviously, even in the presence of strongly electron-withdrawing groups such as hetarenium rings, the C(5)-Cl group is not susceptible toward substitution reactions. Passing an aqueous solution of the chloride (**3**) through anion exchange resin Amberlite® IRA-400 in its hydroxy form resulted in the formation of the hydroxide (**4**) which was isolated as a beige solid. However, on titration of an aqueous solution of 5-chloro-2,6-bispyridiniopyrimidin-4-olate hydroxide (**4**) with 10% aqueous sodium hydroxide to pH 9, nucleophilic attack of an OH^- ion at the α-position of the pyridinium substituent at C(13) of **4** and subsequent pericyclic ring-cleavage occurred, resulting in an orange-colored precipitate of the 5-aminopenta-2,4-dienal appended 2-pyridiniopyrimidin-4-olate (**5**).



Scheme

In contrast to known examples of mesomeric betaines, which can be divided into four major classes by their type of conjugation,[8] the tripoles (**3**) and (**4**) possess an *odd* number of positive and negative charges as a consequence of two overlapped structure elements of cross-conjugated mesomeric betaines. Thus, **3** and **4** are no members of the class of mesomeric betaines due to their overall charges. They can be referred to as mesomeric betainium salts, *i.e.* hybrids between mesomeric betaines and hetarenium salts.

The spectroscopic features of the compounds are as follows: The pyridinium rings of **3** and **4** can readily be distinguished by their ^1H NMR resonance frequencies, the peak assignments of which were established by HH-COSY and CH-COSY experiments (see EXPERIMENTAL). The tripole (**3**) exhibits a strong effect of negative solvatochromism, indicative of a charge-separation in the ground-state of molecules.[9] A functional relationship between UV absorption maxima of the longest-wavelength charge-transfer bands and solvent polarity is found that takes the form of a linear free energy (LFE) relationship. Thus, the UV absorption maxima of the stable 5-chloro-2,6-bispyridiniopyrimidin-4-olate chloride (**3**) shift hypsochromically from 353.00 nm to 318.60 nm on changing the solvent from dichloromethane ($E_T^N = 0.309$) to water ($E_T^N = 1.000$).[9] The effect of negative solvatochromism of **3** is presented in Figure 1.

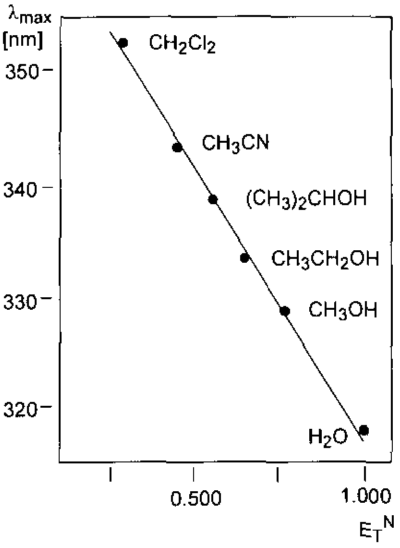


Figure 1

The charge-separation by cross-conjugated partial structures of the tripole (**3**) is also confirmed by results of the single crystal X-Ray analysis:[10] Suitable monoclinic crystals were obtained by slow evaporation of an aqueous solution of **3**. An ORTEP drawing (Figure 2) shows that the betaine (**3**) adopts a nonplanar conformation. Usually, the heteroaromatic character of the pyridinium and the pyrimidine rings restricts deviation from planarity to small values. Thus, the largest torsion angle of the three cyclic structure elements of **3** is about 2.2° [crystallographic numbering: N41-C42-C43-C44; s. Figure 2]. However, the pyridinium substituents at C4 and C6 are twisted by -46.37 (18)° and 5.82(19)° from the pyrimidine plane, respectively. The corresponding interatomic distances C4-N41 and C6-N61 were determined to 145.69(19) pm and 147.97(18) pm, respectively. They are single bonds without significant π-contributions and confirm the existence of cross-conjugated structure elements. Thus, in accordance with the formulation of a heteroaromatic tripole, the positive and negative portions of the molecule are strictly delocalized in separate parts of the common π-electron system that are joined by characteristic unions.[8]

The elemental cell of **3** is presented in Figure 3. The crystal structure is dominated by layering of the molecules. The chloride anions and molecules of water are found between the layers so that there is an array of hydrogen bonds and contacts. Thus, O2 forms a weak hydrogen bond with one of the four molecules of water present in the elemental cell. The chloride anion is heavily solvated. The hydrogen atoms attached to C63 are involved in contacts with the olate group as well as with the chlorine atom Cl3 of another betaine molecule. Considering the positive charges of the pyridinium rings, there is surprisingly a great molecular overlap of betaine molecules of different layers. Thus, the pyridinium rings at C6 of each layer is nearly completely overlapped, whereas the pyridinium rings at C4 and the central pyrimidin-4-olate rings of two layers are separated by the chloride anions and water molecules. Some representative data of the X-Ray crystallographic analysis are given in Table 1 and Table 2.

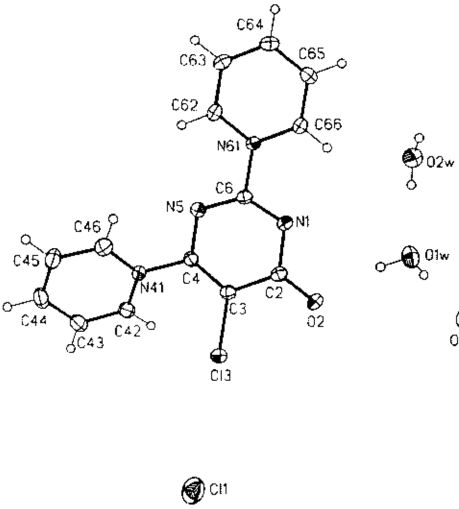


Figure 2

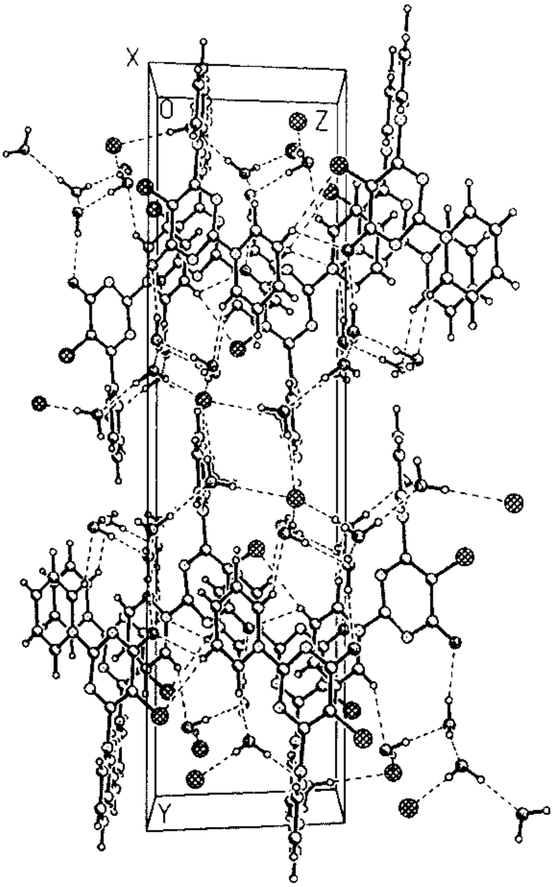


Figure 3

Table 1. Atom Nos. / Selected bond lengths [pm], bond angles [°], and torsion angles [°] of **3**.

N1-C2	137.96(18)	N1-C6-N61	114.22(13)	C6-N1-C2-C3	-2.1(2)
C2-C3	145.2(2)	C6-N1-C2	116.57(13)	O2-C2-C3-Cl3	1.81(2)
C3-C4	135.7(2)	O2-C2-C3	122.70(13)	N1-C2-C3-Cl3	-177.09(10)
C4-N5	134.90(18)	C4-C3-Cl3	123.98(12)	N5-C4-N41-C46	-46.37(18)
C2-O2	124.00(16)	N5-C4-C3	124.26(14)	C3-C4-N41-C46	132.03(15)
N5-C6	130.96(19)	C3-C4-N41	123.11(13)	N1-C6-N61-C66	5.89(19)
C45-C46	137.4(2)	C42-N41-C4	120.57(12)	N5-C6-N61-C66	-175.05(13)
C44-C45	138.1(2)	C66-N61-C62	121.34(12)	N1-C6-N61-C62	-173.24(13)

Table 2. Selected hydrogen bonds of **3**: Distances [pm] and angles [°].

D-H···A	d(D-H)	d(H···A)	d(D···A)	<(DHA)
O(1W)-H(1W2)···O2	82.7(10)	197.6(11)	279.45(15)	170.3(17)
C63-H63···O(2)#5	95	244	310.11(17)	126.8
C63-H63···Cl(3)#5	95	281	370.13(16)	156.8

The ^{1}H NMR spectrum of 5-chloro-6-[[(1*E*,3*E*)-5-oxopenta-1,3-dienyl]amino]-2-pyridiniopyrimidin-4-olate (**5**) shows the characteristic resonance frequencies of a pyridinium substituent as well as of a push-pull-substituted diene with the doublet of an aldehyde proton at 9.40 ppm. The coupling constants $J_{14,15}$ = 14.7 Hz and $J_{12,13}$ = 13.2 Hz prove that the pentadienal moiety of betaine (**5**) is *all-E*-configurated.[13,14] Obviously, the polymethine chain is not involved in the delocalization of the negative charge as no OH protons of pyrimidinol or NH protons of pyrimidinone tautomers are observable. Indeed, the existence of a merocyanine chromophor in **5** is unambiguously proved by the deuterium exchangeable signals of the amino proton 11-H (δ = 9.66 ppm) which split into a doublet due to coupling with 12-H (δ = 8.19 ppm) of the polymethine moiety.[15] This coupling is moreover documented by a HH-COSY spectrum (Figure 4).

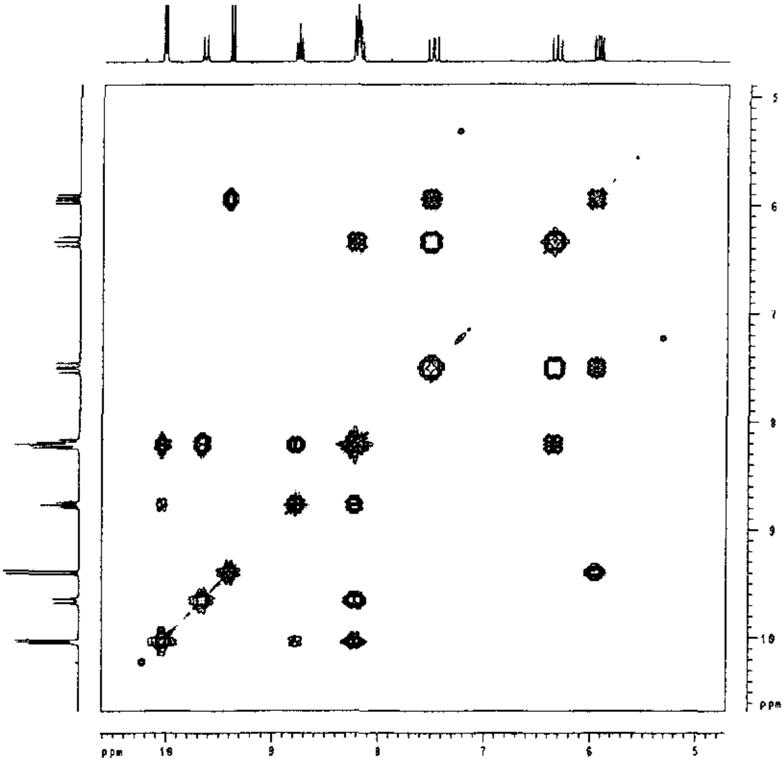


Figure 4

In accordance with the betainic structure, addition of DCl to a DMSO-d_6 solution of **5** results in downfield shifts of all resonance frequencies (Figure 5). Thus, typical values for the MB→cation transformation of the β- and γ-positions of the pyridinium ring are observed.[6] Due to steric hindrance, protonation of the nitrogen atoms of the pyrimidine ring would cause an energetically unfavorable non-planar conformation of the pyridinium and the pyrimidine ring with reduced conjugation, distored intramolecular CT-transitions, and reduced "aromatic C-H / nitrogen lone-pair interactions" which are known to be attractive ones.[5,6] Thus, the 4-olate group seems to be the most probable protonation site of tripole (**5**), forming the pyrimidinol (**6**). However, acidification of an aqueous solution of **5** with 10% hydrochloric acid to pH 2 results in the formation of a light yellow precipitate which could not be isolated. Thus, as evidenced by NMR spectroscopy reconstitution of **5** occurred on evaporating the solution on cooling, whereas drying on heating *in vacuo* resulted in the formation of decomposition products.

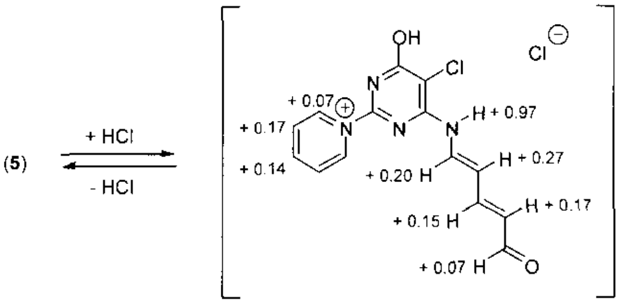


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Figure 5: Chemical shift changes Δδ [ppm]of **5** on protonation with DCl in DMSO-d_6.

In contrast to the tripoles (**3**) and (**4**), compound (**5**) belongs to the class of cross-conjugated mesomeric betaines (CCMB), as it is a *neutral* cross-conjugated molecule which can be exclusively represented by *dipolar* structures in which both the positive and negative charge are delocalized within the π-electron system. As it is isoconjugate with an odd alternant hydrocarbon anion, **5** belongs to an extremely seldom class of mesomeric betaines according to the comprehensive classification proposed by *Ollis*, *Stanforth*, and *Ramsden*.[8]

EXPERIMENTAL

The NMR spectra were acquired on a Bruker ARX 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz). The chemical shift values are expressed in ppm relative to TMS as internal standard. All samples were prepared in DMSO-d_6. IR spectra were determined on KBr disks. UV spectra were measured qualitatively with a Perkin Elmer UV/VIS/NIR spectrophotometer Lambda 19. FABMS spectra were recorded on an AMD M-40 (AMD Intectra GmbH Harbstedt) in the positive ion detection mode in *m*NBA. All melting points were determined on a Boëtius melting apparatus; the values reported are uncorrected. All samples were dried for at least 24 h at 80°C. However, in accordance with known hetarenium salts[7,16] and mesomeric betaines,[5,6] the compounds crystallize with nonstoichiometric amounts of water. The water of hydration of **3** is proved by the X-Ray crystal structure analysis.

5-Chloro-2,6-bispyridiniopyrimidin-4-olate chloride (3).

0.39 g (5.00 mmol) of pyridine was added dropwise to a vigorously stirred suspension of 0.27 g (1.25 mmol) of tetrachloropyrimidine (**1**) in 70 mL of anhydrous ethyl acetate. Then, the reaction mixture was heated at reflux over a period of 1 h. After cooling, the precipitate was filtered off, washed with ethyl acetate, and recrystallized from aqueous ethanol.

Yield: 0.33 g (82%), mp > 90°C (decomp); ^{1}H NMR (HH-COSY): δ = 8.29 (dd, J = 7.7/5.7 Hz, 2H; 3-H), 8.47 (dd, J = 7.9/6.8 Hz, 2H; 6-H), 8.88 (tt, J = 7.7/1.3 Hz, 1H; 4-H), 8.97 (tt, J = 7.9/1.3 Hz, 1H; 7-H), 9.55 (d, J = 6.8 Hz, 2H; 5-H), 9.93 (d, J = 5.7 Hz, 2H; 2-H); ^{13}C NMR (CH-COSY): δ = 114.07 (C-12), 127.95 (C-3), 128.39 (C-6), 140.77 (C-2), 144.73 (C-5), 149.43 (C-7), 149.72 (C-4), 152.86 (C-9)*, 153.42 (C-11)*, 167.04 (C-13);*: peak assignments exchangeable; IR: 1604.2, 1559.6, 1521.2, 1468.1, 1415.7, 1316.4, 1038.7, 1022.8, 778.7, 674.5 cm^{-1}; FABMS: *m/z* = 285.5 (M$^+$; 100). *Anal.* Calcd for $C_{14}H_{10}N_4OCl_2 \cdot 4\ H_2O$: C, 42.76; H, 4.61; N, 14.25. Found: C, 42.86; H, 4.90; N, 14.04.

5-Chloro-2,6-bispyridiniopyrimidin-4-olate hydroxide (4).
150 mL of the anion exchange resin Amberlite® IRA-400 were filled into a column without frit (height: 16 cm, diameter 3 cm) and washed with 2 L of water. Then, 150 mL of a 8% aqueous solution of sodium hydroxide was added and remained in the column for 45 min. The sodium hydroxide was then rinsed out with water until pH 7 was reached. Then, a sample of 200 mg (0.62 mmol) of the tripole (**3**) dissolved in 30 mL of water was added on the anion exchange resin. The elutes were concentrated *in vacuo* at 15°C maximum bath temperature and cooled overnight. Then, the resulting precipitate was filtered off and dried *in vacuo*.
Yield: 0.16 g (85%), mp > 113°C (decomp); ^{1}H NMR: δ = 8.28 (dd, J = 7.7/6.8 Hz, 2H; 3-H), 8.46 (dd, J = 7.9/6.1 Hz, 2H; 5-H), 8.86 (tt, J = 7.7/1.3 Hz, 1H; 4-H), 8.96 (tt, J = 7.9/1.3 Hz, 1H; 7-H), 9.52 (d, J = 6.8 Hz, 2H; 5-H), 9.92 (d, J = 6.1 Hz, 2H; 2-H); ^{13}C NMR not measured because of insufficient solubility; IR: 1604.4, 1560.0, 1521.1, 1468.6, 1415.9, 1316.5 cm^{-1}; FABMS: *m/z* = 285.5 (M$^+$; 100). *Anal.* Calcd for $C_{14}H_{11}N_4O_2Cl \cdot 4\ H_2O$: C, 44.88; H, 5.11; N, 14.94. Found: C, 44.18; H, 4.50; N, 14.93.

5-Chloro-6-[[(1*E*,3*E*)-5-oxopenta-1,3-dienyl]amino]-2-pyridiniopyrimidin-4-olate (5).
A sample of 0.50 g (1.62 mmol) of **4**, dissolved in 50 mL of water, was treated dropwise with a 10% aqueous solution of sodium hydroxide to pH 9, whereupon an orange-colored solid precipitated. The solid was filtered off and subsequently washed with water, ethanol, and ethyl acetate.
Yield: 0.26 g (55 %) of an orange solid, mp > 300°C. ^{1}H NMR: δ = 5.94 (dd, J = 14.7/8.1 Hz, 1H; 15-H), 6.34 (dd, J = 13.2/11.7 Hz, 1H; 13-H), 7.51 (t, J = 14.7/11.7 Hz, 1H; 14-H), 8.19 (dd, J = 13.2/11.4 Hz, 1H; 12-H), 8.22 (dd, J = 7.8/6.9 Hz, 2H; 3-H), 8.78 (t, J = 7.8 Hz, 1H; 4-H), 9.41 (d, J = 8.1 Hz, 1H; 16-H), 9.66 (d, J = 11.4 Hz, 1H, H/D-exchangeable; 11-H), 10.04 (d, J = 6.9 Hz, 2H; 2-H); IR: 1620.3, 1581.8, 1503.3, 1167.9 cm^{-1}; FABMS: *m/z* = 303.7 (M$^+$ + 1; 95), 136.3 (100). *Anal.* Calcd for $C_{14}H_{11}N_4O_2Cl \cdot 3.5\ H_2O$: C, 45.97; H, 4.96; N, 15.31. Found: C, 45.48; H, 4.63; N, 15.39.

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REFERENCES

1. M. T. Davies-Coleman, D. J. Faulkner, G. M. Dubowchik, G. P. Roth, C. Polson, and C. Fairchild, *J. Org. Chem.*, 1993, **58**, 5925; N. Fusetani, N. Asai, S. Matsunaga, K. Honda, and K. Yasumuro, *Tetrahedron Lett.*, 1994, **35**, 3967; H. Anan, N. Seki, O. Noshiro, K. Honda, K. Yasumuro, T. Ozasa, and N. Fusetani, *Tetrahedron*, 1996, **52**, 10849.
2. T. Jahn, G. M. König, A. D. Wright, G. Wörheide, and J. Reitner, *Tetrahedron Lett.*, 1997, **38**, 3883; M. Lounasmaa, P. Hankinen, and S. Lipponen, *Heterocycles*, 1996, **43**, 1365; J. Quetin-Leclerq, P. Couke, C. Delaude, R. Warin, R. Bassleer, and L. Angenot, *Phytochemistry*, 1991, **30**, 1697; M. A. Siddiqui and V. Snieckus, *Tetrahedron Lett.*, 1990, **31**, 1523; A. Ohta, A. Kojima, and Y. Aoyagi, *Heterocycles*, 1990, **31**, 1655.
3. P. A. Limbach, P. F. Crain, and J. A. McCloskey, *Nucleic Acids Res.*, 1994, **22**, 2183; G. Dirheimer, in 'Modified Nucleosides and Cancer,' ed. by G. Glass, Springer-Verlag, Berlin, Heidelberg; 1983; G. Dirheimer, G. Keith, A. P. Sibler, and R. P. Martin, in 'Transfer RNA: Structure, Properties and

Recognition,' ed. by P. R. Schimmel, D. Söll, and J. N. Abelson, Cold Spring Harbor, New York; 1979.

4. T. Fujii, T. Itaya, and K. Ogawa, *Heterocycles*, 1997, **44**, 573.
5. A. Schmidt and M. Nieger, *J. Chem. Soc., Perkin Trans. 1*, 1999, **10**, 1325; A. Schmidt, *Heterocycles*, 1998, **48**, 865; A. Schmidt and M. K. Kindermann, *J. Org. Chem.*, 1998, **63**, 4636; A. Schmidt, A. Hetzheim, and D. Albrecht, *Heterocycles*, 1996, **43**, 2153.
6. A. Schmidt, M. K. Kindermann, and M. Nieger, *Heterocycles,* 1999, **51**, 237; A. Schmidt and M. K. Kindermann, *J. Org. Chem.*, 1997, **62**, 3910.
7. A. Schmidt and A. Hetzheim, *Tetrahedron*, 1997, **53**, 1295.
8. W. D. Ollis, S. P. Stanforth, and C. A. Ramsden, *Tetrahedron*, 1985, **41**, 2239.
9. C. Reichardt, 'Solvents and Solvent Effects in Organic Chemistry,' 2nd ed., VCH Verlagsgesellschaft mbH, Weinheim, 1990.
10. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-113408. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Some crystal data of (**3**): $C_{14}H_{10}ClN_4O$-Cl-4 H_2O; M = 393.22; space group $P2_1/c$ (no. 14); dimensions 0.40 x 0.35 x 0.15 mm^3, a = 9.2948(5), b = 26.6046(17), c = 7.2635(3) Å; β = 106.526(3)°; V = 1721.95(16) Å^3, D_c = 1.517 MG m^{-3}, Z = 4, μ(MoKα) = 0.411 mm^{-1}; T = 123(2) K; F(000) = 816, 14544 reflections were collected in a Nonius KappaCCD diffractometer ($2\Theta_{max.}$ = 56.4°, $-12 \le h \le 12$, $-35 \le k \le 35$, $-9 \le l \le 9$), 3815 symmetry independent reflections (R_{int} = 0.0316) were used for the structure solution (direct methods)[11] and refinement (full-matrix least-squares on F^2,[12] 250 parameters, 46 restraints), non-hydrogen atoms were refined anisotropically, H atoms localized by difference electron density, aromatic hydrogen atoms were refined using a riding model, other free; wR2 (all data) = 0.076 [R1 = 0.032 for 2801 $I>2\sigma(I)$].
11. G. M. Sheldrick, SHELXS-97, Acta Cryst., 1990, **A46**, 467.
12. G. M. Sheldrick, SHELXL-97, University of Göttingen, 1997.
13. K. Kigasawa, K. Ohkubo, T. Kohagisawa, H. Shimizu, S. Saitoh, and T. Kametani, *Heterocycles,* 1976, **4**, 1257.
14. D. Reinehr and T. Winkler, *Angew. Chem.*, 1981, **93**, 911; *Angew. Chem., Int. Ed. Engl.*, 1981, **20**, 881; T. Uno, K. Okumura, and Y. Kuroda, *J. Org. Chem.*, 1981, **46**, 3175.
15. K. E. Wilzbach and D. J. Rausch, *J. Amer. Chem. Soc.*, 1970, **92**, 2178.
16. cf. K. C. Waterman, D. V. Speer, A. Streitwieser, G. C. Look, J. G. Stack, and K. O. Nguyen, *J. Org. Chem.* 1988, **53**, 583; K. A. Smith, K. C. Waterman, and A. Streitwieser, Jr, *J. Org. Chem.* 1985, **50**, 3360; A. S. Feng, D. V. Speer, S. G. DiMagno, M. S. Konings, and A. Streitwieser, *J. Org. Chem.* 1992, **57**, 2902; A. S. Koch, A. S. Feng, T. A. Hopkins, and A. Streitwieser, *J. Org. Chem.* 1993, **58**, 1409.

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