Synthesis of Novel Adamantylalkoxyurea Derivatives from 2-(1-Adamantylimino)-1,3-oxathiolane

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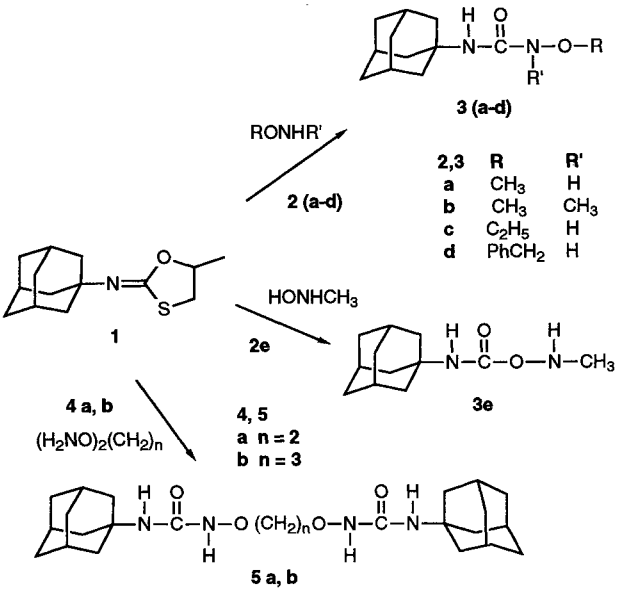
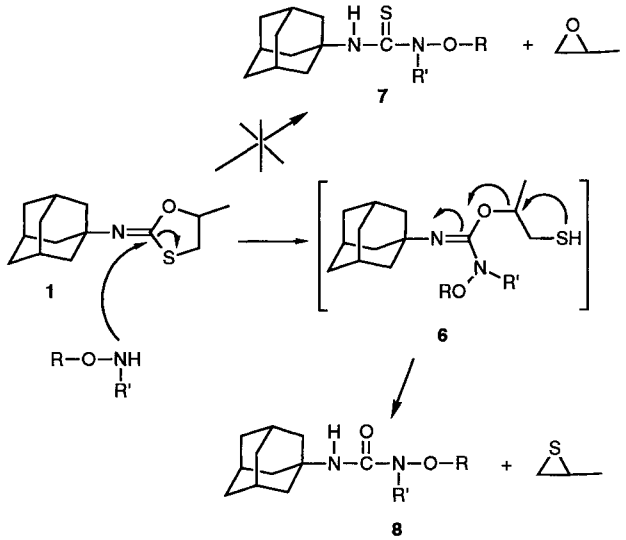
2-(1-Adamantylimino)-5-methyl-1,3-oxathiolane **1** was synthesised from the reaction between adamantan-1-ol and 1-thiocyanopropan-2-ol in sulphuric acid. Compound **1** undergoes ring opening followed by elimination to afford novel adamantane alkoxyureas **3a–d** and **5a,b** with a number of oxyamino nucleophiles **2a–d** and **4a,b.**

A number of adamantane compounds has for many years been recognised to exhibit antiviral activity especially those related to the flu[1] and herpes viruses.[2] In our continued effort to study the chemistry of adamantane compounds and also to synthesise new adamantane derivatives as potential antiviral agents, we found that 2-(1-adamantylimino)-5-methyl-1,3-oxathiolane **1** can be easily synthesised from the reaction between adamantan-1-ol and 1-thiocyanopropan-2-ol in the presence of sulphuric acid following a method we recently described.[3] Oxathiolane derivatives have demonstrated many interesting biological properties and have been used as nematocide,[4] anticancer[5] and more recently, as anti-HIV agents,[6,7] In this paper we report the reactivity of compound **1** with a number of alkoxyamine nucleophiles to give novel adamantylalkoxyurea derivatives (Scheme 1). In a number of reports, alkoxyurea derivatives have shown a wide spectrum of biological activities.[8,9,10] As far as we are aware it is the first time that an oxathiolane derivative such as compound **1** have been used to obtain alkoxyurea derivatives, the latter have been synthesised previously from the reaction between *O*-alkylhydroxylamines and isocyanates.[10]



Scheme 1

2-(1-Adamantylimino)-5-methyl-1,3-oxathiolane **1** was obtained in 76% yield as a mixture of *Z* and *E* isomers as found previously.[3] Reaction between **1** and alkoxyamines **2a–d** at 95°C gave adamantane alkoxyureas in varying yield (see Table). The suggested mechanism of this reaction is depicted in Scheme 2 and involves nucleophilic addition of the oxyamino group to the electron deficient imino carbon of 2-(1-adamantylimino)-5-methyl-1,3-oxathiolane **1** resulting in the opening of the oxathiolane ring. It is interesting to note that after nucleophilic addition of the alkoxyamine group, ring cleavage can occur either at C–O or C–S bond. Preferential C–S bond cleavage was observed since no thiourea compounds **7** were isolated in the reaction. This may be due to the weaker C–S bond together with facile elimination of 2-methylthiiarane by intramolecular cyclisation of intermediate **6** to form the adamantylalkoxyurea derivative **8**. Analogous reactions involving the elimination of a thiiarane ring have been previously reported for example in the reaction between 2-dimethylimmonio-1,3-oxathiolane with sodium ethylate[11] and in the alkaline hydrolysis of acetylated vicinal hydroxy thiols.[12,13] Although the suggested intermediate **6** could exist as a zwitterion, the latter is probably not stable enough to be isolated. This further supports the suggestion of the favoured elimination of 2-methylthiiarane and formation of the adamantylalkoxy derivative. Interestingly the reaction is less efficient when *N*-methylmethoxyamine **2b** is used as a nucleophile. Furthermore in the case of *N*-methylhydroxylamine **2e**, *N*-(1-adamantyl)-*O*-methylaminocarbamate **3e** was obtained instead of the corresponding alkoxyurea derivative involving nucleophilic attack preferentially through oxygen instead of the nitrogen, and this can possibly be accounted for by steric considerations.



Scheme 2

Table. Adamantyl Alkoxyureas **3(a–d)**, **5(a, b)** and *N*-(1-Adamantyl)-*O*-(methylamino)carbamate **3e**

Product	Time (h)	Yield (%)	Mp (°C)	IR (Nujol) ν (cm^{-1})	^1H NMR ($CDCl_3$) δ, J (Hz)	^{13}C NMR ($CDCl_3$) δ	FAB MS *m/z* (%)
3a	24	93	117–118	3420, 3382, 3180, 3076, 1662, 1540	6.94 (s, 1 H, NHO), 5.55 (s, 1 H, NH), 3.74 (s, 3 H, CH_3), 2.10 (m, 9 H, Ad), 1.78 (m, 6 H, Ad)[a]	158.3 (C=O), 64.0 (CH_3O), 51.0 (Ad), 42.0 (Ad), 36.3 (Ad), 29.5 (Ad)[a]	225 ($M+H^+$, 100), 149 (AdN^+, 29), 135 (Ad^+, 50)[a]
3b	34	17	62–63	3377, 1656, 1521	5.62 (s, 1 H, NH), 3.62 (s, 3 H, CH_3), 3.01 (s, 3 H, CH_3), 1.99 (m, 9 H, Ad), 1.66 (m, 6 H, Ad)	158.8 (C=O), 60.8 (CH_3O), 50.5 (Ad), 41.8 (Ad), 36.1 (Ad), 36.0 (CH_3N), 29.3 (Ad)	239 ($M+H^+$, 100), 149 (AdN^+, 51)
3c	34	86	110–111	3389, 3151, 3076, 1660, 1542	7.38 (s, 1 H, NHO), 5.58 (s, 1 H, NH), 3.93 (q, 2 H, J = 7.0, CH_2O), 2.09 (m, 9 H, Ad), 1.76 (m, 6 H, Ad), 1.32 (t, 3 H, J = 7.0, CH_3)	159.1 (C=O), 71.8 (CH_3O), 51.1 (Ad), 42.2 (Ad), 36.5 (Ad), 29.7 (Ad), 13.9 (CH_3)	239 ($M+H^+$, 100), 150 ($AdNH^+$, 11)
3d	34	73	101–102	3420, 3183, 3085, 1682, 1531	7.29 (s, 5 H, Ph), 7.07 (s, 1 H, NHO), 5.22 (s, 1 H, NH), 4.67 (s, 2 H, CH_2O), 1.94 (m, 3 H, Ad), 1.78 (m, 6 H, Ad), 1.55 (m, 6 H, Ad)	158.8 (C=O), 135.9 (Ph), 129.5 (Ph), 128.9 (Ph), 78.6 (CH_2O), 51.0 (Ad), 41.9 (Ad), 36.4 (Ad), 29.6 (Ad)	301 ($M+H^+$, 100), 149 (AdN^+, 48)
3e	1[b]	42	162–163	3362, 3310, 1630, 1576	5.27 (s, 1 H, NH), 4.93 (m, 1 H, NHO), 2.75 (d, 3 H, J = 4.0, CH_3), 2.02 (m, 9 H, Ad), 1.71 (m, 6 H, Ad)	158.9 (C=O), 50.8 (Ad), 42.8 (Ad), 36.7 (Ad), 29.8 (Ad), 26.9 (CH_3N)	225 ($M+H^+$, 47), 209 ($M^+ - CH_3$, 100), 150 ($AdNH^+$, 25)
5a	3[c]	41	165–166	3386, 3204, 1667, 1530	7.60 (s, 2 H, 2 NHO), 5.77 (s, 2 H, 2 NH), 4.33 (s, 4 H, 2 CH_2O), 2.06 (m, 18 H, 2 Ad), 1.73 (m, 12 H, 2 Ad)	158.7 (C=O), 73.1 (CH_2O), 51.1 (Ad), 41.9 (Ad), 36.2 (Ad), 29.4 (Ad)	447 ($M+H^+$, 100), 270 ($M+H^+$ – AdNCO, 50), 150 ($AdNH^+$, 41)
5b	3[c]	39	289–290	3420, 3341, 3204, 3070, 1662, 1535	7.24 (s, 2 H, 2 NHO), 5.75 (s, 2 H, 2 NH), 4.04 (t, 4 H, J = 5.9, 2 CH_2O), 2.11 (m, 18 H, 2 Ad), 1.97 (m, 2 H, CH_2), 1.79 (m, 12 H, 2 Ad)	158.5 (C=O), 74.0 (CH_2O), 51.0 (Ad), 42.0 (Ad), 36.3 (Ad), 29.4 (Ad), 26.8 (CH_2)	461 ($M+H^+$, 100), 284 ($M+H^+$ – AdNCO, 25), 150 ($AdNH^+$, 30)

[a] Ad = 1-Adamantyl.
[b] Refluxing in dioxane.
[c] Refluxing in ethanol.

We have also extended the above reaction by treating **1** with a number of bisoxyamino compounds such as **4a,b**. The latter were obtained by treating the corresponding dibromoalkane with *N*-hydroxyphthalimide in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene to give the bis(phthalimidooxy)alkanes. Subsequent acid hydrolysis (conc. HCl and glacial acetic acid) afforded the corresponding bis(aminooxy)alkanes **4a,b** in 60–80% yield. Reaction between **1** and **4a,b** gave the expected products **5a,b** in 39–41% yield (refer to Scheme 1 and Table). In general, the ^1H NMR spectrum of the alkoxyureas characteristically showed chemical shifts responsible for the -OCH_2- group to occur between δ = 3.93 and 4.67, the NH proton exhibited a signal between δ = 5.27 and 5.77 and RONH showed signals between δ = 6.94–7.38.

We have shown in this paper that adamantylalkoxyurea derivatives can be synthesised from adamantyl oxathiolane. This reaction has advantages over the previous method of preparation as it does not involve unstable and toxic isocyanates.[10] The antiviral activity of compounds **3a–e** and **5a,b** is presently being studied at the MRC Collaborative Centre, Mill Hill, London and the results will be presented elsewhere.

Compounds **2a–e** were purchased from Aldrich and Fluka Chemical Company. Melting points were obtained on Gallenkemp apparatus and are uncorrected. NMR were measured on a JOEL EX90 spectrometer at 90 MHz (^1H) and 22 MHz (^{13}C) using residual solvent peak as the internal reference. Infrared spectra were obtained on a Nicolet 5ZDX FT-IR spectrophotometer. FAB MS were measured on a VGZAB-E low resolution at the EPSRC Mass Spectrometry Service Centre, University of Wales, Swansea, UK.

1,3-Di(aminooxy)propane Dihydrochloride (4b):
To a solution of *N*-hydroxyphthalimide (8.68 g, 0.05 M) in anhyd dimethylformamide (50 mL), 1.8-diazabicyclo[5.4.0.]undec-7-ene (7.96 mL, 0.05 M) was added dropwise with stirring to give a very deep red solution. To this solution was added 1,3-dibromopropane (2.7 mL, 0.025 M) and the mixture was heated at 85°C for 1.5 h during which time the deep red coloration faded to a colorless solution. The resulting solution was poured into ice and the precipitate filtered and washed with cold water (50 mL) followed by MeCN (50 mL). The crude 1,3-diphthalimidooxypropane was recrystallised from butanol.

A suspension of 1,3-diphthalimidooxypropane (5.0 g, 0.013 mol) in HCl/glacial HOAc (50 mL, 20:30) was heated at 115°C for 3 h to give a clear solution. All the solvent and reagents were removed in vacuo. H_2O (30 mL) was added to the solid and the suspension was filtered and washed with HCl (6 M). The combined filtrate was collected and reduced to dryness. The crude product was recrystallised from EtOH/H_2O to give the title compound (80%). Mp 174°C.

^1H NMR (δ, DMSO-d_6): 11.12 (s, 6 H, 2 × ONH_3^+), 4.14 (t, 4 H, J = 6.2 Hz, 2 × OCH_2), 1.92 (m, 2 H, J = 6.2 Hz, CH_2).

^{13}C NMR (δ, DMSO-d_6): 73.00 (2 × OCH_2), 29.00 1 × CH_2).

1,2-Di(aminooxy)ethane Dihydrochloride (4a):
The same procedure described above was followed to give 1,2-diaminooxyethane dihydrochloride in 60%. Mp 224°C.

^{1}H NMR (δ, DMSO-d_6): 11.12 (s, 6H, 2 × ONH_3^+), 4.14 (s, 4H, 2 × OCH_2).

^{13}C NMR (δ, DMSO-d_6): 71.00 (2 × OCH_2).

2-(1-Adamantylimino)-5-methyl-1,3-oxathiolane (1):
A solution of ammonium thiocyanate (5 g, 0.065 mol) and propylene oxide in glacial HOAc (7 mL, 0.10 mol) was added dropwise to a solution of 1-adamantanol (5 g, 0.033 mol) in H_2SO_4 (20 mL, d 1.84) at 5–10 °C. The reaction was cooled on ice followed by neutralisation with Na_2CO_3. The solid formed was filtered and recrystallised from 1,2-dichloroethane to give the pure product (6.3 g, 76%). Mp 117–118 °C (mixture of *Z* and *E* isomers).

^{1}H NMR (δ, $CDCl_3$): 4.60 (m, 1H, CHO), 3.20 (m, 2H, CH_2S), 2.07 (m, 3H, Ad), 1.94 (m, 6H, Ad), 1.70 (m, 6H, Ad), 1.49 (d, 3H, J = 6.1 Hz, CH_3).

^{13}C NMR (δ, $CDCl_3$): 156.0 (C=N), 153.9 (C=N), 80.2 (CHO), 56.1 (Ad, C–N), 52.8 (Ad, C–N), 42.5 (CH_2S), 41.7 (Ad), 39.3 (CH_2S), 36.4 (Ad), 29.6 (Ad), 19.5 (CH_3), 18.8 (CH_3).

Compound **1** was also isolated as its hydrochloride and was obtained by the addition of HCl/Et_2O solution to **1** dissolved in Et_2O. The white precipitate formed was filtered and dried. Mp 156–157 °C.

^{1}H NMR (δ, $CDCl_3$): 13.55 (s, 1H, NH), 5.43 (m, 1H, CHO), 3.80 (m, 1H, CH_2S), 3.40 (m, 1H, CH_2S), 2.22 (m, 9H, Ad), 1.75 (m, 6H, Ad).

^{13}C NMR (δ, DMSO-d_6): 162.3 (C=N), 89.5 (CHO), 58.0 (Ad, C–N), 41.0 (Ad), 35.8 (Ad), 35.0 (CH_2S), 28.7 (Ad), 18.1 (CH_3).

Alkoxyamines 2a–e and 4a,b:
Free bases of alkoxyamines **2a–e** and **5a,b** were obtained by distilling the corresponding hydrochloride salts over solid KOH. The temperatures at which alkoxyamines were distilled are as follows: H_2NOCH_3 **(2a)** at 49 °C, CH_3NHOCH_3 **(2b)** at 42 °C, H_2NOEt **(2c)** at 65 °C, H_2NOCH_2Ph **(2d)** at 118 °C/30mmHg, CH_3NHOH **(2e)** at 115 °C, $H_2NOCH_2CH_2ONH_2$ **(4a)** at 98 °C/30mmHg, $H_2NOCH_2CH_2CH_2ONH_2$ **(4b)** at 112–114 °C/30mmHg.

1-(1-Adamantyl)-3-alkoxyureas; General Procedure:
A solution of 2-(1-adamantylimino)1,3-oxathiolane (2 mmol) and alkoxyamine (4 mmol) in $CHCl_3$ (2 mL) was heated at 95 °C in a closed vial until reaction was completed. The solution was reduced in vacuo and the residue dissolved in Et_2O. The resulting Et_2O solution was washed with dilute HCl (10 mL) and after drying and evaporation, the product was obtained in 39–93% yields after recrystallisation from hexane (refer to Table).

Bisadamantyl Alkoxyureas; General Procedure:
A solution of 2-(1-adamantylimino)-1,3-oxathiolane (10 mmol) and alkoxyamine (4 mmol) in EtOH was boiled under reflux for 3 h. After the solvent was removed in vacuo, the residue was dissolved in $CHCl_3$ and washed with dilute HCl (10 mL) followed by H_2O (10 mL). Subsequent drying and evaporation of the solvent gave the crude product which was recrystallised from toluene.

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