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Oxidation of Substituted 2-Thiouracils and Pyrimidine-2-thione with Ozone and 3,3-Dimethyl-1,2-dioxirane.

Crestini Claudia[b], Enrico Mincione[b], Raffaele Saladino*[b], Rosario Nicoletti[a].

a Dipartimento di Chimica Università degli studi di Roma "La Sapienza", p.le Aldo Moro 5, 00185 Roma, Italy.

b Dipartimento Agrochimico Agrobiologico Università degli studi di Viterbo "La Tuscia", Via San Camillo de Lellis, 01100 Viterbo, Italy.

Abstract: Ozone and 3,3-dimethyl-1,2-dioxirane react with substituted 2-thiouracils and pyrimidine-2-thione to afford several interesting desulfurized products. The effect of the solvent, protic as opposed to nonprotic, on the course of oxidation was striking.

Sulfur containing derivatives are important in the pyrimidine series, mainly because their different reactions make them convenient intermediates. Among these reactions, the oxidation of mercapto-pyrimidines is a very useful synthetic procedure for the pyrimidine ring functionalization. Mercapto groups in any position may be removed in favour of hydrogen by oxidative desulfurization using alkaline hydrogen peroxide[1] or they may be oxidized to disulfides with iodine[2a] (in alkali), nitrous acid and peroxides[2b]. Moreover, several synthetic methods are available for the conversion of thioamide moiety, present in thiouracils, into the corresponding amide. For example, dimethyl sulfoxide with acids[3], manganese dioxide[4] and halogen-catalysed methods[5] have been used. However, the different reagents used for these conversions have varying degree of success as well as limitations due to side reactions.

Because of possible biological implications, the oxidation of nucleic acids and their components has been extensively studied[6]. It was noted[7] that in most cases the primary products of nucleic acid components are not well known because of the complexity of product mixtures and the tendency of initial products to undergo further reactions. In the course

of our studies we found that a powerful and selective oxidant for oxidation of uracil derivatives, pyrimidine nucleosides[8] and thiopyrimidine and thiopurine nucleosides[9], which performs under strictly neutral conditions, is dimethyldioxirane[10]. The oxidations performed with dimethyldioxirane often have the advantages of simple procedure, mild reaction conditions, ease of product isolation even in the case of sensitive epoxides of enol ethers[11], silyl enol ethers[12] and α,β-unsaturated ketones, acids, esters and lactones[13].

In a recent communication[14] we have reported the oxidative desulfurization of substituted 2-thiouracils and pyrimidine-2-thione with ozone. In connection with this study, with the aim to find a new, mild and selective procedure for the oxidation of thioamide moiety in 2-thiouracils, we examined the dimethyldioxirane[10] as oxidizing agent in comparison with ozone.

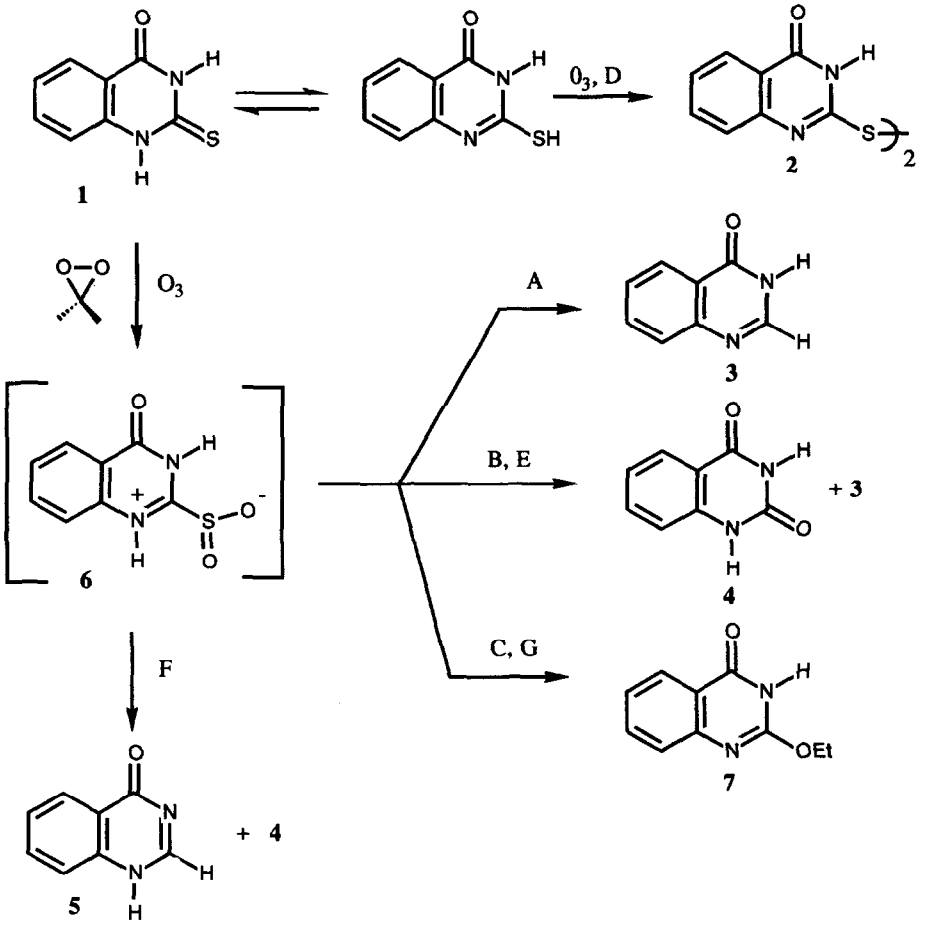
Because ozone and dimethyldioxirane might be expected to react with 2-thiouracils at either of two reactive centers, the 5,6-double bond and the thioamide moiety, we started to study the oxidation of 2-mercapto-4(3H)-quinazolinone **1** which lacks a reactive 5,6-double bond. When ozone was passed through a suspension of **1** in CH_2Cl_2 at 25°C a rapid solubilization was observed; after evaporation and purification the disulfide **2** was obtained in good (69%) yield. Compound **2** was stable when submitted to further ozonation. The reaction takes a different course in glacial acetic acid at 25°C giving rise to the formation of 4(3H)-quinazolinone **3** in 82% yield[15]. Moreover, the same reaction carried out in acetic acid-water (1:1 v/v) gave a separable mixture of 2,4(1H,3H)-quinazolindione **4** (75%) and a small amount of **3** (13%), while no reaction took place using only water as solvent (Scheme 1, Table 1, entry 1).

When the oxidation was performed using a freshly prepared solution of dimethyldioxirane[10c] in the same solvents (avoiding acidic conditions) we found different products. In fact, the oxidation of **1** performed in CH_2Cl_2 at 25°C yielded **3** (45%) and **4** (40%), while disulfide **2** was not recovered. In the formation of compound **4** the moisture present in the distilled dioxirane-acetone solution is an essential ingredient; in fact, the yield of **4** became lower if the dioxirane-acetone solution was dried over $MgSO_4$ before use[16].

Dimethyldioxirane oxidation of **1** in water is very interesting. The reaction performed at 25°C gave a white precipitate easily recovered by filtration; after evaporation of the filtrate the uracil derivative **4** was obtained in 21% yield (Scheme 1, Table 1, entry 2). The white precipitate was characterized by the same RF in TLC analysis ($CHCl_3$:CH_3OH=9.5:0.5) and by the same MS spectrum (m/z M^+= 146) of the 4(3H)-quinazolinone **3**,

even if further spectroscopic studies proved some different absorptions. In particular, this product showed the carbonyl absorption band in the I.R. spectra at lower wave numbers (1690 cm^{-1}) than those characteristic for compound **3** (1710 cm^{-1})[17].

SCHEME 1



Method A: ozone, glacial acetic acid, 25 °C, 0.5 h. Method B: ozone, acetic acid-water (1:1 v/v), 25 °C,1h. Method C: ozone, CH_2Cl_2-EtOH (1:1 v/v), 25 °C. Method D: ozone, CH_2Cl_2, 25 °C, 0.5 h. Method E: dioxirane,CH_2Cl_2, 25 °C. Method F: dioxirane, H_2O, 25 °C. Method G: dioxirane, CH_2Cl_2-EtOH (1:1 v/v), 25 °C.

Moreover, the chemical shift of the proton at the peri-position to the CO was at higher δ (8.20 ppm) than that of **3** (8.10 ppm), and the chemical shift of the C-2 atom in ^{13}C-NMR was at higher δ (148.54 ppm) than **3** (145.70 ppm).

Entry	Substrate	Method[a]	Product(s)	Yield(%)
1	1	D	2	69
		A	3	82
		B	4	75
2	1	E	3	45
			4	40
		F	4	21
			5	70
3	1	C	7	85
		G	7	77
4	8a	B	9a	73
	8b	B	9b	68
	8c	B	9c	77
	8d	B	9d	31
			10d	45
	8a	A	11a	92
			9a	5
	8b	A	11b	53
			9b	16
	8c	A	11c	35
			8c	30
	8d	A	11d	10
			9d	28
			10d	33
5	8b	E	9b	40
			11b	37
	8d	E	9d	55
			11d	32

Table1: Oxidation of substituted 2-thiouracils. All oxidations were carried out using 1 mmol of substrate and an flow of 10 mL/min or a freshly prepared solution of dimethyldioxirane in acetone.
[a] Method A: ozone, glacial acetic acid, 25 °C, 0.5 h. Method B: ozone, acetic acid-water (1:1 v/v), 25 °C, 1h. Method C:ozone,CH_2Cl_2-EtOH (1:1 v/v), 25 °C, 1h. Method D: ozone, CH_2Cl_2, 25 °C, 0.5 h. Method E: dioxirane, CH_2Cl_2, 25 °C, 0.5 h. Method F: dioxirane, H_2O, 25 °C. Method G: dioxirane, CH_2Cl_2-EtOH (1:1 v/v), 25 °C, 1h.

These data, in agreement with the results reported by Hagiwara[18] on the intramolecular alkyl rearrangements and tautomerism of quinazolinone derivatives, allowed us to consider the unknown product as the kinetic isomer of **3**, the 4(1H)-quinazolinone **5**[19], characterized by the carbon-nitrogen double bond located at an α,β-conjugated position to the CO group.

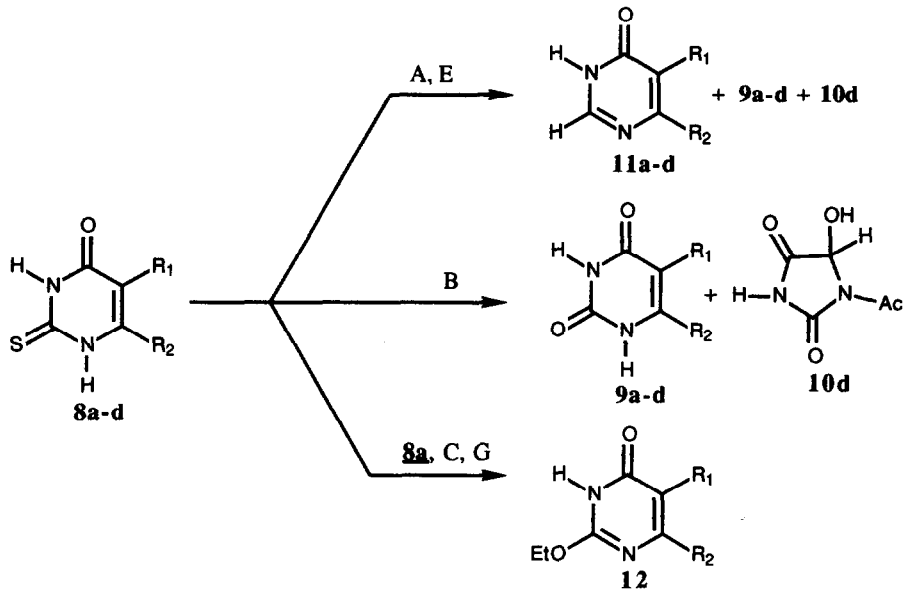
This hypothesis was chemically proved heating **5** in toluene; 4(3H)-quinazolinone **3** was obtained in quantitative yield. Probably, the isolation of **5** in the oxidation with dioxirane in water is possible owing to its low solubility in the reaction medium. To the best of our knownledge this is the first synthetic method for the unambiguous preparation of **5**. The data presented so far show that the effect of the solvent, protic as opposed to nonprotic, on the course of these oxidations, is striking.

It is resonable to suggest that the tautomeric equilibria might play an important role in the reactions since ozone and dimethyldioxirane should give different products if they react with the thioamide sulfur atom in the thione or thiol form. No data are available on the tautomeric equilibrium constant of 2-thiouracils in solvents of different polarity but investigations reported by Katritzky[20] on similar equilibrium of pyridines derivatives show that the pyridone form, dominant in aqueous solutions, falls roughly linearly with the solvent polarity: in cyclohexane solution comparable amounts of pyridone and hydroxy-pyridine are present. It has been reported[21] that there are analogies in the pyrimidines and pyridines tautomerism. In aqueous solution the potential hydroxy and mercapto compounds exist predominantly as pyrimidinones or pyrimidinethiones, whereas in nonprotic solvents the hydroxy or mercapto form is present in appreciable amount. Probably, in protic solvents the predominance of the thione tautomer makes easier the nucleophilic attack of the thiocarbonyl sulfur atom on ozone[22] and dimethyldioxirane molecules[23] with the formation of the corresponding sulphine (not shown) that in turn migth be rapidly oxidized to a sulfinic (or persulfinic) acid intermediate **6**. This intermediate, not isolated in our case, depending on the reaction conditions can lose sulphur dioxide to give compound **3**, whereas in presence of water it may be hydrolyzed to yield the corresponding pyrimidinone **4** as the main product. In non protic solvent the presence of the mercapto form could aid the formation of disulfide **2**; while dimethyldioxirane performs preferentially the oxygen atom transfer to thio-carbonyl moiety to give compounds **3** and **4**.

It is known that pyrimidine sulfonic acid derivatives undergo nucleophilic displacement of the whole sulfur containing group to yield 2-hydrazino-, 2-diethylamino-, 2-azido- and 2-methoxy-pyrimidines[24]. On the basis of these data, in order to test our hypothesis on the presence of intermediate **6** in the pathway of the reaction, we have performed the oxidation of **1** with ozone and dimethyldioxirane in CH_2Cl_2 in presence of ethanol as nucleophile (1:1 v/v): only compound **7** was obtained in good yield (Scheme 1, Table 1, entry 3).

The selective oxidation of thioamide moiety in presence of a reactive double bound was then studied in the case of several 5,6-substituted 2-thiouracils **8a-d**. Ozonation of 6-methyl-5-n-octyl-4(3H)-2-thio-pyrimidone **8a**, 6-methyl-5-isobutyl-4(3H)-2-thio-pyrimidone **8b**, 2-mercapto-4(3H)-tetrahydroquinazolinone **8c** and 6-methyl-4(3H)-2-thio-pyrimidone **8d** performed in acetic acid-water (1:1 v/v) gave the expected uracil derivatives **9a-d** in good yield ; in the case of **8d**, the hydantoin derivative **10d**, derived from ozonolysis of the 5,6-double bond[25], was isolated as the main product. When the ozonation was performed in glacial acetic acid a separable mixture of C-2 desulfurized products **11a-d**, uracil derivatives **9a-d** and hydantoin derivative **10d** was obtained (Scheme 2, Table 1, entry 4).

SCHEME 2



8a, 9a, 11a, 12: R_1=n-octyl, R_2=CH_3. **8b, 9b, 11b**: R_1=i-butyl, R_2=CH_3.
8c, 9c, 11c : R_1=R_2= -CH_2-($CH2)_2$-CH_2. **8d, 9d, 10d, 11d** : R_1=H, R_2=CH_3.
For method A, B, C, E and G see Scheme 1 and Table 1.

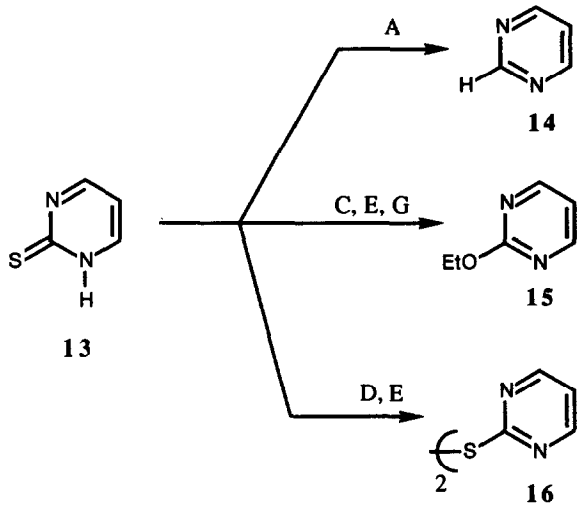
The unexpected isolation of the uracil derivatives in glacial acetic acid might be explained with the presence of traces of moisture, even if an alternative pathway, the 1,3-dipolar cycloaddition of ozone to carbon-sulfur double bond[22] can not be completely ruled out. It is interesting to note that the ozonolysis of the 5,6-double bond, characterized by the formation of the hydantoin derivative **10d**, becames possible only if there is not substituent in the C-5 position. Ozonation

of **8a-d** in dry CH_2Cl_2 did not give the disulfides, probably due to the lower amount of the thiol form than in the case of compound **1**.

The reaction of **8b** and **8d** with dimethyldioxirane in CH_2Cl_2, at 25°C, afforded a mixture of the corresponding C-2 desulfurized products **11b,11d** and the uracil derivatives **9b,9d** (Scheme 2, Table 1, entry 5), while the hydantoin derivative **10d** was not isolated. The oxidation of **8a** with ozone and dimethyldioxirane in CH_2Cl_2-EtOH mixture (1:1 v/v) afforded, as expected, 2-ethoxy-6-methyl-5-n-octyl-4(3H)-pyrimidinone **12** in good yield (Scheme 2, Table 1, entry 6).

These data show that substituted 2-thiouracils **8a-d** react with ozone and dimethyldioxirane selectively at the carbon-sulfur double bond, and no other possible reactions occur.

SCHEME 3



For methods A, C, D, E, G see scheme 1.

Finally, to test the generality of the results obtained by the oxidation with ozone and dimethyldioxirane we studied the oxidation of 2-thio-pyrimidine **13**. Ozonation of **13** afforded, as like as in the case of substituted 2-thiuracils, pyrimidine **14** in glacial acetic acid, 2-ethoxy-pyrimidine **15** in CH_2Cl_2-EtOH mixture and pyrimidine-2-disulfide **16** in CH_2Cl_2 (Scheme 3, Table 2).

The reaction of **13** with dimethyldioxirane in CH_2Cl_2/EtOH mixture afforded **15** in good yield, while disulfide **16** was unexpectedly isolated in the reaction carried out in CH_2Cl_2. The last data show that the oxidation of compound **13** with dimethyldioxirane performed in CH_2Cl_2

proceeds selectively through the oxidation of sulfur atom to disulfide easier than the oxygen-atom insertion, in contrast with the results obtained in the oxidation of compounds **1**, **8b** and **8d**.

Probably in this case the aromaticity of the substrate plays an important role in the pathway of the oxidation.

A rough comparison between the two reagents considered can be attempted. Dimethyldioxirane oxidation of 2-thiouracil derivatives **1**, **8b** and **8d** proceeds differently from the ozonation. For instance, poor results are given by ozone oxidation of compound **1** in water, while dimethyldioxirane oxidation of this compound in water gives rise to the interesting product **5**. Moreover, dimethyldioxirane oxidation of compounds **8b** and **8d** performed in CH_2Cl_2 gives the desulfurized products **9b**, **11b** and **9d**, **11d**, without the presence of hydantoin derivatives. On the other hand, by a careful choice of the experimental conditions, ozone appears to be more selective than dimethyldioxirane in the synthesis of disulfides. In fact, several substrates give only disulfides in good yields when submitted to ozonation, whereas dimethyldioxirane affords, in some cases, mixtures of products.

Substrate	Method[a]	Product(s)	Yield(%)
13	A	14	64
	C	15	72
	D	16	82
	G	15	53
	E	16	77

Table 2: Oxidations of pyrimidine-2-thione. All oxidations were carried out using 1 mmol. of substrate and an flow of 10 mL/min. or a freshly prepared solution of dimethyl-dioxirane in acetone.

[a] Method A: ozone, glacial acetic acid, 25 °C, 0.5 h. Method C: ozone, CH_2Cl_2-EtOH (1:1 v/v),25 °C, 1h. Method D: ozone, CH_2Cl_2, 25 °C, 0.5 h. Method E: dioxirane, CH_2Cl_2, 25 °C, 0.5 h. Method G: dioxirane, CH_2Cl_2-EtOH (1:1 v/v), 25 °C, 1h.

Experimental

NMR spectra were recorded on a Varian XL 300 (300 MHz) spectrometer and are reported in δ values. Infrared spectra were recorded on a Perkin Elmer 298 spectrophotometer using NaCl plates. Microanalyses were performed by C. Erba 1106 analyzer. Mass spectra were recorded on a

Kratos MS80 spectrometer. Melting points were obtained on a Reichert Kofler apparatus and are uncorrected. All solvents were ACS reagent grade and were redistilled and dried according to standard procedures. Chromatographic purifications were performed on columns packed with Merck silica gel 60, 230-400 mesh for flash technique. Thin-layer chromatography was carried out using Merck platten Kieselgel 60 F254.

Starting Compounds

Commercially available 2-mercapto-4(3H)-quinazolinone **1**, 2-mercapto-4(3H)-tetrahydroquinazolinone **8c**, 6-methyl-2-thio-4(3H)-pyrimidone **8d** and 2-thio-pyrimidine **13** (Aldrich, Co.) were used without further purification. 6-Methyl-5-n-octyl-4(3H)-2-thio-pyrimidone **8a** and 6-methyl-5-isobutyl-4(3H)-2-thio-pyrimidone **8b** were synthesized according to the procedure reported by Basnàk and Farkas[26].

6-Methyl-5-n-octyl-4(3H)-2-thio-pyrimidone **8a**- m.p. 163-165 °C (Found: C, 61.48; H, 8.75; N, 11.11. $C_{13}H_{22}N_2OS$, requires C, 61.38; H, 8.71; N, 11.01); ν_{max} ($CHCl_3$) 1680 (CO) and 1540 (C=C) cm^{-1}; δH (300 MHz; DMSO-d_6) 12.15 (1H, broad singlet, NH), 12.00 (1H, broad singlet, NH), 2.55 (2H, m, CH_2), 2.28 (3H, s, CH_3), 1.20 (12H, m, CH_2), 0.80 (3H, m, CH_3); δ^{13}C (300 Mz; DMSO-d_6) 174.27 (C), 161.67 (C), 148.35 (C), 115.11 (C), 31.32 (CH_2), 28.90 (CH_2), 28.69 (CH_2), 28.0 (CH_2), 23.98 (CH_2), 22.10 (CH_2), 15.55 (CH_3), 13.87 (CH_3); m/z 254 (M^+, 31%).

6-Methyl-5-isobutyl-4(3H)-2-thio-pyrimidone **8b**- m.p. 152-154 °C (Found: C, 54.48; H, 7.09; N, 14.11. $C_9H_{14}N_2OS$, requires C, 54.52; H, 7.12; N, 14.13); ν_{max} 1680 (CO) and 1535 (C=C) cm^{-1}; δH (300 MHz; DMSO-d_6) 12.15 (2H, broad singlet, NH),2.50 (2H, m, CH_2), 2.28 (3H, s, CH_3), 1.45 (1H, m, CH), 0.90 (6H, m, CH_3); m/z 198 (M^+, 21%).

Ozonation of compounds **1**, **8a-d** and **13**. General procedure.

2 mmol of substrate were dissolved in 15 ml of the appropriate solvent and placed in a 100 ml, three-necked flask equipped with a magnetic stirrer, a gas inlet tube, and a bubble flow meter. The solution was allowed to react with an ozone-oxygen stream (flow of 10 ml/min) until the substrate disappeared. The resulting mixture was purged with nitrogen for 20 min, transferred to a round bottomed flask and concentrated in vacuo. When necessary, the residue was purified by flash-chromatography using chloroform:methanol (9.0:1.0) as eluant.

2',2'-Di-[4(3H)-quinazolidyl]-disulfide **2**- (244 mg, 69%), m.p. 203-204 °C (Found: C, 54.18; H, 2.85; N, 15.77. $C_{16}H_{10}N_4O_2S$, requires C, 54.22; H,

2.84; N, 15.80); ν_{max} ($CHCl_3$) 3100 (CH), 1700 (CO) and 1600 (C=N) cm^{-1}; δH (300 MHz; DMSO-d_6) 12.15 (2H, broad singlet, NH), 7.61 (8H, m, Ph); $\delta^{13}C$ (300 Mz; DMSO-d_6) 163.05 (C), 154.4 (C), 148.87 (C), 134.74 (CH), 126.45 (CH), 125.84 (CH), 124.51 (CH), 119.47 (C); m/z 177 (M^+/2, 11%).

4(3H)-quinazolinone **3**- (239 mg, 82%), m.p.218-220 °C [lit.[27],m.p. 216-219 °C] (Found: C, 65.78; H, 4.06; N, 19.10. $C_8H_6N_2O$, requires C, 65.69; H, 4.14; N, 19.17); ν_{max} ($CHCl_3$) 3100 (CH) and 1710 (CO) cm^{-1}; δH (300 MHz; DMSO-d_6) 12.15 (1H, broad singlet, NH), 8.10 (1H, s, CH), 8.05 (1H, m, CH), 7.70 (3H, m, CH); $\delta^{13}C$ (300 Mz; DMSO-d_6) 161.13 (C), 149.12 (C), 145.73 (CH), 134.60 (CH), 127.51 (CH), 126.12 (CH), 122.93 (C); m/z 146 (M^+, 65%).

2-Ethoxy-4(3H)-quinazolinone **7**- (323 mg, 85%), m.p. 177-179 °C (Found: C, 63.07; H, 5.21; N, 14.65. $C_{10}H_{10}N_2O_2$, requires C, 63.15; H, 5.30; N, 14.73); ν_{max} ($CHCl_3$) 3100 (CH), 1710 (CO) and 1600 (C=N) cm^{-1}; δH (300 MHz; DMSO-d_6) 12.10 (1H, broad singlet, NH), 7.70 (4H, m, Ph), 4.25 (2H, q, J= 7 Hz, CH_2), 1.70 (3H, t, J= 7 Hz, CH_3); $\delta^{13}C$ (300 Mz; DMSO-d_6) 163.26 (C), 154.01 (C), 149.68 (C), 137.41 (CH), 126.44 (CH), 125.48 (CH), 124.42 (CH), 119.40 (C), 63.28 (CH_2), 14.12 (CH_3); m/z 190 (M^+, 20%).

6-Methyl-5-n-octyl-2,4(1H,3H)-pyrimidindione **9a**- (357 mg, 73%), m.p. 176-178 °C (Found: C, 63.39 H, 9.32; N, 11.77. $C_{13}H_{22}N_2O_2$, requires C, 65.51; H, 9.30; N, 11.75); ν_{max} ($CHCl_3$) 1720 and 1685 (CO) cm^{-1}; δH (300 MHz; $CDCl_3$) 2.15 (2H, m, CH_2), 2.05 (3H, s, CH_3), 1.15 (12H, m, CH_2), 0.85 (3H, m, CH_3); m/z 238 (M^+, 18%).

6-Methyl-5-isobutyl-2,4(1H,3H)-pyrimidindione **9b**- (274 mg, 68%), m.p. 174-176 °C (Found: C, 59.25; H, 7.70; N, 15.42. $C_9H_{14}N_2O_2$, requires C, 59.32; H, 7.74; N, 15.37); ν_{max} ($CHCl_3$) 1720 and 1680 (CO) cm^{-1}; δH (300 MHz; $CDCl_3$) 2.50 (2H, m, CH_2), 2.10 (3H, s, CH_3), 1.35 (1H, m, CH), 0.80 (6H, m, CH_3); m/z 182 (M^+, 27%).

2,4(1H,3H)-Tetrahydro-quinazolinone **9c**- (255 mg, 77%), m.p. 298-300 °C [lit.[28], m.p. 299-301 °C] (Found: C, 57.70; H, 6.10; N, 16.91. $C_8H_{10}N_2O_2$, requires C, 57.82; H, 6.06; N, 16.85); ν_{max} ($CHCl_3$) 1705 and 1640 (CO) cm^{-1}; δH (300 MHz; DMSO-d_6) 2.15 (4H, m, CH_2), 1.58 (4H, m, CH_2); m/z 166 (M^+, 14%).

6-Methyl-2,4(1H,3H)-pyrimidindione **9d**- Compound **9d** (78 mg, 31%), m.p. 316-318 °C [lit.[29], m.p. 317-318 °C] was identical (RF, mixed m.p. and spectroscopical data) to an authentic commercially sample (Aldrich, Co.).

1-Acetyl-5-hydroxyhydantoin **10d**- (142 mg, 45%) m.p. 139-142 °C [lit.[25], m.p. 139-143 °C]; δH (300 MHz; DMSO-d_6) 11.65 (1H, broad singlet, NH), 7.53 (1H, broad singlet, NH), 5.60 (1H, d, J=8 Hz, CH), 2.62 (3H, s, CH_3); m/z 158 (M^+, 12%).

6-Methyl-5-n-octyl-4(3H)-pyrimidinone **11a**- (408 mg, 92%), m.p. 77-79 °C (Found: C, 70.30; H, 10.09; N, 12.51. $C_{13}H_{22}N_2O$, requires C, 70.23; H, 9.97; N, 12.60); ν_{max} ($CHCl_3$) 1650 (CO) cm^{-1}; δH (300 MHz; $CDCl_3$) 8.0 (1H, s, CH), 2.25 (2H, m, CH_2), 2.13 (3H, s, CH_3), 1.19 (12H, m, CH_2), 0.95 (3H, m, CH_3); $\delta^{13}C$ (300 Mz; $CDCl_3$) 164.36 (C), 161.24 (C), 145.10 (CH), 125.90 (C), 31.60 (CH_2), 29.52 (CH_2), 29.21 (CH_2), 29.0 (CH_2), 27.86 (CH_2), 25.42 (CH_2), 22.36 (CH_2), 21.07 (CH_3), 13.77 (CH_3); m/z 222 (M^+, 8%).

6-Methyl-5-isobutyl-4(3H)-pyrimidinone **11b**- (176 mg, 53%), m.p. 79-81°C (Found: C, 65.10, H, 8.57; N, 16.79. $C_9H_{14}N_2O$, requires C, 65.03; H, 8.49; N, 16.85); ν_{max} ($CHCl_3$) 1650 (CO) cm^{-1}; δH (300 MHz; $CDCl_3$) 8.05 (1H, s, CH), 2.45 (2H, m, CH_2), 2.20 (3H, s, CH_3), 1.35 (1H, m, CH), 0.80 (6H, m, CH_3); $\delta^{13}C$ (300 Mz; $CDCl_3$) 163.57 (C), 160.59 (C), 145.31 (CH), 125.96 (C), 30.65 (CH_2), 29.83 (CH_3), 20.59 (CH), 13.42 (CH_3); m/z 166 (M^+, 23%).

4(3H)-tetrahydro-quinazolinone **11c**- (106 mg, 35%), m.p.208-209°C (Found: C, 63.90, H, 6.68; N, 18.60. $C_8H_{10}N_2O$, requires C, 63.98; H, 6.71; N, 18.65); ν_{max} ($CHCl_3$) 1660 (CO) cm^{-1}; δH (300 MHz; $CDCl_3$) 8.0 (1H, s, CH), 2.49 (2H, m, CH_2), 2.29 (2H, m, CH_2), 1.40 (4H, m, CH_2); $\delta^{13}C$ (300 Mz; $CDCl_3$) 164.0 (C), 152.20 (C), 146.0 (CH), 128.15 (C), 28.50 (CH_2), 26.15 (CH_2), 21.75 (CH_2), 21.68 (CH_2); m/z 150 (M^+, 13%).

6-Methyl-4(3H)-pyrimidinone **11d**- (22 mg, 10%), m.p.115-117°C (Found: C, 54.50, H, 5.41; N, 25.36. $C_5H_6N_2O$, requires C, 54.54; H, 5.49; N, 25.44); ν_{max} ($CHCl_3$) 1660 (CO) cm^{-1}; δH (300 MHz; DMSO-d_6) 10.95 (1H, broad singlet, NH), 9.02 (1H, s, CH), 6.05 (1H, s, CH), 2.49 (3H, s, CH_3); $\delta^{13}C$ (300 Mz; DMSO-d_6) 165.0 (C), 158.20 (CH), 153.05 (C), 98.87 (CH), 24.84 (CH_3); m/z 110 (M^+, 30%).

6-Methyl-5-n-octyl-2-ethoxy-4(3H)-pyrimidinone **12**- (484 mg, 91%), oil ν_{max} ($CHCl_3$) 1650 (CO) cm^{-1}; δH (300 MHz; $CDCl_3$) 4.38 (2H, d, J=7 Hz, CH_2), 2.40 (2H, m, CH_2), 2.22 (3H, s, CH_3), 1.43 (3H, t, J=7 Hz, CH_3), 1.28 (12H, m, CH_2), 0.85 (3H, m, CH_3); $\delta^{13}C$ (300 Mz; $CDCl_3$) 165.66 (C), 161.20 (C), 153.83 (C), 117.83 (C), 60.47 (CH_2), 31.70 (CH_2), 29.50 (CH_2), 29.47 (CH_2), 29.31 (CH_2), 29.12 (CH_2), 28.48 (CH_2), 25.06 (CH_2), 21.43 (CH_3), 13.97 (CH_3), 13.85 (CH_3); m/z 266 (M^+, 21%).

Oxidation of compounds **1**, **8b**, **8d** and **13** with dimethyldioxirane. General procedure.

The dimethyldioxirane solution was prepared using the procedure reported by Murray [10c] and the dioxirane content (Ca. 0.07N) was assayed with methyl-phenyl-sulfide yielding the corresponding sulfoxide; the latter being determined by ^1H-NMR. The reactions were carried out by adding freshly prepared solution of the dioxirane to solutions of the required substrate (2 mmol) in the appropriate solvent (5 ml) at 25°C, until the substrate disappeared (TLC eluent chloroform:methanol=8.0:2.0). The resulting solution was transferred to a round bottomed flask and concentrated in vacuo (when present, the precipitate was recovered by filtration before the evaporation). The residue was purified by flash-chromatography using chloroform:methanol=9.0:1.0 as eluant.

4(1H)-quinazolinone **5**- (204 mg, 70%), m.p.218-220°C (Found: C, 65.65; H, 4.15; N, 19.03. $C_8H_6N_2O$, requires C, 65.65; H, 4.14; N, 19.17); ν_{max} ($CHCl_3$) 3100 (CH) and 1690 (CO) cm^{-1}; δH (300 MHz; DMSO-d_6) 12.13 (1H, broad singlet, NH), 8.85 (1H, s, CH), 8.20 (1H, m, CH), 7.70 (3H, m, CH); $\delta^{13}C$ (300 Mz; DMSO-d_6) 160.04 (C), 148.54 (CH), 142.27 (C), 135.98 (CH), 128.63 (CH), 126.82 (CH), 123.05 (CH), 121.76 (C); m/z 146 (M^+, 18%).

Pyrimidine **14**- Compound **14** (96 mg, 64%), b.p. 123-124 °C [lit.[30], b.p. 123-124 °C], was identical to an authentic commercially sample (Aldrich, Co.).

2-Ethoxy-pyrimidine **15**- (179 mg, 72%), b.p. 46-48 °C/ 1.1 mm, ν_{max} ($CHCl_3$) 3100 (CH) and 1580 (C=C) cm^{-1}; δH (300 MHz; $CDCl_3$) 8.60 (2H, d, J=4 Hz, CH), 7.05 (1H, t, J=4 Hz, CH), 4.45 (2H, q, J=7 Hz, CH_2), 1.45 (3H, t, J=7 Hz, CH_3); m/z 124 (M^+, 19%).

2,2'-Di-pyrimidil-disulfide **16**- (149 mg, 77%), m.p. 139-140 °C [lit.[31], m.p. 139-140 °C], ν_{max} ($CHCl_3$) 1575 (C=C) cm^{-1}; δH (300 MHz; $CDCl_3$) 8.55 (2H, d, J=3.8 Hz, CH), 7.18 (1H, t, J=3.8 Hz, CH); m/z 222 (M^+, 9%).

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