

Sulfonic and Phosphonic Acids Formed by Bisulfite and Phosphite Adduct Formation with Pyrimidinones

Tore Benneche, Per Strande and Kjell Undheim

Department of Chemistry, University of Oslo, N-0315 Oslo 3, Norway

Benneche, T., Strande, P. and Undheim, K., 1987. Sulfonic and Phosphonic Acids Formed by Bisulfite and Phosphite Adduct Formation with Pyrimidinones. – Acta Chem. Scand., Ser. B 41: 448–454.

By analogy with carbonyl compounds, π -electron deficient 2-pyrimidinones form adducts with sodium bisulfite and phosphite esters. Both the 3,4- and the 3,6-bisulfite adducts were found. The 3,4-isomer was often predominant and was obtained isomerically pure by selective precipitation from an aqueous solution. The adduct formation is reversible in aqueous solution. The adduct was also readily cleaved by trifluoroacetic acid. With tris(trimethylsilyl) phosphite, regiospecific formation of the 3,4-adduct was observed. The corresponding 3,4-dihydro-4-phosphonic acid was prepared by methanol cleavage of the silyl ester function.

The 2(1*H*)-pyrimidinone system is π -electron deficient and highly polarized. It readily forms 1:1 adducts with organometallic reagents,¹ is reduced by metal hydrides to the corresponding dihydro derivatives,² and forms 1:1 adducts with alcohols and thiols.³ We have previously pointed out that this system possesses chemical properties which are comparable with those of the carbonyl group.⁴ Expanding on this analogy, there is evidence that the addition of bisulfite to the carbonyl group to form bisulfite addition compounds⁵ has its counterpart in the addition to the polarized C(5)–C(6) double bond in uracils and cytosines.⁶ The bisulfite adducts are sulfonic acid salts and hence would be expected to have much higher water solubility than the parent heterocycle.

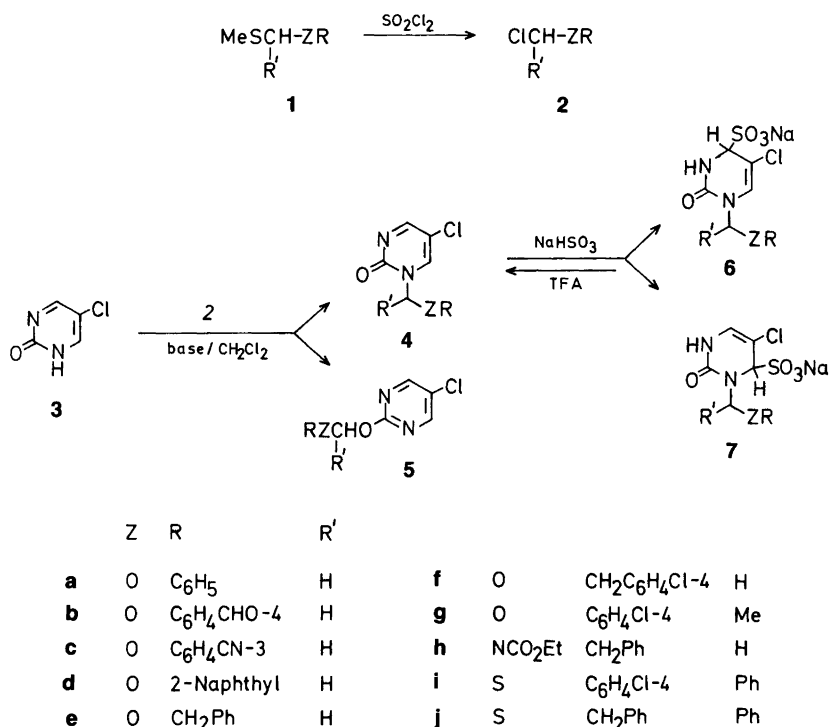
The solubility properties of 1-substituted 2(1*H*)-pyrimidinones are of particular interest since such compounds have been found to affect the cell-cycle during mitosis by possessing reversible metaphase arresting properties.⁷ These compounds frequently have low water solubility, however, but it has now been found that this can largely be overcome by making bisulfite adducts. The adducts show the same *in vitro* biological activity as the parent compounds, consistent with reversibility of adducts formation.⁸ Biological use

of bisulfites, however, must be carefully controlled because heavy loads may cause mutagenesis.⁶

Bisulfites have been found to add to C-4 or C-6 to give 3,4- and 3,6-dihydro sulfonic acid derivatives of the 5-halo-2(1*H*)-pyrimidinone. The addition takes place at ambient temperature in aqueous NaHSO₃, or with a co-solvent like DMF, or in a two-phase system. The reaction proceeds well under slightly acidic conditions, but neutral conditions can also be used, which is of importance when the N-1 substituent is acid-sensitive in aqueous media.

The major product was the 3,4-adduct **6**. Typically, evaporation of the mixture following reaction of **4b** and a slight excess of sodium bisulfite in aqueous solution gave a product mixture consisting of the 3,4- and 3,6-adducts **6b** and **7b** in a ratio of 3:1; all the starting material (**4b**) had reacted. The adduct formation is reversible and the isomer ratios will most likely depend on the reaction conditions. The 3,4-adduct, the major isomer, appears to be the less soluble in water, and was precipitated selectively from concentrated aqueous solutions. The yield of product obtained by this technique will depend on the relative water solubilities, the less soluble isomer being more readily precipitated.

It is noteworthy that in the case of the *p*-formyl



Scheme 1.

derivative **4b**, the use of one equivalent of bisulfite led to selective adduct formation with the heterocyclic ring. This is somewhat surprising since unhindered aldehydes such as *p*-methoxybenzaldehyde, which in this connection is a close analogue of **4b**, readily add bisulfite.⁹

The bisulfite adducts contain 1–2 molecules of water which were difficult to remove. Drying at elevated temperatures led to decomposition. As solids, the bisulfite adducts are stable in the cold.

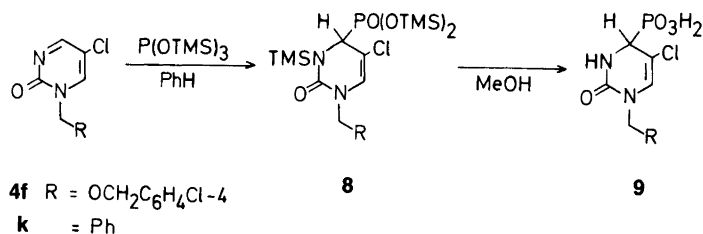
The assignments of structure to the adducts are based on previously obtained ¹H NMR spectroscopic data for dihydropyrimidinones, which show that the H-4 proton resonates at higher field in the 3,4-dihydro isomers than the H-6 proton in the 3,6-dihydro isomers. The reverse is true for H-6 and H-4, respectively.^{1b,10} With both isomers available, a distinction and an assignment of structure can be made. The major isomer, the 3,4-adduct, is also the one to be expected for stereochemical reasons.

With trifluoroacetic acid in the cold the bisulfite adducts **6** and **7** were rapidly cleaved with

regeneration of the parent heterocycle **4**. This reversal of the bisulfite adduct formation by trifluoroacetic acid has been developed into a method for the separation of the mixture of *N*-alkylated (**4**) and *O*-alkylated (**5**) products which are formed in the alkylation reactions. Since the *O*-alkylated products **5** do not add bisulfite, separation is achieved by stirring a mixture of **4** and **5** in a two-phase system consisting of dichloromethane/water containing sodium bisulfite. The *O*-alkylated isomer **5** is then found in the organic phase, while the *N*-alkylated isomer occurs in the aqueous phase as bisulfite adduct. Freeze-drying of the aqueous phase and treatment with trifluoroacetic acid gives the pure *N*-alkylated isomer **4**.

Limitations would be placed on the method by the presence of substituents in the *O*-alkylated product which either form bisulfite adducts or salts.

We have also studied the formation and properties of the phosphonic acids **9**. The method used for their preparation was based on reported reactions between carbonyl compounds and



Scheme 2.

phosphites. Thus, α,β -unsaturated carbonyl compounds react with phosphite esters in phenol or ethanol in the 1,4-manner,¹¹ whereas tris(trimethylsilyl) phosphite gives the 1,2-adducts in high yields when reacted with aldehydes, ketones and α,β -unsaturated aldehydes; α,β -unsaturated ketones give the 1,4-adducts.¹²

We find that tris(trimethylsilyl) phosphite readily adds to the pyrimidinones **4f** and **4k**. Only one product was formed. The spectroscopic data were consistent with formation of the 3,4-adduct (**8**). This is also the regiochemistry expected with the bulky phosphite reagent, which would interfere with the 1-substituent. An IR spectrum (CDCl_3) of the adduct showed a strong band at 1705 cm^{-1} , consistent with silylation at N-3, and a free carbonyl group as in structure **8**. The silylated products **8** are hydrolyzed to the phosphonic acids **9** on treatment of the esters **8** with methanol at ambient temperature.

The phosphonic acids as sodium salts are water soluble. The compounds do not show significant metaphase arresting properties,⁸ a finding which is consistent with irreversibility of the C-P bond formation in aqueous solution. The phosphonic acids **9** were also resistant to cleavage of the C-P bond when left to stand in trifluoroacetic acid at ambient temperature.

Experimental

The ^1H NMR spectra were recorded at 60 MHz or 200 MHz. The mass spectra under electron impact conditions were recorded at 70 eV ionization energy. Isobutane was used for chemical ionizing mass spectra (CI); the spectra are presented as m/z (% rel. int.).

O,S-Acetals **1a–1f** were prepared by the reaction of chloromethyl methyl sulfide with the sodium salt of the benzyl alcohol or the phenol in the presence of sodium iodide in 1,2-dimethoxy-

ethane according to the literature procedure.¹³ Compound **1f** has previously been described.¹⁴

4-Formyl-1-(methylsulfenyl)methoxybenzene (1b). The yield was 82%, b.p. $96\text{--}106^\circ\text{C}/0.1\text{ mmHg}$. ^1H NMR (CDCl_3): δ 2.28(SMe), 5.23 (SCH_2O), 7.0–8.0(Ar), 9.93(CHO).

3-Cyano-1-(methylsulfenyl)methoxybenzene (1c). The yield was 98% of crude product. ^1H NMR (CDCl_3): δ 2.30 (SMe), 5.21(SCH_2O), 7.2–7.6 (Ar).

α -Chloroalkyl ethers (2a–2f) were prepared by treatment of the *O,S*-acetals with sulfonyl chloride essentially as previously described.¹⁴ Compounds **2a**¹⁵, **2d**¹⁶ and **2f**¹⁴ have been reported previously.

1-Chloromethoxy-4-formylbenzene (2b). The yield was 68%, b.p. $86\text{--}90^\circ\text{C}/0.1\text{ mmHg}$. ^1H NMR (CDCl_3): δ 5.96(OCH_2Cl), 7.0–8.0(Ar), 9.95(CHO).

1-Chloromethoxy-3-cyanobenzene (2c). The yield was 68%, b.p. $80\text{--}92^\circ\text{C}/0.1\text{ mmHg}$. ^1H NMR (CDCl_3): δ 5.95(OCH_2Cl), 7.1–7.5(Ar).

4-Chloro-1- α -chloroethoxybenzene (2g). The yield was 29%, b.p. $65\text{--}69^\circ\text{C}/0.1\text{ mmHg}$. ^1H NMR (CCl_4): δ 1.90(d,3H, J 6 Hz), 5.97 (q, 1H, J 6 Hz), 6.8–7.4(Ar).

α -Chlorobenzyl 4-chlorophenyl sulfide (2i). A solution of benzyl 4-chlorophenyl sulfide (4.68 g, 20 mmol) and *N*-chlorosuccinimide (2.44 g, 20 mmol) in dry tetrachloromethane (50 ml) was stirred under N_2 at ambient temperature for 1 h. The mixture was filtered, the filtrate shaken with aqueous NaCl and the dried (MgSO_4) solution

evaporated. The crude product (5.40 g, 95 %) was used in the subsequent reaction without further purification. $^1\text{H NMR}$ (CCl_4): δ 6.04 (CH), 7.1–7.6 (2 Ar).

Compounds **2h**¹⁷ and **2j**¹⁸ have been described previously.

General procedure for the preparation of 1-alkylated 2(1H)-pyrimidinones (4). The chloromethyl ether, sulfide or carbamate **2** (2 mmol) in dichloromethane (4 ml) was added dropwise with stirring under N_2 to a solution which had been prepared from 5-chloro-2(1H)-pyrimidinone (2 mmol) and triethylamine (2 mmol) in dichloromethane (20 ml). The reaction mixture was stirred at ambient temperature for 24 h and aqueous NaCl was then added; the organic layer was separated, dried (MgSO_4) and evaporated to give the crude product which was a mixture of the *N*- and *O*-alkylated isomers **4** and **5** in 80–95 % yield. The isomers could be separated by the lower solubility of the *N*-alkylated isomer in diethyl ether or by chromatography. We were only interested in the isolation and purification of the *N*-alkylated isomer.

Compounds **4a** and **4d** have been described previously.¹⁹

5-Chloro-1-(4-formylphenoxy)methyl-2(1H)-pyrimidinone (4b). The *N*- and *O*-alkylated isomers were separated by extraction with diethyl ether. The undissolved *N*-alkylated product **4b** was obtained in 42 % yield, m.p. 183 °C. Anal. $\text{C}_{12}\text{H}_9\text{ClN}_2\text{O}_3$: C, H. $^1\text{H NMR}$ (CDCl_3): δ 6.00 (CH_2N), 7.0–8.0 (Ar, H-6), 8.67 (H-4, d, *J* 3 Hz), 10.00 (CHO). MS: 264(6, M), 145(29), 143(100), 118(9), 116(24).

5-Chloro-1-(3-cyanophenoxy)methyl-2(1H)-pyrimidinone (4c). The *N*- and *O*-alkylated isomers were separated by extraction with diethyl ether. The undissolved *N*-alkylated product **4c** was isolated in 43 % yield, m.p. 194 °C. Anal. $\text{C}_{12}\text{H}_8\text{ClN}_3\text{O}_2$: C, H. $^1\text{H NMR}$ ($\text{DMSO}-d_6/\text{CDCl}_3$): δ 5.82 (CH_2), 7.3–7.5 (Ar), 8.60 (H-4 and H-6). MS: 261(11, M), 145(32), 143(100), 118(8), 116(25).

5-Chloro-1-[1-(4-chlorophenoxy)ethyl]-2(1H)-pyrimidinone (4g). The *N*- and *O*-alkylated isomers, total yield and ratio 95 % and 5:2, respectively ($^1\text{H NMR}$), were separated by extraction with light petroleum. The undissolved *N*-alkylated product **4g** was isolated in 37 % yield, m.p. 101 °C. Anal. $\text{C}_{12}\text{H}_{10}\text{Cl}_2\text{N}_2\text{O}_2$: C, H. $^1\text{H NMR}$ (CDCl_3): δ 1.73 (CH_3CH_2 , d, *J* 6 Hz), 6.5–7.5 (Ar, CHCH_3), 7.97 and 8.42 (H-6 and H-4, respectively, *J* 3 Hz). MS: 282(2, M), 159(32), 157(100), 156(16), 155(12), 154(45).

*5-Chloro-1-[1-(*N*-ethoxycarbonyl)benzylamino]methyl-2(1H)-pyrimidinone (4h).* The *N*- and *O*-alkylated isomers, total yield and ratio 80 % and 4:2, respectively ($^1\text{H NMR}$), were separated by extraction with diethyl ether. The undissolved *N*-alkylated product **4h** was obtained in 53 % yield, m.p. 143 °C. Anal. $\text{C}_{15}\text{H}_{16}\text{N}_3\text{O}_3$: C, H. $^1\text{H NMR}$ (CDCl_3): δ 1.31 and 4.22 (EtO), 4.73 (CH_2Ph), 5.23 (CH_2N), 7.20 (Ph), 8.03 and 8.48 (H-6 and H-4, respectively, *J* 3 Hz). IR (KBr): 1670 and 1720 cm^{-1} . MS (CI): 324/322 (0.6/1.7, M+H), 194(19), 193(11), 192(100).

1-(α -Benzylthiobenzyl)-5-chloro-2(1H)-pyrimidinone (4j). Compound **4j** was isolated in 33 % yield as a solid when treated with diethyl ether; m.p. 126 °C. Anal. $\text{C}_{18}\text{H}_{15}\text{ClN}_2\text{OS}$: C, H. $^1\text{H NMR}$ (CDCl_3): δ 7.12 (NCHS), 7.27 (Ph), 7.33 (Ph), 8.12 and 8.30 (H-6 and H-4, respectively, d, *J* 3 Hz). MS: 251(2), 221(5), 219(16), 213(38), 212(30), 91(100).

*General procedure for the preparation of sodium 1-substituted 5-chloro-2-oxo-2-*l*,2,3,4-tetrahydropyrimidine-4-sulfonate (6).* A 37 % aqueous solution of sodium bisulfite (4.4 ml, 21 mmol) was added to a suspension of the 1-substituted 5-chloro-2(1H)-pyrimidinone (14 mmol) in water (60 ml). The pH was adjusted to ca. 7 and the mixture was stirred at ambient temperature for 4 h. It was then heated at 100 °C for 5–10 min, the almost clear solution was filtered hot and the filtrate left to stand at 5 °C. The product **6** crystallized out and was recrystallized from a small volume of water. No attempts were made to adjust the volume of water to the relative solubility of the respective compound. In some cases, therefore, a considerable amount of the product may remain in solution. The products are hydrated and were therefore not subjected to ele-

mental analyses; they were identified by NMR spectroscopy and their homogeneity was checked by chromatography.

Sodium 5-chloro-1-(4-formylphenoxy)methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4-sulfonate (6b). Compound **6b** was precipitated in 49 % yield. $^1\text{H NMR}$ (D_2O): δ 4.36 (H-4,s), 5.28 and 5.57($\text{CH}_2\text{N,d,J}$ 9 Hz), 6.87(H-6,S), 7.1–8.0(Ar), 9.88(CHO,s).

Sodium 5-chloro-1-(3-cyanophenoxy)methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4-sulfonate (6c). The precipitate of compound **6c** was triturated with water, acetone and diethyl ether; yield 73 %. $^1\text{H NMR}$ ($\text{DMSO-}d_6$): δ 4.03(H-4,d,J 3 Hz), 5.27 and 5.52($\text{CH}_2\text{N,d,J}$ 9 Hz), 6.85 (H-6,s), 7.3–7.8(Ar).

Sodium 5-chloro-1-(2-naphthoxy)methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4-sulfonate (6d). The precipitate of compound **6d** was triturated with water, acetone and diethyl ether; yield 77 %. $^1\text{H NMR}$ ($\text{DMSO-}d_6$): δ 4.38(H-4,d,J 2 Hz), 5.30 and 5.60($\text{CH}_2\text{O,d,J}$ 9 Hz), 6.88(H-6,s), 7.1–8.0(Ar).

Sodium 5-chloro-1-[1-(4-chlorophenoxy)ethyl]-2-oxo-1,2,3,4-tetrahydropyrimidine-4-sulfonate (6g). Compound **6g** was precipitated in 90 % yield. $^1\text{H NMR}$ ($\text{DMSO-}d_6$): δ 1.50 and 6.42 ($\text{CH}_3\text{CH,J}$ 6 Hz), 4.37(H-4,s), 6.70(H-6,s), 7.0–7.7(Ar).

Sodium 5-chloro-1-[(N-ethyloxycarbonyl)benzylamino]methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4-sulfonate (6h). Compound **6h** was precipitated in 37 % yield. $^1\text{H NMR}$ ($\text{DMSO-}d_6$): δ 1.21 and 4.14(Et), 4.33(H-4,s), 4.50(CH_2 ,s), 4.87 (CH_2 ,s), 6.31(H-6,s), 7.32(Ar).

Sodium 5-chloro-1-[α -(4-chlorophenylsulfenyl)]benzyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4-sulfonate (6i). Compound **6i** was precipitated in 50 % yield. $^1\text{H NMR}$ ($\text{DMSO-}d_6$): δ 4.31(H-4,d,J 3 Hz), 6.80(H-6,s), 7.2–7.8 (9H,Ar,CHN).

Sodium 5-chloro-1- α -(phenylsulfenyl)benzyl-2-oxo-1,2,3,4-tetrahydropyrimidine-4-sulfonate (6j). Compound **6j** was precipitated in 97 %

yield. $^1\text{H NMR}$ ($\text{DMSO-}d_6$): δ 3.90(H-4,s), 4.0 and 4.4(CH_2 S), 6.60(CHS), 6.9(H-6,s).

Use of an organic solvent in the preparation of compound 6c. A mixture of 5-chloro-1-(3-cyanophenoxy)methyl-2(1H)-pyrimidinone (0.52 g, 2 mmol) and sodium metabisulfite (0.57 g, 3 mmol) in DMF (15 ml) and water (2 ml) was stirred at 60°C for 1 h before the solvent was distilled off at reduced pressure. Water was added to the residue, and the solid was collected and washed with acetone and diethyl ether; yield 0.50 g (69 %). Physical data are given above.

Use of a two-phase system in the preparation of compound 6c. A mixture of 5-chloro-1-(3-cyanophenoxy)methyl-2(1H)-pyrimidinone (0.52 g, 2 mmol), sodium metabisulfite (0.76 g, 4 mmol) and triethylbenzylammonium chloride (ca. 50 mg) in chloroform (15 ml) and water (20 ml) was stirred at ambient temperature for 48 h. The product precipitated, and was filtered off and washed with chloroform, acetone and diethyl ether; yield 55 %.

Sodium 1-(4-formylphenoxy)methyl-5-chloro-2-oxo-1,2,3,4-tetrahydropyrimidine-4-sulfonate (6b) and sodium 1-(4-formylphenoxy)methyl-5-chloro-2-oxo-1,2,3,6-tetrahydropyrimidine-6-sulfonate (7b). The bisulfite adduct formation with 1-(4-formylphenoxy)methyl-5-chloro-2(1H)-pyrimidinone was carried out as described above. The product, after evaporation of the water, was shown by $^1\text{H NMR}$ to be a mixture of the adducts **6b** and **7b** in the ratio 3:1. $^1\text{H NMR}$ data for the 3,4-dihydro-4-sulfonate (**6b**) are given above. $^1\text{H NMR}$ data for the 3,6-dihydro-6-sulfonate (**7b**) ($\text{DMSO-}d_6$): δ 4.63(H-6,s), 5.48 and 5.98 ($\text{CH}_2\text{N,d,J}$ 9 Hz), 6.38(H-4,s), 7.1–8.0(Ar), 9.88 (CHO).

Cleavage of the bisulfite adducts 6 and 7 with regeneration of compound 4. The general procedure is exemplified by the cleavage of 5-chloro-1-(4-formylphenoxy)methyl-2-oxo-1,2,3,4(3,6)-tetrahydropyrimidine-4(6)-sulfonate. The latter (133 mg, 0.36 mmol) was added to trifluoroacetic acid, the mixture stirred at ambient temperature for 10 min and the solvent evaporated. The residue was extracted with dichloromethane and the solution shaken with aqueous NaHCO_3 , dried

(MgSO₄) and evaporated. The yield of the parent compound **4b** was 68 %.

General procedure for the separation of 1-alkyl-5-chloro-2(1H)-pyrimidinones (4) and 2-alkoxy-5-chloropyrimidines (5). A mixture of the *N*- and *O*-alkylation products was prepared as described in the alkylation procedure above, except that diethylamine was used as the base instead of triethylamine. The mixture of the crude *N*- and *O*-alkylation products (4.0 mmol) was dissolved in dichloromethane (10 ml) and a solution of sodium metabisulfite (0.77 g, 4.0 mmol) in water (10 ml) containing tetraethylammonium chloride (catalytic amount) was added. The mixture was stirred vigorously for 24 h at ambient temperature, the organic phase was separated, washed with water and the dried (MgSO₄) solution evaporated to yield the pure *O*-alkylated isomer. The combined aqueous phase and washings were shaken with dichloromethane and the aqueous solution freeze-dried. The product, a mixture of the 3,4-dihydro-4-sulfonate (**6**) and the 3,6-dihydro-6-sulfonate (**7**), was added to trifluoroacetic acid (6 ml) at 0 °C. The mixture was stirred at ambient temperature for 15 min before being added dropwise to a vigorously stirred two-phase system consisting of aqueous saturated NaHCO₃ (50 ml) and dichloromethane (50 ml) at 0 °C. The phases were separated and the aqueous phase was extracted with dichloromethane; the organic solutions were combined and shaken with aqueous saturated NaHCO₃, and the dried (MgSO₄) solution evaporated to yield the *N*-alkylated isomer.

The recovery of the pure *N*- and *O*-alkylated isomers from the crude isomer product mixture was in the range 70–90 %.

5-Chloro-1-(phenoxy)methyl-2(1H)-pyrimidinone (4a) and 5-chloro-2-(phenoxy)-methoxy-pyrimidine (5a). The yield of the crude isomer product was 79 %; the isomer ratio **4a/5a** was 2:1. After separation, the overall yields of isomers **4a**¹⁹ and **5a**¹⁹ were 33 and 19 %, respectively.

1-(Benzyloxy)methyl-5-chloro-2(1H)-pyrimidinone (4e) and 2-(benzyloxy)methoxy-5-chloropyrimidine (5e). The yield of the crude isomer product was 89 %; the ratio of **4e/5e** was 1:1. After separation, both the isomer **4e** and the isomer **5e** were obtained in 38 % yield.

Product 4e: m.p. 122 °C (EtOAc). Anal. C₁₂H₁₁ClN₂O₂: C, H. ¹H NMR (CDCl₃): δ 4.71 (CH₂Ph), 5.42(CH₂N), 7.4(Ph), 7.74(Ph), 7.74 and 8.53 (H-6 and H-4, respectively, d, *J* 3 Hz). MS(Cl): 251/249(11/7, M+H), 223(17), 221(53), 144(7), 91(100).

Product 5e: m.p. 33–36 °C. Anal. C₁₂H₁₁ClN₂O₂: C, H. ¹H NMR (CDCl₃): δ 4.82(CH₂Ph), 5.6 (OCH₂O), 7.3–7.5(Ph), 8.50(H-4/6,s). MS: 0(M), 222(2), 220(7), 219(4), 144(27), 91(100).

5-Chloro-1-(4-chlorobenzyloxy)methyl-2(1H)-pyrimidinone (4f) and 5-chloro-2-(4-chlorobenzyloxy)methoxy-pyrimidine (5f). The yield of the crude isomer product was 81 %; the ratio of **4f/5f** was 1:1. The overall yields of the separated products **4f** and **5f** were 33 and 39 %, respectively.

Product 4f: m.p. 147 °C (acetone). Anal. C₁₂H₁₀Cl₂N₂O₂: C, H. ¹H NMR (CDCl₃): δ 4.62 (s, 2H), 5.32(s, 2H), 7.25(Ar), 7.78 and 8.47(H-6 and H-4, respectively, *J* 3 Hz). MS: 256(5), 254(6), 144(28), 127(33), 125(100), 102(14), 86(22).

Product 5f: m.p. 99 °C. Anal. C₁₂H₁₀Cl₂N₂O₂: C, H. ¹H NMR (CDCl₃): δ 4.70(s, 2H), 5.58 (s, 2H), 7.23(Ar), 8.41(H-4 and H-6,s). MS: 256(3), 254(4), 144(27), 127(35), 125(100).

5-Chloro-1-α-(4-chlorophenylsulfenyl)benzyl-2(1H)-pyrimidinone (4i) and 5-chloro-2-α-(4-chlorophenylsulfenyl)benzyloxy-pyrimidine (5i). The yield of crude isomer product was 96 %; the isomer ratio **4i/5i** was 4:3.

Product 4i: m.p. 144 °C (CH₂Cl₂–light petroleum). Anal. C₁₇H₁₂Cl₂N₂OS: C, H. ¹H NMR (acetone-*d*₆/DMSO-*d*₆): δ 7.0–7.7(9H, 2Ar, CHN), 8.42 and 8.72 (H-6 and H-4, respectively, *J* 3 Hz). IR(KBr): 1660 cm⁻¹. MS: 362(2, M), 325(5), 233(12), 221(32), 219(100).

Product 5i: m.p. 104 °C (MeOH). Anal. C₁₇H₁₂Cl₂OS: C, H. ¹H NMR (acetone-*d*₆): δ 7.2–7.6(9H, 2Ar), 7.93(SCHO), 8.55(2H, H-4, 6).

5-chloro-1-(4-chlorobenzyloxy)methyl-2-oxo-3,4-dihydropyrimidine-4-phosphonic acid (9f). A mixture of tris(trimethylsilyl) phosphite²⁰ (1.40 g, 6.0 mmol) and 5-chloro-1-(4-chlorobenzyloxy)-methyl-2(1H)-pyrimidinone (0.87 g, 3.0 mmol) in dry benzene (15 ml) was stirred under N₂ at ambient temperature for 4 h, and the solvent and excess tris(trimethylsilyl) phosphite were removed under reduced pressure. The residual product was bis(trimethylsilyl) 5-chloro-1-(4-chloro-

benzyloxy)methyl-2-oxo-3-trimethylsilyl-3,4-dihydropyrimidine-4-phosphonate (**8f**). The crude product was treated with methanol (7 ml), the mixture stirred at ambient temperature for 3 h, and the precipitated product collected by filtration; yield 0.60 g (54 %) m.p. > 260°C. Anal. C₁₂H₁₃Cl₂N₂O₅P: C, H. ¹H NMR (DMSO-*d*₆): δ 4.05(H-4, d, *J* 10 Hz), 4.50(CH₂Ar), 4.70 and 4.91 (CH₂N, d, *J* 9 Hz), 6.60(H-6, d, *J* 5 Hz), 7.4 (Ar). MS: 144(18), 143(8), 142(55), 141(16), 125(14), 113(19), 107(84), 77(100).

1-Benzyl-5-chloro-2-oxo-3,4-dihydropyrimidine-4-phosphonic acid (**9k**). Compound **9k** was prepared from 1-benzyl-5-chloro-2(1*H*)-pyrimidinone²¹ as above, except that the reaction time was 20 h at ambient temperature and 4 h at 80°C; yield 66 %, m.p. 226°C (decomp.). Anal. C₁₁H₁₂ClN₂O₄P: C, H. ¹H NMR (DMSO-*d*₆): δ 4.04(H-4, d, *J* 10 Hz), 4.55(CN₂N, broad s), 6.55 (H-6, d, *J* 5 Hz), 7.32(Ph). MS: 222(9), 220(26), 115(4), 114(4), 91(100).

References

- (a) Rise, F. and Undheim, K. *J. Chem. Soc., Perkin Trans I* (1985) 1997; (b) Rise, F., Rømming, C. and Undheim, K. *Acta Chem. Scand., Ser. B* 39 (1985) 459.
- Høseggen, T., Rise, F. and Undheim, K. *J. Chem. Soc., Perkin Trans. I* (1986) 849.
- (a) Gacek, M., Ongstad, L. and Undheim, K. *Acta Chem. Scand., Ser. B* 33 (1979) 150; (b) Rise, F. and Undheim, K. *Unpublished work*.
- Rasmussen, A., Rise, F. and Undheim, K. *Acta Chem. Scand., Ser. B* 39 (1985) 235.
- Gilbert, E. E., Ed., *Sulphonation and Related Reactions*, Interscience Publishers, New York 1965.
- Hayatsu, H. *Prog. Nucleic Acid Res. Mol. Biol.* 16 (1976) 75.
- Gacek, M., Undheim, K., Oftebro, R. and Laland, S. G. *FEBS Lett.* 98 (1979) 355.
- Oftebro, R. and Undheim, K. *Unpublished data*.
- Petrenko-Kritschenko, P. and Dolgopolooff, T. *Annalen* 341 (1905) 165.
- Rise, F. and Undheim, K. *J. Organomet. Chem.* 291 (1985) 139.
- Harvey, R. G. *Tetrahedron* 22 (1966) 2561.
- Sekine, M., Yamamoto, I., Hashizume, A. and Hata, T. *Chem. Lett.* (1977) 485.
- Corey, E. J. and Bock, M. C. *Tetrahedron Lett.* (1975) 3269.
- Benneche, T., Strande, P. and Undheim, K. *Synthesis* (1983) 752.
- Benneche, T. and Undheim, K. *Acta Chem. Scand., Ser. B* 36 01982) 409.
- Barber, J. J., Fuller, R. F., Green, K. B. and Zwartouw, H. T. *J. Appl. Chem.* 3 (1953) 266.
- Jaeger, G., Titter, W. and Metzger, L. *Ger. Offen.* 2, 119, 518 (1972).
- Mitchell, R. H. *Tetrahedron Lett.* (1973) 4395.
- Benneche, T. and Undheim, K. *Acta Chem. Scand., Ser. B* 37 (1983) 345.
- Sekine, M., Okimoto, K., Yamada, K. and Hata, T. *J. Org. Chem.* 46 (1981) 2097.
- Gacek, M. and Undheim, K. *Acta Chem. Scand., Ser. B* 35 (1981) 69.

Received March 4, 1987.