

SOME REACTIONS OF SULTONES

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ABSTRACT

Condensation of 2,4-dimethyl-1,3-butadiene-1,4-sultone **1** with phenylenediamines gave the sultams **2a-c**. The sultams **2** react with phenylisocyanate, *p*-anisylisocyanate or *p*-chlorophenylisocyanate to give the phenylurea derivatives **2d-l**. Sultam **2c** reacts with acetone, acetophenone, benzophenone, benzaldehyde or *p*-anisaldehyde to yield the Schiff bases **3a-e**. The reaction of **2b,c** with *p*-acetamidobenzenesulphonyl chloride affords the sulphonamide derivatives **4a,b**. Hydrolysis of **4b** yields **5**. The compound **2c** reacts with acetyl chloride, benzoyl chloride, *p*-chlorobenzoyl chloride or benzyl chloride to yield **6a-d**.

INTRODUCTION

It is known that sultones react with amines to give either sulphonic acids or sultams¹⁻⁴. This reaction has been applied to 2,4-dimethyl-1,3-butadiene-1,4-sultone **1**⁵, which condenses with *o*-, *m*- or *p*-phenylenediamine to give the sultams **2a-c**. The structure of **2** is based on correct analytical and spectroscopic data.

Phenylurea derivatives are known for their larvicidal activity and are stable in soil and water⁶. The phenylurea derivatives **2d-l** are readily formed when **2a-c** are allowed to react with phenylisocyanate, *p*-anisylisocyanate or *p*-chlorophenylisocyanate. The structures of the products reported rest on correct analytical and spectroscopic data.

Treatment of **2c** with acetone, acetophenone, benzophenone, benzaldehyde or *p*-anisaldehyde yielded the corresponding Schiff bases **3a-e**, respectively. The structures of **3a-e** are supported by analytical and spectral data.

Sulphonamide derivatives are well known for their bacteriological activity and have been used widely under the name sulpha drugs as bacteriostatic agents⁷. Thus, when the sultams **2b** and **2c** were allowed to react with *p*-acetamidobenzenesulphonyl chloride, they gave the sulphonamide derivatives **4a** and **4b**. Hydrolysis of **4b** with boiled alkali gave **5**. On the other hand, in the reaction of **2c** with acid chlorides such as acetyl chloride, benzoyl chloride or *p*-chlorobenzoyl chloride, HCl was evolved, with the formation of the amides **6a-c**. Treatment of **2c** with benzyl chloride yielded **6d**. The structures of **6a-d** are based on analytical and spectroscopic data.

EXPERIMENTAL

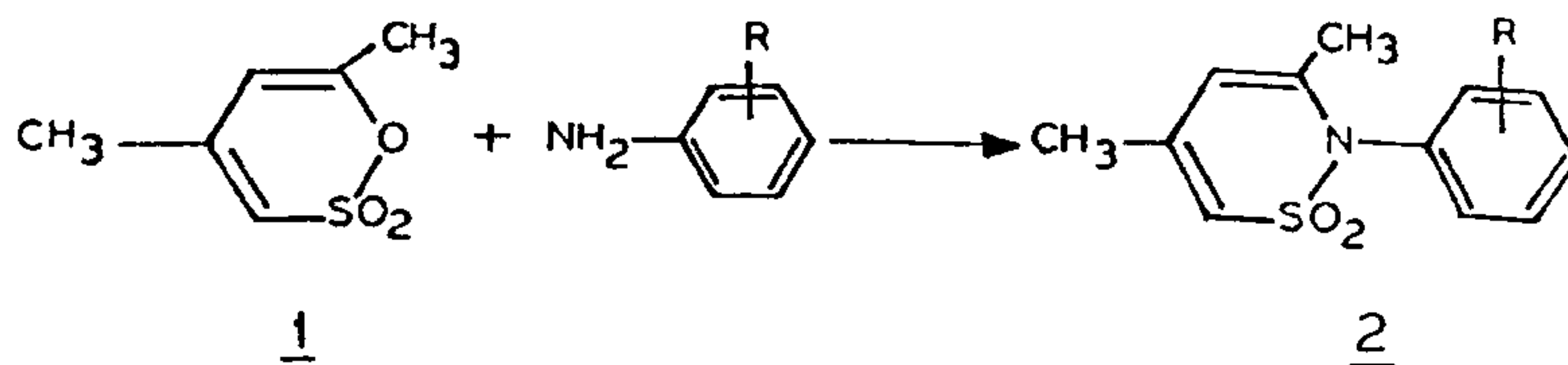
Reaction of 2,4-dimethyl-1,3-butadiene-1,4-sultone with o-, m- and p-phenylenediamine

A mixture of equimolecular amounts of the sultone **1** and the amine in a dry vessel was heated in an oil bath. The reaction began at 130°C with evolution of water vapour. The temperature was kept at 130°C for an hour, then elevated to 150°C till the evolution of H₂O ceased. The reaction mixture was left to cool and a few drops of methanol were added. The separated solid was filtered off and crystallized from ethanol to give **2a-c**.

2,4-Dimethyl-*N*-(2-aminophenyl)-1,3-butadiene-1,4-sultam (**2a**): M.p. 145°C; yield 62%. IR: 3470, 3370 cm⁻¹ (NH₂), 1610, 1350 cm⁻¹, (two conjugated double bonds), 1270 cm⁻¹ (SO₂-N in sultam). C₁₂H₁₄N₂O₂S (250.44), calcd. C 57.55 H 5.63 N 11.20, found C 57.65 H 5.81 N 11.11.

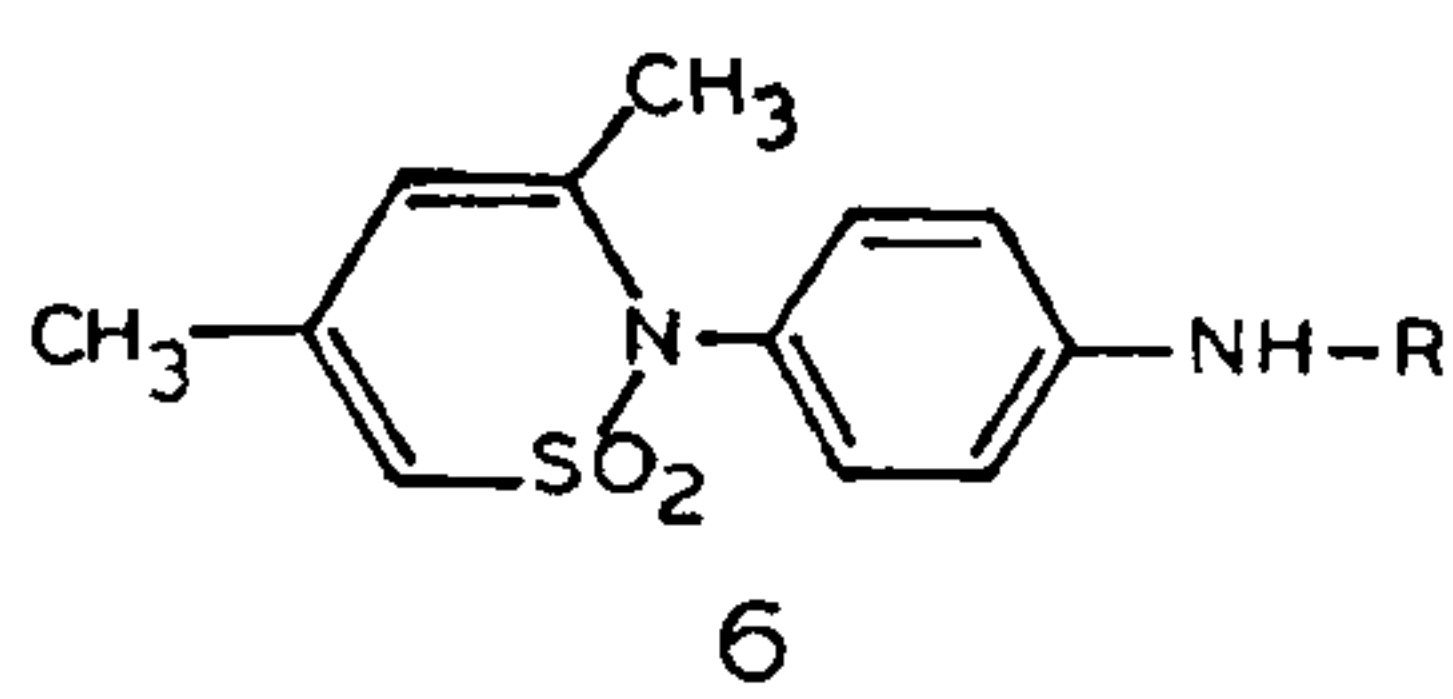
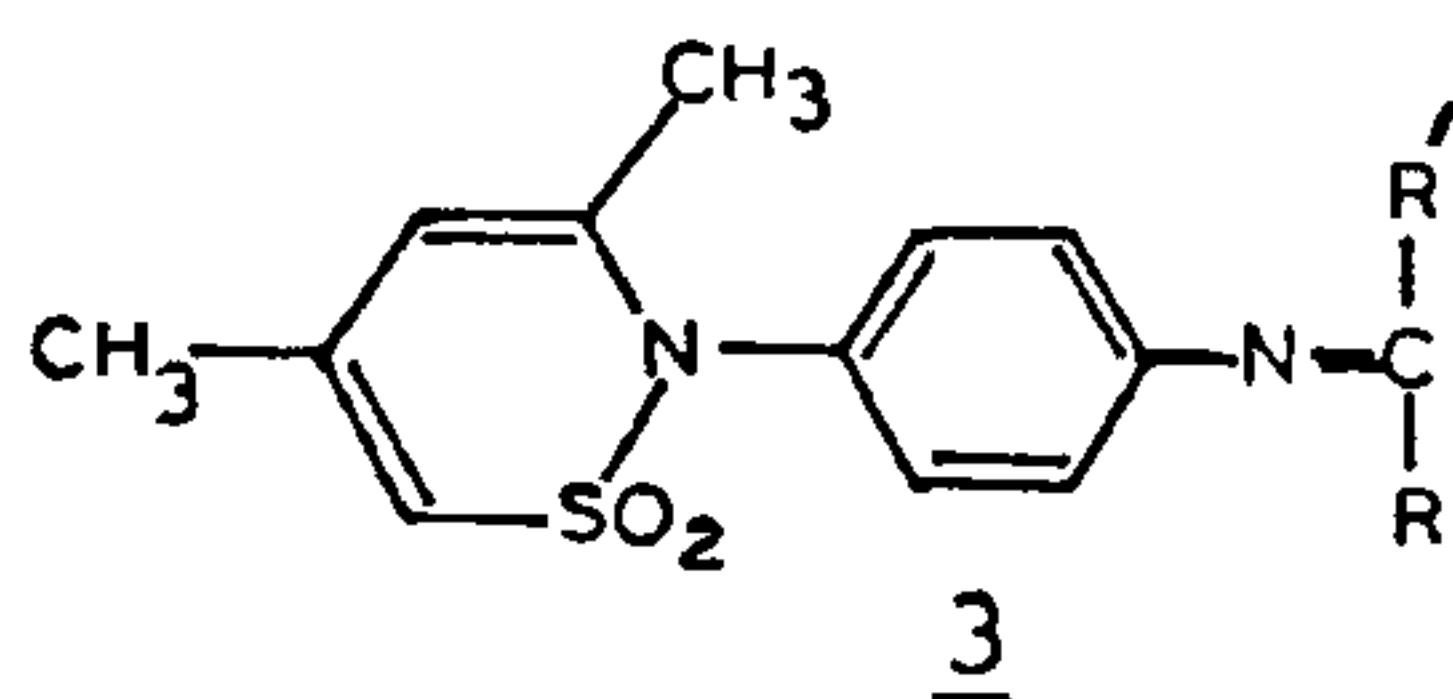
2,4-Dimethyl-*N*-(3-aminophenyl)-1,3-butadiene-1,4-sultam (**2b**): M.p. 155°C; yield 72%. IR: 3475, 3370 cm⁻¹ (NH₂), 1610, 1350 cm⁻¹ (two conjugated double bonds), 1280 cm⁻¹ (SO₂-N in sultam). ¹H NMR: δ = 7.2, 7.05 (NH₂ protons), 6.4-6.8 (*m* 4H aromatic protons), 5.8, 5.4 (*a* 1-H, 3-H sultam) 2.1, 1.9 (*s* 2CH₃). C₁₂H₁₄N₂O₂S (250.44), calcd. C 57.55 H 5.63 N 11.20 S 12.80, found C 57.61 H 5.62 N 11.00 S 13.00.

2,4-Dimethyl-*N*-(4-aminophenyl)-1,3-butadiene-1,4-sultam (**2c**): M.p. 164°C; yield 80%. IR: 3500, 3370 cm⁻¹ (NH₂), 1600-1350 cm⁻¹ (two conjugated double bonds), 1270 cm⁻¹ (SO₂-N in sultam). C₁₂H₁₄N₂O₂S (250.44), calcd. C 57.55 H 5.63 N 11.20, found C 57.50 H 5.61 N 11.61.



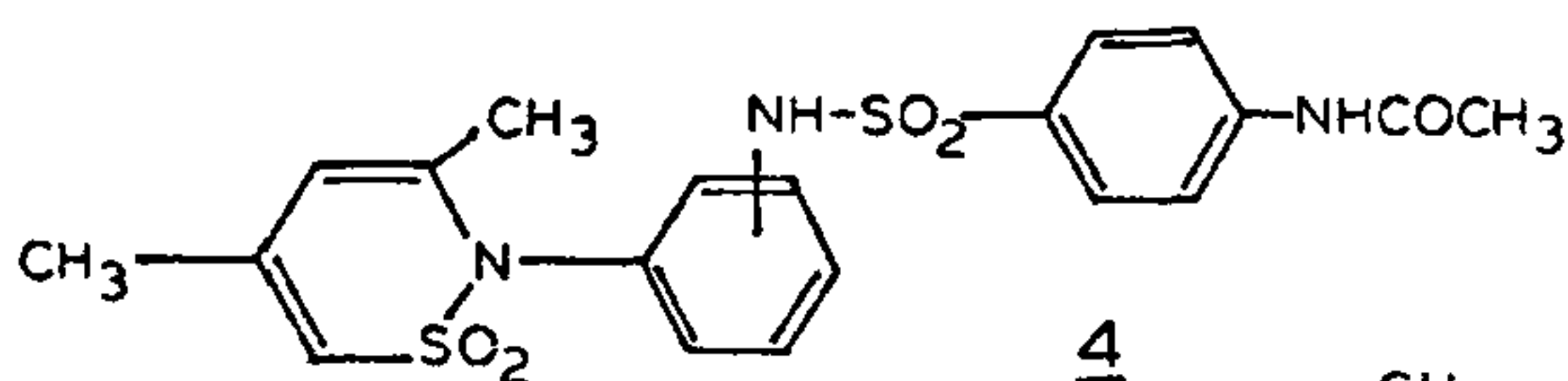
- 2a, R = *o*-NH₂
 2b, R = *m*-NH₂
 2c, R = *p*-NH₂
 2d, R = *o*-NH-CO-NH-C₆H₅
 2e, R = *o*-NH-CO-NH-C₆H₄OCH₃(*p*)
 2f, R = *o*-NH-CO-NH-C₆H₄Cl(*p*)

- 2g, R = *m*-NH-CO-NH-C₆H₅
 2h, R = *m*-NH-CO-NH-C₆H₄OCH₃(*p*)
 2i, R = *m*-NH-CO-NH-C₆H₄Cl(*p*)
 2j, R = *p*-NH-CO-NH-C₆H₅
 2k, R = *p*-NH-CO-NH-C₆H₄OCH₃(*p*)
 2l, R = *p*-NH-CO-NH-C₆H₄Cl(*p*)

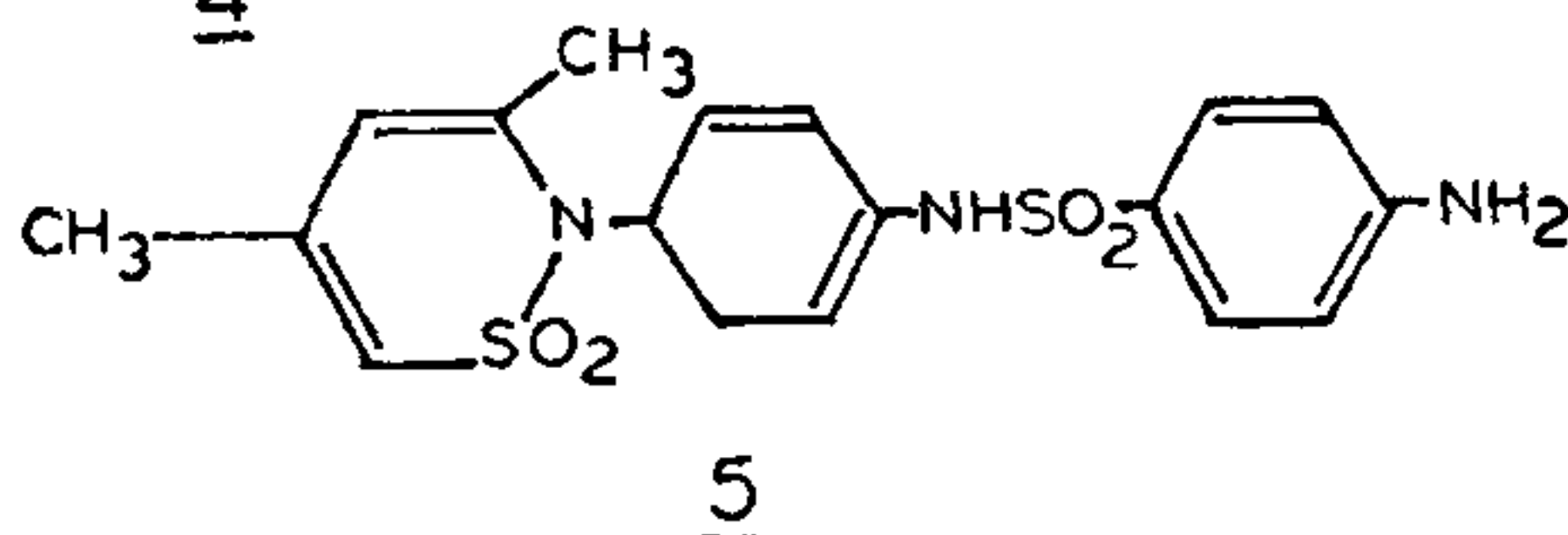


3	R	R'
a	CH ₃	CH ₃
b	CH ₃	C ₆ H ₅
c	C ₆ H ₅	C ₆ H ₅
d	H	C ₆ H ₅
e	H	C ₆ H ₄ OCH ₃ (<i>p</i>)

- 6a, R = COCH₃
 6b, R = COC₆H₅
 6c, R = COC₆H₄Cl(*p*)
 6d, R = CH₂-C₆H₅



4a, (*m*) ; 4b, (*p*)



Reaction of the sultams 2a-c with isocyanates; formation of 2d-l

To a solution of the sultam 2 (2.5 g) in sodium-dried benzene (40 ml), 2 ml of phenylisocyanate, *p*-anisylisocyanate or *p*-chlorophenylisocyanate and a

few drops of triethylamine were added. The solution was refluxed for 5 h. The product separated was filtered off, washed with benzene and crystallized from methanol to give 2d-l.

N-Phenyl-*N'*-[2-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl]-urea (2d): M.p. 203°C; yield

75%. IR: 1700 cm^{-1} (CO-N) 1270 cm^{-1} (SO_2 -N sultam). $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ (369.44), calcd. C 61.77 H 5.18, found C 61.50 H 5.51.

N-4-Methoxyphenyl-*N'*-[2-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl]-urea (**2e**): M.p. 223°C ; yield 80%. IR: 1700 cm^{-1} (CO-N), 1270 cm^{-1} (SO_2 -N in sultam). $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_4\text{S}$ (399.47), calcd. C 60.13 H 5.29, found C 60.21 H 5.32.

N-4-Chlorophenyl-*N'*-[2-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl]-urea (**2f**): M.p. 237°C ; yield 79%. IR: 1700 cm^{-1} (CO-N), 1290 cm^{-1} (SO_2 -N sultam). $\text{C}_{19}\text{H}_{18}\text{N}_3\text{O}_3\text{S}\text{Cl}$ (403.88), calcd. C 56.50 H 4.46, found C 56.81 H 4.23.

N-Phenyl-*N'*-[3-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl]-urea (**2g**): M.p. 205°C ; yield 80%. IR: 1700 cm^{-1} (CO-N), 1270 cm^{-1} (SO_2 -N sultam). $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ (369.44), calcd. C 61.77 H 5.18 N 11.37 S 8.67, found C 61.51 H 5.01 N 11.20 S 8.55.

N-4-Methoxyphenyl-*N'*-[3-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl]-urea (**2h**): M.p. 225°C ; yield 79%. IR: 1700 cm^{-1} (CO-N), 1270 cm^{-1} (SO_2 -N sultam). $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_4\text{S}$ (399.47), calcd. C 60.13 H 5.29, found C 60.50 H 5.50.

N-4-Chlorophenyl-*N'*-[3-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl]-urea (**2i**): M.p. 230°C ; yield 84%. IR: 1700 cm^{-1} (CO-N), 1270 cm^{-1} (SO_2 -N sultam). $\text{C}_{19}\text{H}_{18}\text{N}_3\text{O}_3\text{S}\text{Cl}$ (403.88), calcd. C 56.50 H 4.46 N 10.40, found C 56.40 H 4.41 N 10.62.

N-Phenyl-*N'*-[4-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl]-urea (**2j**): M.p. 200°C ; yield 84%. IR: 1700 cm^{-1} (CO-N), 1280 cm^{-1} (SO_2 -N sultam). $^1\text{H NMR}$: $\delta = 8.8, 9$ (*s* two CONH), 7.75–7.2 (*m* 9H aromatic), 6.6, 5.8 (*s* 1-H, 3-H sultam) 2.1, 1.9 (2CH₃). $\text{C}_{19}\text{H}_{19}\text{N}_3\text{O}_3\text{S}$ (396.44), calcd. C 61.77 H 5.18 N 11.37, found C 62.00 H 5.21 N 11.52.

N-4-Methoxyphenyl-*N'*-[4-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl]-urea (**2k**): M.p. 220°C ; yield 80%. IR: 1700 cm^{-1} (CONH), 1270 cm^{-1} (SO_2 -N sultam). $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_4\text{S}$ (399.47), calcd. C 60.13 H 5.29, found C 60.29 H 5.48.

N-4-Chlorophenyl-*N'*-[4-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl]-urea (**2l**): M.p. 300°C ; yield 80%. IR: 1700 cm^{-1} (CO-N), 1280 cm^{-1} (SO_2 -N). $^1\text{H NMR}$: $\delta = 9, 8.85$ (*s* two CONH), 7.65–7.25 (*m* 8H aromatic), 6.6, 5.8 (1-H, 3-N sultam), 2.05, 1.85 (*s* 2CH₃). $\text{C}_{19}\text{H}_{18}\text{N}_3\text{O}_3\text{S}\text{Cl}$ (403.88), calcd. C 56.50 H 4.46, found C 56.60 H 4.50.

Reaction of **2c** with carbonyl compounds; formation of (**3a–e**)

A solution of the sultam **2c** (0.01 mol) in 50 ml

ethanol was treated with the appropriate carbonyl compound (acetone, acetophenone, benzophenone, benzaldehyde and *p*-anisaldehyde) (0.02 mol). A few drops of piperidine were added. The solution was refluxed for four hours. After concentration and cooling the solid product was crystallized from ethanol to give **3a–e**.

Reaction of **2c** with acetone; formation of **3a**: M.p. 185°C ; yield 62%. IR: 1620 cm^{-1} (C=N), whereas νCO and νNH_2 were absent. $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ (290.41), calcd. C 62.04 H 6.24, found C 62.00 H 6.01.

Reaction of **2c** with acetophenone; formation of **3b**: M.p. 175°C ; yield 60%. IR: 1630 cm^{-1} (C=N). $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ (352.45), calcd. C 68.15 H 5.71, found C 68.01 H 5.50.

Reaction of **2c** with benzophenone; formation of **3c**: M.p. 180°C ; yield 67%. IR: 1625 cm^{-1} (C=N). $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_2\text{S}$ (414.52), calcd. C 72.43 H 5.34, found C 72.11 H 5.60.

Reaction of **2c** with benzaldehyde; formation of **3d**: M.p. 170°C ; yield 82%. IR: 1600 cm^{-1} (C=N). $^1\text{H NMR}$: $\delta = 8.7$ (*s* N=CH), 7.96–8, 7.4–7.6 (*m* 9H aromatic), 6.6, 5.8 (1-H, 3-H sultam), 2.1, 1.85 (*s* 2CH₃). $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ (338.43), calcd. C 67.43 H 5.36, found C 67.45 H 5.28.

Reaction of **2c** with *p*-anisaldehyde; formation of **3e**: M.p. 120°C ; yield 62%. IR: 1600 cm^{-1} (C=N). $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ (368.45), calcd. C 65.19 H 5.47 S 8.70, found C 65.11 H 5.20 S 9.00.

Reaction of the sultam **2b** or **2c** with acid chlorides or benzyl chloride; formation of **4a,b** or **6a–d**.

To a solution of the sultam (0.01 mol), in acetone (40 ml) and pyridine (1 ml), the appropriate acid chloride or benzyl chloride (0.015 mol) was added. The reaction mixture was refluxed for two hours and the solvent driven off. The product was filtered off, washed with water, dried and crystallized from acetic acid to give **4a,b** or **6a–d**.

4-Acetamidobenzene-*N*-3-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl-sulphonamide (**4a**): M.p. 250°C ; yield 76%. IR: 3350 cm^{-1} (NH), 1360 cm^{-1} (CO), 1290 cm^{-1} (SO_2 -N), 1610–1350 cm^{-1} (two conjugated double bonds). $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_5\text{S}_2$ (447.32), calcd. C 53.69 H 4.73, found C 53.31 H 4.80.

4-Acetamidobenzene-*N*-4-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl-*N*)-phenyl-sulphonamide (**4b**): M.p. 127°C ; yield 67%. $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_5\text{S}_2$ (447.32), calcd. C 53.69 H 4.73 N 9.39, found C 53.86 H 5.01 N 9.71.

N-(4-Acetamidophenyl)-2,4-dimethyl-1,3-butadiene-1,4-sultam (**6a**): M.p. 220°C ; yield 75%. IR: 3350 cm^{-1}

(NH), 1690cm^{-1} (CO), 1290cm^{-1} (SO₂-N). C₁₄H₁₆N₂O₃S (292.36), calcd. C 57.51 H 5.51 N 9.58, found C 57.10 H 5.80 N 9.70.

N-4-(Benzoylamino)-phenyl-2,4-dimethyl-1,3-butadiene-1,4-sultam (6b): M.p. 215°C; yield 84%. IR: 3350cm^{-1} (NH), 1290cm^{-1} (SO₂-N), 1960cm^{-1} (CO). ¹H NMR: δ = 8.7 (s NH), 8–7.4 (m 9H aromatic), 6.6, 5.8 (s 1-H, 3-H sultam), 2.1, 1.85 (s 2CH₃). C₁₉H₁₈N₂O₃S (354.42), calcd. C 64.39 H 5.11 N 7.90, found C 64.69 H 5.31 N 7.85.

2,4-Dimethyl-*N*-4-(4-chlorobenzoylamino)-phenyl-1,3-butadiene-1,4-sultam (6c): M.p. 192°C; yield 90%. IR: 3350cm^{-1} (NH), 1290cm^{-1} (SO₂-N). C₁₉H₁₇N₂O₃SCL (388.87), calcd. C 58.68 H 4.40, found C 58.62 H 4.51.

2,4-Dimethyl-*N*-4-(benzylamino)-phenyl-1,3-butadiene-1,4-sultam (6d): M.p. 190°C; yield 73%. C₁₉H₂₀N₂O₂S (340.44), calcd. C 67.03 H 5.92 N 8.22, found C 67.41 H 5.82 N 8.42.

Hydrolysis of 4b; formation of 5

A solution of 4b (4.4 g, 0.01 mol) in 5% NaOH solution (40 ml) was refluxed for five hours. After cooling, 2 N HCl was added gradually with stirring

till pH was 6–7. The separated product was filtered off, washed, dried and crystallized from ethanol.

4-Aminobenzene-*N*-4-(2,4-dimethyl-1,3-butadiene-1,4-sultamyl)-phenyl-sulphonamide (5); M.p. 240°C; yield 56%. IR: $3450, 3350\text{cm}^{-1}$ (NH₂), absorption due to C=O is absent. C₁₈H₁₉N₃O₄S₂ (405.30), calcd. C 53.31 H 4.72 N 10.36, found C 53.49 H 4.51 N 10.

13 June 1988; Revised 12 September 1988

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ANNOUNCEMENT

ADENOSINE AND ATP—PROGRESS IN RESEARCH AND THERAPEUTIC POTENTIAL

(25 and 26 September 1989, Royal College of Physicians, London, UK)

In recent years, the discovery of a number of purinoceptor subtypes has prompted an explosion of interest in research on purine nucleosides and nucleotides, e.g. adenosine, ADP and ATP. These substances exert potent and selective effects in a variety of tissues, from the nervous system and all types of muscle, to endothelial, epithelial, secretory and immune cells. Intense efforts are currently under

way in both academia and industry, aimed at developing selective agonists and antagonists for the different subclasses of purinoceptors, and at exploring the therapeutic potential of such compounds. This meeting will review the progress that has been made to date. For details contact: Dr Renata Duke, IBC Technical Services Ltd., Bath House (3rd Floor), 56 Holborn Viaduct, London EC1A 2EX, UK.
