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Title compounds bearing substituents on C(2), C(6) and C(8) were prepared from a newly synthesized pyrimidine derivative **11**. The new pyrimidine **11** was generated from compound **2** through two different synthetic schemes. In one pathway, compound **2** was nitrosated, reduced and alkylated to produce compounds **9**, **10** and **11** respectively (Scheme). In an alternate route using compound **2** as the starting material, a coupling reaction using the diazonium salt derived from *p*-methylaniline afforded the azo derivative **7**, which was subsequently alkylated and reductively cleaved to form compounds **8** and **11** respectively (See Scheme). Compound **11** was annulated to the corresponding hypoxanthine derivatives **12-14**; compounds **12** and **13** were chlorinated with phosphorus oxychloride, then reacted with amines to yield compound **17** and **20** respectively. Compounds **21**, **22** and **23** were obtained by oxidation of the corresponding sulfide as depicted in Scheme. Alkylation of the thiol function of **1** gave a mixture of **3** and **4**. Compound **3** was chlorinated to **5**. Nitration of **5** resulted in electrophilic aromatic substitution of the aryl ring and concomitant oxidation of the sulfide to the sulfoxide, producing **6**.

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In an earlier paper in this series [1] we reported the synthesis of N^6 substituted adenines and 8-azaadenines by displacement of a benzylsulphonyl group at the C(6) position. Because of our continuing interest in adenine derivatives, we report the synthesis of 2-benzylthiolsubstituted adenines. The ability of the benzylthiolgroup to act as a precursor to the benzylsulphonyl moiety as a leaving group at C(2) position was investigated, as previously reported for this functionality on C(6) [1], but replacement of the benzylsulphonyl function with a variety of nucleophilic amines at C(2) position was not possible. However C(2) benzylsulphanyladenines could be a new class of ligands at P_2Y purinoreceptors. Recent reports [2-9] have identified potent P_2Y purinoreceptor agonists as derivatives of adenosine-5-monophosphate in which an alkylthiol group is bound to C(2) as a key structural feature.

A number of synthetic routes are available for the preparation of 2-thioalkylpurines. One scheme employs the intact purine ring. In this methodology, a halogen of a 2-halopurine can be substituted by a thioalkyl group [10], or the thiol function of a 2-thioxopurine can be alkylated [11]. Alternatively, the introduction of a thioalkyl function (by alkylation of the thiol) on a pyrimidine nucleus can be accomplished prior to cyclization to the purine [12].

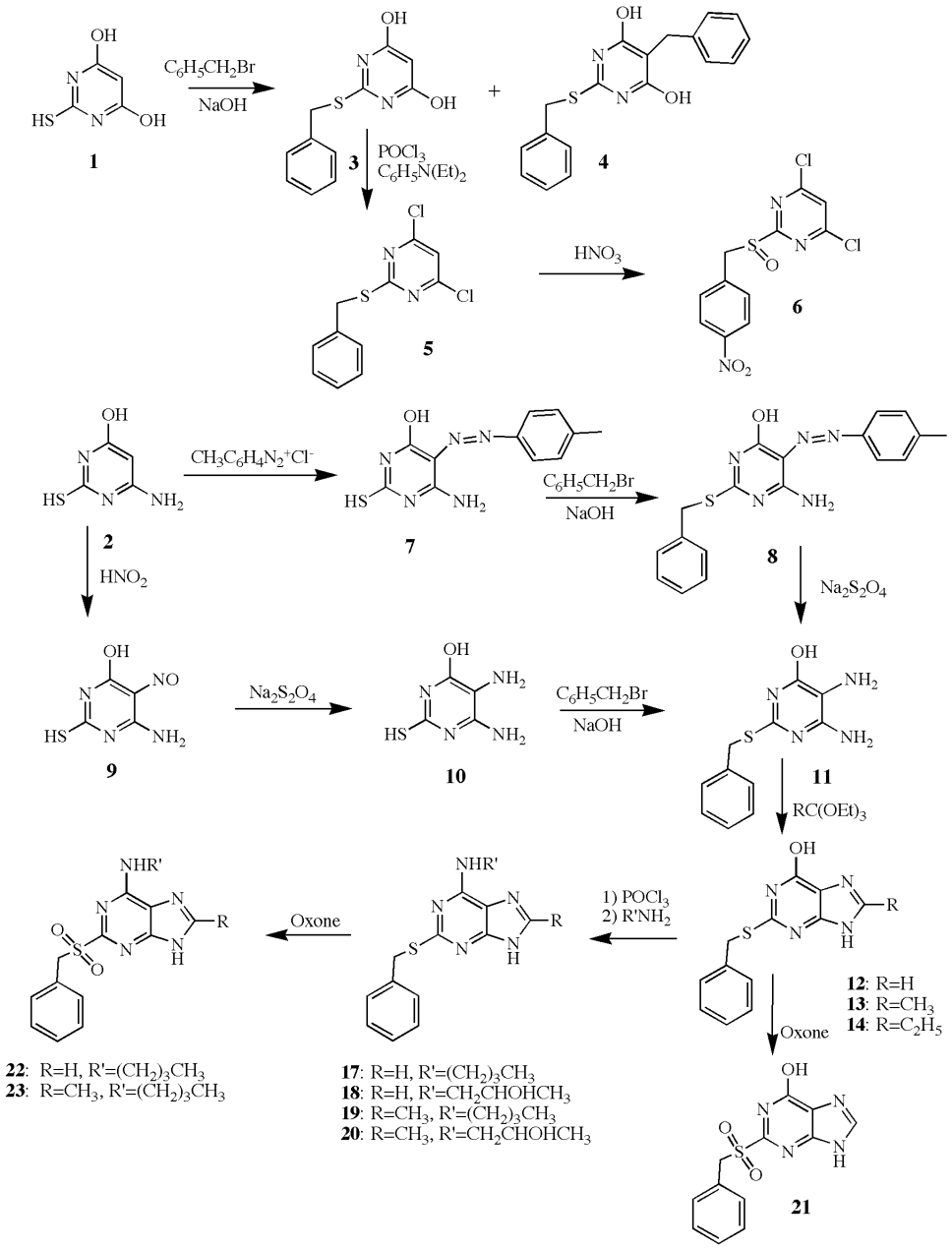
However, we elected to use the commercially available thiobarbituric acid derivative **1** or 4-amino-thiobarbituric acid **2** as starting products (Scheme). Initially, compound **1** was benzylated resulting in a mixture of products **3** [13] and **4**. Then we attempted an electrophilic substitution to introduce a functional group at C(5) position which would lead ultimately to the formation of a purine ring. For example, compound **3**, obtained by benzylation of **1**, was nitrated to produce a very complex reaction mixture from which no product could be isolated. When **3** was treated with phosphorus oxychloride, the corresponding dichloro derivative **5** [13] was isolated. However, nitration of this compound resulted in a poor yield of **6**. The desired introduction of a nitro group at the 5-position did not occur.

The benzylation of **1** and the nitration of **5** deserve some comments. When we attempted to reproduce the benzylation of pyrimidine **1** to prepare **3**, as recently described in the literature [13], we obtained the expected S-alkylated product but we also observed a benzylation at C(5) to form compound **4**. The two compounds **3** and **4** were isolated by column chromatography and characterized by a ^{1}H nmr spectrum. The ^{1}H nmr spectrum of **4** reveals signals at 3.52 and 4.38 δ, indicative of two sets of methylene protons. Aromatic protons signals have a total intensity corresponding to ten protons. In the spectrum of **3** a signal at 5.17 δ, attributable to a proton bound to C(5) is present, which is lacking in that of compound **4**. The correct structure of **6** was assigned on the basis of analytical data (elemental analysis, mass spectrum, ^{1}H nmr spectrum). In fact, in the ^{1}H nmr spectrum the pattern of aromatic protons signals revealed the presence of a *p*-nitro substituent. The magnetic non equivalence of the benzylic protons suggested they were adjacent to a chiral center; this chiral center could only be the sulfur atom in an oxidation state corresponding to a sulfoxide group. In addition, the signal attributable to H-C(5) at 8.22 δ, clearly indicated the absence of a nitro group in this position. Our inability to isolate a C(5)-nitro derivative by nitration of **5** may indicate this product is formed only in very low yield or not at all, owing to inactivation of the pyrimidine ring bearing two electron withdrawing chlorine atoms, which is detrimental to electrophilic substitution reactions.

In another approach to functionalization of C(5), compound **2** was transformed in **11** following two parallel routes. The first concerns the treatment of **2** with the diazonium salt obtained from *p*-methylaniline affording **7**; this reaction was followed by the alkylation of the thiol function with benzyl chloride giving **8**. Compound **8** was converted to compound **11** by reductive cleavage of a diazo group employing a aqueous sodium hydrosulfite solution. Alternatively, compound **2**, following a known path for the synthesis of 5-^{15}N4-amino-6-hydroxy-5-nitroso-2-thiopyrimidine [14], was transformed in a 5-nitroso derivative **9** [15], followed by nitroso group reduction to **l0** [16] which, in turn, was treated by benzylchloride to obtain **11** [12].

Compound **11** was annulated to form the hypoxanthines **12**-**14**. Hypoxanthine **12** had previously been reported by alkylation of 6-hydroxy-2-mercaptopurine [11]. These hypoxanthines, in turn were converted to amino derivatives **17**-**20**, by successive use of phosphorus oxychloride and alkylamine, a procedure employed by Nugent & coworkers [13].

Scheme



The reaction product from **12** and phosphorus oxychloride was used directly, without characterization, to prepare compounds **17** and **18** by reaction with *n*-butylamine and 1-amino-2-propanol respectively. Compound **18** was previously synthesized by another route [17]. The chloride formed from the reaction of **13** and phosphorus oxychloride [18] was also converted to the amino derivatives **19** and **20**, by reaction with appropriate amines.

Sulfonyl derivatives **21**, **22** and **23**, were derived from **12**, **17** and **19** respectively, by treatment with a monopersulfate compound (Oxone®, Aldrich). All the sulfones showed a good stability toward nucleophilic displacement as they were recovered unchanged after prolonged heating with *n*-butylamine at 130 °C in a closed steel vial. The lack of reactivity of **21**, **22** and **23** in which the sulfonyl substituent should be a good leaving group may be explained in the following way. In basic conditions, ionization of the weak acids lead to an anion formation. Electron delocalization of the anionic structure suggests that C(2) of purine ring in these compounds may be an electron-rich site, therefore not conducive to nucleophilic displacement.

The structures of all the newly prepared compounds were easily assigned upon the basis of known reaction mechanisms and were confirmed by analytical and spectroscopic methods (ir, ms and ^{1}H nmr).

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. IR spectra in Nujol mulls were recorded on a Perkin-Elmer Model 1310 spectrometer. ^{1}H nmr spectra were recorded on a Varian Gemini 200 spectrometer; chemical shifts are expressed in δ units from TMS as an internal standard; solvents employed are specified in the Table. Mass spectra were performed on a Hewlett-Packard GC/MS System 5988A. TLC was performed on precoated silica gel F_{254} plates (Merck). Flash-column chromatographies were performed using Merck Kieselgel 60 (230-400 mesh). Microanalyses (C H N) were carried out on a Carlo Erba elemental analyser (Model 1106) and were within ±0.4% of the theoretical values.

4,6-Dihydroxy-2-phenylmethylsulphanyl-pyrimidine (**3**) [11] and 4,6-Dihydroxy-5-phenylmethyl-2-phenylmethylsulphanyl-pyrimidine (**4**).

To a solution of 4,6-dihydroxy-2-thiopyrimidine (**1**) (5.22 g, 36 mmoles) in 52 mL of 95% ethanol, 11.2 mL of a 3.25 *N* solution (36 mmoles) of sodium hydroxide was added and the resulting mixture was refluxed for 30 minutes. Then, 4.3 mL (36 mmoles) of benzyl bromide was added and the reaction mixture was stirred under reflux for 2 hours. The white precipitate was collected by filtration, washed with ice-water, ethanol and flash-chromatographed on silica gel using chloroform-methanol 97:3 as the eluent. Both compounds **3** (4.55 g, 54%, mp >320 °C dec.

Table

Mass Spectra, ^{1}H nmr Spectra and Elemental Analyses

Comp.	Mass *m/z* M$^+$(%) Base	^{1}H nmr (δ,ppm)	Analyses C, H, N Calcd./Found %		
4	324(1.1) 91	DMSO-d_6: 7.46-7.19 (m, 12H, 10H arom + 2H exch); 4.38 (s, 2H, aliph); 3.52 (s, 2H, benzyl)	66.64	4.97	8.64
			66.72	5.03	8.77
6	331(1) 136	DMSO-d_6: 8.22 (s, 1H, arom); 8.17 (d, J=8.8 Hz, 2H, arom); 7.42 (d, J=8.8 Hz, 2H, arom) 4.70 (d, J=13.2 Hz, 1H, benzyl); 4.50 (d, J=13.2 Hz, 1H, benzyl)	39.93	2.22	12.43
			39.78	2.12	12.65
7		DMSO-d_6: 12.93 (br s, 1H, exch); 10.17 (s, 1H, exch); 9.00 (br s, 1H, exch); 7.83 (d, J=8.2 Hz, 2H, arom); 7.30 (d, J=8.2 Hz, 2H, arom); 2.34 (s, 3H, aliph)	50.56	4.24	26.80
			50.31	4.35	26.65
8	351(18) 91	DMSO-d_6: 9.88 (br s, 1H, exch); 7.52 (d, 2H, arom); 7.43 (d, 2H, arom); 7.26 (m, 5H, arom); 4.32 (s, 2H, benzyl); 3.31 (s, 2H, exch); 2.32 (s, 3H, aliph)	61.52	4.88	19.93
			61.53	4.71	20.05
13	270(25) 91	DMSO-d_6: 7.30 (m, 5H, arom); 4.41 (s, 2H, benzyl); 3.34 (s, 1H, exch); 2.38 (s, 3H, C(8)-Me)	57.34	4.44	20.57
			57.19	4.29	20.73
14	286(21) 91	DMSO-d_6: 12.13 (br s, 1H, exch); 7.30 (m, 5H, arom); 4.42 (s, 2H, benzyl); 2.71 (q, J=7.4 Hz, 2H, aliph); 1.25 (t, J=7.4 Hz, 3H, aliph)	58.72	4.93	19.57
			58.52	5.09	19.77
17	313(38) 91	DMSO-d_6: 12.85 (s br, 1H, exch); 7.96 (s 1H, C(8)-H); 7.79 (br, 1H, exch); 7.42 (m, 2H, arom); 4.37 (s, 2H, benzyl); 3.42 (m, 2H, aliph); 1.53 (m, 2H, aliph); 1.32 (m, 2H, aliph); 0.88, (t, J=7.2 Hz, 3H, aliph)	61.31	6.11	22.34
			61.55	5.99	22.49
18	315 (22) 91	DMSO-d_6: 12.80 (s, 1H, exch); 8.05 (m, 1H, exch); 7.97 (s br, 1H, C(8)-H); 7.42 (m, 2H, arom); 7.29 (m, 3H, arom); 4.36 (s, 2H, benzyl); 3.83 (m,1H, aliph), 3.39 (m, 2H, aliph); 1.05 (d, J=6.4 Hz, 3H, aliph)	57.12	5.43	22.21
			56.92	5.55	19.98
19	327(36) 91	DMSO-d_6: 12.48 (s, 1H, exch); 7.61 (s, 1H, exch); 7.46 (m, 2H, arom); 7.30 (m, 3H, arom); 4.35 (s, 2H, benzyl); 3.42 (m, 2H, aliph); 2.38 (s, 3H, C(8)-Me); 1.53 (m, 2H, aliph); 1.29 (m, 2H, aliph); 0.86 (t, J=5.2 Hz, 3H, aliph)	62.36	6.46	21.39
			62.11	6.59	21.48
20	304(10) 91	DMSO-d_6:12.52 (s, 1H, exch), 7.41 (m, 2H, arom); 7.28(m, 3H, arom); 4.76 (m, 1H, exch), 4.34 (s, 2H, benzyl); 3.83 (m, 1H, aliph); 3.39 (m, 2H, aliph) 2.38 (s, 3H, C(8)-Me); 1.04 (d, J=6.4 Hz, 3H, aliph)	58.34	5.58	21.26
			58.01	5.62	21.49
21		DMSO-d_6: 13.75 (s br, 1H, exch); 8.46 (s, 1H, C(8)-H); 7.34 (m, 5H, arom); 4.95 (s, 2H, benzyl); 3.45 (s, br 1H, exch)	49.65	3.47	19.30
			49.78	3.68	19.52
22	345(1) 91	DMSO-d_6: 8.33 (m, 1H, exch); 8.32 (s 1H, C(8)-H); 7.29 (m, 5H, arom); 4.85 (s, 2H, benzyl); 3.48 (m, 2H, aliph); 1.59 (m, 2H, aliph); 1.37 (m, 2H, aliph); 0.89 (t, J=7.2 Hz, 3H, aliph)	55.63	5.54	20.27
			55.30	5.24	19.99
23		DMSO-d_6: 8.17 (m, 1H, exch); 7.30 (m, 5H, arom); 4.82 (s, 2H, benzyl); 3.42 (m, 2H, aliph); 2.45 (s, 3H, C(8)-Me); 1.56 (m, 2H, aliph); 1.32 (m, 2H aliph); 0.85 (t, J=7.2 Hz, 3H, aliph)	56.81	5.89	19.48
			57.09	6.21	19.24

[11]), and **4**, an oil, (4.19 g, 36% yield) were obtained. Analytical and spectral data are reported in the Table.

4,6-Dichloro-2-phenylmethylsulphanyl-pyrimidine (**5**) [11].

A mixture of 2.6 g (11 mmoles) of **3**, *N*,*N*-diethylaniline (4 mL) and phosphorus oxychloride (11.4 mL) was stirred under reflux at 90 °C for 2 hours. After evaporation, the mixture was treated with ice and the aqueous phase was extracted with ethyl acetate. The organic phase was flash-chromatographed on silica gel using *n*-hexane-toluene 1:1 as the eluent to give pure compound **5** as an oil (2.2 g, 72%).

4,6-Dichloro-2-(*p*-nitrophenyl)-methylsulphinyl-pyrimidine (**6**).

96% Nitric acid (2.15 mL) was added slowly to 0.54 g (2.0 mmoles) of **5** cooled in an ice-bath at 0-5 °C. After the addition was complete, the reaction mixture was stirred to a room temperature for 1 hour. Addition of ice afforded **6** (0.59 g, 90%). Analytical and spectral data are reported in the Table.

4-Amino-6-hydroxy-2-thio-5-*p*-toluenazopurine (**7**).

Solution A was prepared by addition of a solution of sodium nitrite (2.8 g, 40 mmoles) in 40.2 mL of water to a solution of *p*-toluidine (4.3 g, 39 mmoles) in 11.8 mL of 37% hydrochloric acid. Separately, solution B, consisting of 3.8 g (26 mmoles) of **2** in 12 mL of 2.4 *N* sodium hydroxide was prepared and cooled to 0-5 °C. Solution A, cooled to 0 °C in an ice-bath, was added dropwise to iced solution B and the reaction mixture was stirred at 0 °C for 1 hour. The orange mixture obtained was treated with hydrochloric acid until the pH reaches 3 or 4; and the red solid obtained was collected by filtration and dried to give **7** (6.5 g, 98%, mp 280 °C). Analytical and spectral data are reported in the Table.

4-Amino-2-phenylmethylsulphanyl-6-hydroxy-5-*p*-toluenazopyrimidine (**8**).

A solution of **7** (1.00 g, 38 mmoles), 1.2 mL of water, 0.15 g (38 mmoles) of sodium hydroxide and 6 mL of ethanol was heated for few minutes. Then benzyl chloride (4.8 g, 38 mmoles) was added. The resulting mixture was stirred under reflux until pH was 7. The yellow precipitate was filtered and dried to give **8** (0.9 g, 70%, mp 235 °C). Analytical and spectral data are reported in the Table.

4-Amino-6-hydroxy-5-nitroso-2-thiopyrimidine (**9**).

A solution of **5** (2.28 g, 15 mmoles) in 65 mL of 1 *N* hydrochloric acid was cooled to 0 °C. A solution of sodium nitrite (1.20 g, 17 mmoles) in 6 mL of water was added dropwise. The resulting red suspension was stirred for 7 hours. The precipitate obtained was washed with ice-water, ethanol and acetone to give **9** (2.3 g, 87%, mp 270 °C dec. Lit.[12]>240 °C)

4,5-Diamino-6-hydroxy-2-thiopyrimidine (**10**).

To a solution of **9** (5.3 g, 31 mmoles) in 120 mL of 1 *N* sodium hydroxide (12.2 g, 0.11 mole), sodium hydrosulfite (12.25 g, 0.11 mole) was added and the mixture was stirred at room temperature for 20 hours. The white solid afforded compound **10** (4.66 g, 96%, mp>350 °C. Lit.[12]mp>240 °C).

4,5-Diamino-2-phenylmethylsulphanyl-6-hydroxy-pyrimidine (**11**).

A mixture of **10** (2.50 g, 16 mmoles), 0.62 g. of sodium hydroxide, 5 mL of water and 6 mL of ethanol was heated for a few minutes, then 1.96 g (15.6 mmoles) of benzyl chloride was added and the resulting mixture was heated under reflux. When the pH of mixture was 7 the heating was discontinued. The white precipitate afforded **11** (2.9 g, 70%, mp 180 °C. Lit. [12] 185-187 °C).

2-Phenylmethylsulphanylhypoxanthine (**12**).

To a mixture of triethyl orthoacetate (28.2 g, 0.17 mole) and 12 *N* HCl (0.14 mL), compound **11** (4.6 g, 18 mmoles) was added. The reaction mixture was stirred at room temperature for 12 hours. The precipitate was crystallized from ethanol-*n*-hexane to give pure compound **12** (3.2 g, 70%, mp >300 °C. Lit. [11] mp >300 °C).

2-Phenylmethylsulphanyl-8-methylhypoxanthine (**13**).

To a mixture of triethyl orthoacetate (28.2 g, 0.17 mole) and acetic anhydride (17.7 g, 0.17 mole), compound **11** (4.6 g, 18 mmoles) was added. The reaction mixture was stirred at 120 °C for ninety minutes and the precipitate gave pure compound **13** (2.2 g, 44%, mp 240 °C). Analytical and spectral data are reported in the Table.

2-Phenylmethylsulphanyl-8-ethyl-hypoxanthine (**14**).

To a mixture of triethyl orthopropionate (6.2 g, 35 mmoles) and acetic anhydride (3.8 g, 37 mmoles), compound **11** (1.0 g, 18 mmoles) was added. The reaction mixture was stirred at 120 °C for ninety minutes and the precipitate gave pure compound **14** (2.3 g, 45%, mp 130 °C). Analytical and spectral data are reported in the Table.

6-Chloro-2-phenylmethylsulphanylpurine (**15**) and 6-Chloro-2-phenylmethyl-sulphanyl-8-methylpurine (**16**).

To a mixture of **12** or **13** (4.0 mmoles) and *N*,*N*-diethylaniline (0.60 g, 40 mmoles), phosphorus oxychloride (6.1 g, 40 mmoles) was added and the resulting mixture was stirred at 110 °C for 5 hours. After evaporation the residue was used for the next reaction without purification.

2-Phenylmethylsulphanyl-N^6-substitutedadenines (**17**, **18**).

A mixture of **15** (17 mmoles), an appropriate amine (34 mmoles) and ethanol (1 mL) was stirred at 120 °C in a steel vial for 5 hours. The residue obtained was crystallized from ethanol to give **17** (0.48 g, 90%, mp 240 °C, the literature [17] reports melting point 250 °C) or **18** (0.48 g, 90% yield, mp 150 °C dec). Analytical and spectral data are reported in the Table.

2-Phenylmethylsulphanyl-N^6-substituted-8-methyladenine (**19**, **20**).

A mixture of **16** (17 mmoles), an appropriate amine (34 mmoles) and ethanol (1 mL) was stirred at 120 °C in a steel vial for 5 hours. The residue obtained was crystallized from ethanol to give **19** (0.48 g, 85% yield, mp 175 °C) or **20** (0.5 g, 90% yield, mp 245 °C) Analytical and spectral data are reported in the Table.

2-Phenylmethylsulphonyl-8-methylhypoxantine (**21**).

A mixture of **12** (2.72 g, 10 mmoles) in methanol (40 mL) was cooled to 0 °C, and a solution of 18.45 g of Oxone® in 40 mL of water was added. The resulting mixture was stirred at room temperature for 4 hours and then diluted with water to obtain a white precipitate that was collected by filtration and dried to give **21** (1.5 g, 50%, mp 268 °C). Analytical and spectral data are reported in the Table.

2-Phenylmethylsulphonyl-*N*6-substituted-8-methyladenines (**22**, **23**).

A mixture of **17** or **19** (1.1 mmoles) in 4 mL ethanol) was cooled to 0 °C, and a solution of Oxone® (2.0 g in 4 mL of water) added. The resulting mixture was stirred at room temperature for 12 hours and then diluted with water to obtain a white precipitate that was collected by filtration and dried to afford **22** (0.23 g, 55% yield, mp 130 °C) or **23** (0.19 g, 45% yield, mp 190 °C). Analytical and spectral data are reported in the Table.

REFERENCES AND NOTES

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[18] ^{1}H Nmr spectrum for 2-phenylmethyl-6-chloro-8-methyl-adenine in DMSO-d_6: 7.46 (m, 2H, arom); 7.30 (m, 3H, arom); 4.42 (s, 2H, benzyl); 2.55 (s, 3H, aliph).