

REACTIONS WITH SULTONE, SYNTHESIS OF 1,3,4- OXADIAZOLYL-SULTAM DERIVATIVES

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ABSTRACT

2,4-Dimethyl-1,3-butadiene-1,4-sultone 1 reacted with 2-aminomethylbenzoate to give 2. Reaction of 2 with hydrazine hydrate or ammonia solution gave the acid hydrazide 3a or the amide 3b, respectively. On hydrolysis of 2 with sodium methoxide the corresponding acid 4 was obtained. The reaction of 3a with benzaldehyde, salicylaldehyde or 4-anisaldehyde afforded the corresponding arylidene carboxyhydrazide 5a-c, respectively. Treatment of 5a-c with acetic anhydride gave the corresponding 1,3,4-oxadiazole derivatives 6a-c, respectively. Reaction of 3a with isocyanates or isothiocyanates gave the corresponding semicarbazide derivatives 7a-d.

INTRODUCTION

1,3,4-oxadiazole and related compounds can be used as potential hypoglycemic agents¹. On the other hand, 5-membered heterocyclic compounds, including oxadiazoles are reported to be analgesic, antipyretic and antiinflammatory agents^{2,3}. Encouraged by these reports and in continuation of our work⁴⁻⁸ in the field of sultams, it is reported here the synthesis of 1-substituted-1,3,4-oxadiazolyl sultams.

DISCUSSION

N-[3-Methoxycarboxyphenyl]-2,4-dimethyl-1,3-butadiene-1,4-sultam **2** was obtained from the reaction of 2,4-dimethyl-1,3-butadiene-1,4-sultone **1** with 3-amino-methyl-benzoate. Treatment of **2** with hydrazine hydrate gave the corresponding hydrazide **3a**. Reaction of **2** with aqueous ammonia at room temperature afforded the corresponding amide **3b**. On the other hand **2** was hydrolyzed with alcoholic sodium methoxide solution to the corresponding acid **4**.

Infrared spectra of **2**, **3a,b** and **4** showed absorption bands in region of 1290-1270 cm^{-1} for (C-SO₂-N- in sultam), $\nu_{\text{C=O}}$ at 1720-1640 cm^{-1} , ν_{NH} at 2980 cm^{-1} and ν_{NH_2} at 3420, 3030 cm^{-1} . ¹H-NMR spectrum of **2** revealed signals at $\delta = 7.4-7.6$ (m, 4H, aromatic protons), 6.0 (s, 1H, C-1, sultam), 5.5 (s, 1H, C-3, sultam), 3.4 (s, 3H, CH₃ of ester), 1.4 (s, 3H, CH₃) and 1.2 (s, 3H, CH₃). ¹H-NMR spectrum of **3a** showed $\delta = 10$ (s, 1H, NH), 7.5-7.9 (m, 4H, aromatic protons), 6.6 (s, 1H, C-1, sultam), 5.9 (s, 1H, C-3, sultam), 4.5 (s, 2H, NH₂), 2.1 (s, 3H, CH₃) and 1.8 (s, 3H, CH₃). ¹³C-NMR spectrum of **3a** showed signals at $\delta = 20.75$, 21.05 (2CH₃) and 10 signals in the region 106.6-145.1 (10 carbons for aromatic and sultam ring) and 164.38 (CO). ¹H-NMR spectrum of **3b** showed $\delta = 7.6-7.8$ (m, 4H, aromatic protons), 6.8 (s, 1H, C-1, sultam proton), 5.8 (s, 1H, C-3, sultam proton), 2.1 (s, 3H CH₃) and 1.8 (s, 3H CH₃). ¹H-NMR spectrum of **4** showed $\delta = 7.8-7.5$ (m, 4H, aromatic protons), 6.8 (s, 1H, sultam), 4.6 (s, 1H, C-1, sultam), 2.0 (s, 3H, CH₃) and 1.8 (s, 3H, CH₃).

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Condensation of **3a** with benzaldehyde, salicylaldehyde or 4-anisaldehyde afforded the corresponding arylidene carboxyhydrazides **5a-c**, respectively. The target 1,3,4-oxadiazole derivatives **6a-c** were obtained via acetylation and concomitant cyclization of the arylidene carboxyhydrazides **5a-c** using acetic anhydride. Infrared spectra of **5a-c** showed $\nu_{(-SO_2-N-in\ sultam)}$ at 1290-1260 cm^{-1} , $\nu_{C=O}$ at 1710-1630 cm^{-1} , ν_{NH} at 3300-3030 cm^{-1} and ν_{OH} at 3370 cm^{-1} . ^1H-NMR spectrum of **5a** showed $\delta = 12$ (s, 1H, NH), 8.5 (s, 1H, N=CH), 8.0-7.5 (m, 9H, aromatic), 6.7 (s, 1H, C-1, sultam), 5.9 (s, 1H, C-3, sultam), 2.1 (s, 3H, CH₃) and 1.7 (s, 3H, CH₃). ^1H-NMR spectrum of **5b** revealed $\delta = 11.2$ (s, 1H, NH), 8.5 (s, 1H, N=CH), 7.5-6.7 (m, 8H, aromatic), 6.7 (s, 1H, C-1, sultam), 5.8 (s, 1H, C-3, sultam), 2.0 (s, 3H, CH₃) and 1.8 (s, 3H, CH₃). ^1H-NMR spectrum of **5c** showed $\delta = 8.2-7.8$ (m, 9H, aromatic and N=CH protons), 6.8 (s, 1H, C-1, sultam), 6.0 (s, 1H, C-3, sultam), 4.1 (s, 3H, OCH₃), 2.4 (s, 3H, CH₃), 2.0 (s, 3H, CH₃). The mass fragmentation pattern of **2** and **5c** exhibited molecular ion peaks at m/z at 229 and 347, respectively, in addition to the peaks at m/z 262 [$C_{13}H_{12}NO_3S$]⁺, 198 [$C_{13}H_{12}NO$]⁺ and 170 [$C_{12}H_{12}N$]⁺ (Chart 1,2). The infrared spectra of **6a-c** showed absorption bands in the region 1290-1270 cm^{-1} (-SO₂-N-, sultam). ^1H-NMR spectrum of **6a** showed $\delta = 8-7.5$ (m, 9H, aromatic protons), 7.25 (s, 1H, C-H, proton), 6.6 (s, 1H, C-1, sultam), 5.9 (s, 1H, C-3, sultam), 2.3 (s, 3H, COCH₃), 2.1 (s, 3H, CH₃) and 1.9 (s, 3H, CH₃). ^1H-NMR spectrum of **6b** showed $\delta = 8-7.3$ (m, 10H, aromatic, C-H and -OH protons), 6.9 (s, 1H, C-3, sultam), 6.7 (s, 1H, C-1, sultam), 2.3 (s, 3H, CO.CH₃), 2.0 (s, 3H, CH₃) and 1.8 (s, 3H, CH₃).

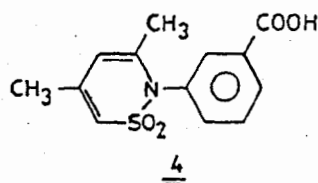
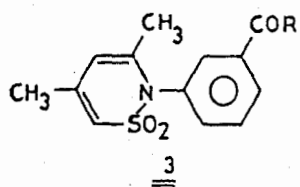
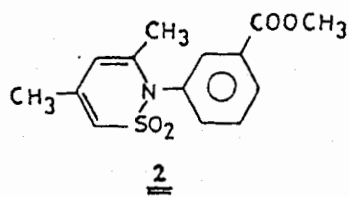
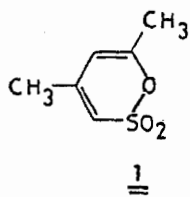
N-[3-Hydrazinocarboxyphenyl]-2,4-dimethyl-1,3-butadiene-1,4-sultam **3a** re-acted with phenylisocyanate, p-tolylisocyanate, phenylisothiocyanate or allyliso-thiocyanate to give the corresponding semi-carbazide derivatives **7a-d**, respectively.

Infrared spectra of **7a-d** showed $\gamma_{(-SO_2-N-in\ sultam)}$ at 1290-1275 cm^{-1} , $\gamma_{C=O}$ at 1690-1610 cm^{-1} , γ_{NH} at 3325-3150 cm^{-1} and $\gamma_{C=S}$ at 1560-1510 cm^{-1} . 1H -NMR spectrum of **7c** showed $\delta = 10.8$ (s, 2H, 2NH), 9.8 (s, 1H, NH), 7.9-7.2 (m, 9H, aromatic protons), 6.8 (s, 1H, C-1, sultam), 5.8 (s, 1H, C-3, sultam proton), 2.2 (s, 3H, CH_3) and 1.8 (s, 3H, CH_3).

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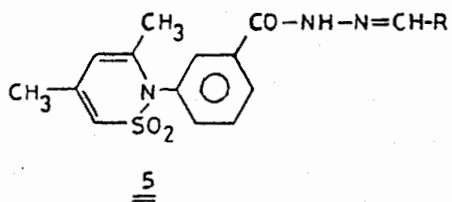
Table 1 Characterization Data of the Synthesized Compounds

Comp. No.	Mol. Formula	M.p. °C	Yield %	Analysis (Calc./Found) %		
				C%	H%	N%
2	C ₁₄ H ₁₅ NO ₄ S (293)	116-117	53	57.33	5.11	4.77
				57.93	4.83	5.06
3a	C ₁₃ H ₁₅ N ₃ O ₃ S (293)	139-140	89	53.24	5.11	14.33
				53.75	5.13	14.40
3b	C ₁₃ H ₁₄ N ₂ O ₃ S (278)	160-161	43	56.11	5.03	10.07
				55.99	4.73	9.97
4	C ₁₃ H ₁₃ NO ₄ S (279)	192-193	79	55.91	4.65	5.01
				55.32	4.56	4.47
5a	C ₂₀ H ₁₉ N ₃ O ₃ S (381)	115-116	73	62.99	4.98	11.02
				63.20	5.44	11.18
5b	C ₂₀ H ₁₉ N ₃ O ₄ S (397)	188-189	87	60-45	4.78	10.57
				60-55	5.02	10.21
5c	C ₂₁ H ₂₁ N ₃ O ₄ S (411)	109-111	76	61.31	5.10	10.21
				60.93	4.91	9.78
6a	C ₂₂ H ₂₁ N ₃ O ₄ S (423)	142-143	53	62.41	4.96	9.92
				62.08	4.94	9.30
6b	C ₂₂ H ₂₁ N ₃ O ₅ S (439)	162-163	51	60.13	4.78	9.56
				59.53	4.65	9.83
6c	C ₂₃ H ₂₃ N ₃ O ₅ S (453)	174-176	40	60.92	5.07	9.27
				60.83	4.65	9.10
7a	C ₂₀ H ₂₀ N ₄ O ₄ S (412)	185-6	70	58.25	4.85	13.59
				57.88	5.38	13.01
7b	C ₂₁ H ₂₂ N ₄ O ₄ S (426)	212-213	81	59.15	5.16	13.14
				59.34	5.63	13.49
7c	C ₂₀ H ₂₀ N ₄ O ₃ S ₂ (428)	146-48	68	56.07	4.85	13.08
				56.81	5.23	12.89
7d	C ₁₇ H ₂₀ N ₄ O ₃ S ₂ (392)	103-104	59	52.04	5.10	14.28
				51.93	4.99	14.52

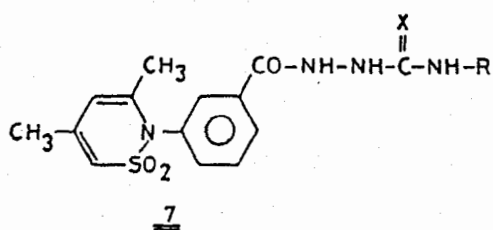
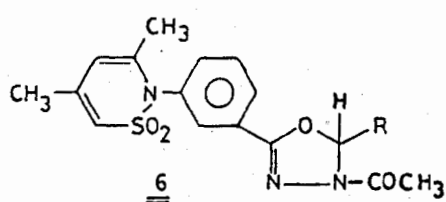


3a, R = -NH-NH₂

3b, R = -NH₂

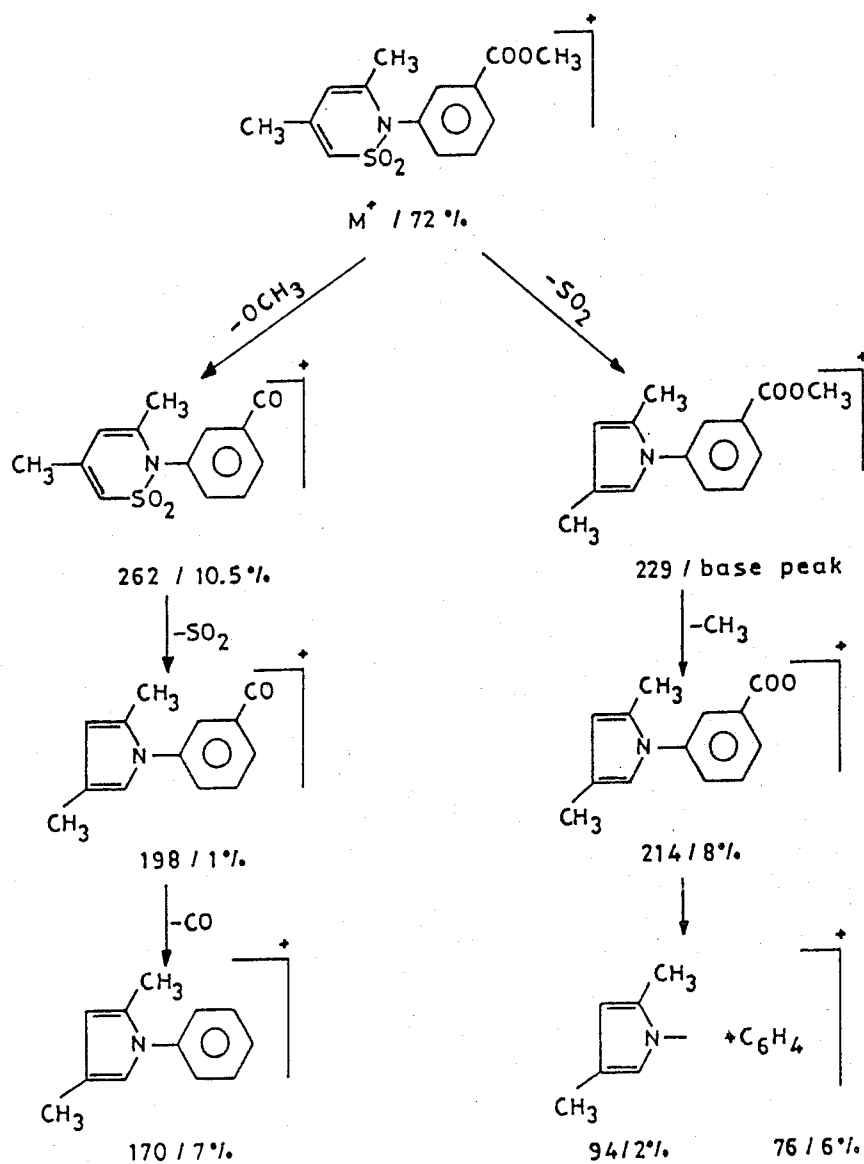


5, 6	R
a,	C ₆ H ₅
b,	2-OHC ₆ H ₄
c,	4-CH ₃ OC ₆ H ₄

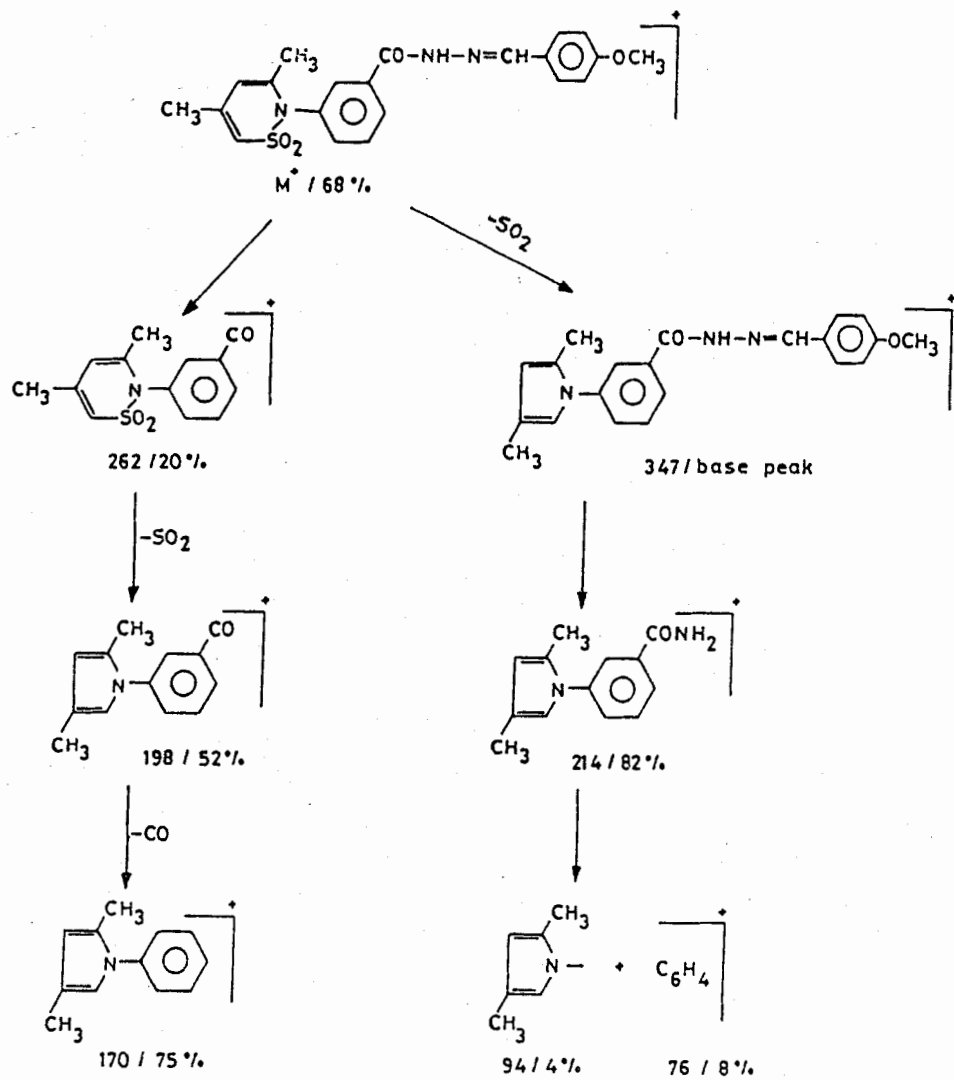


7	R	X
a,	C ₆ H ₅	O
b,	4-CH ₃ C ₆ H ₄	O
c,	C ₆ H ₅	S
d,	CH ₂ -CH=CH ₂	S

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(Chart -1)



(Chart -2)

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EXPERIMENTAL

All melting points are uncorrected. The IR-spectra were measured on Perkin-Elmer spectrophotometer 297 using KBr water technique, analysis, $^1\text{H-NMR}$ and mass spectra were carried out by the Micro-Analytical Unit, Cairo University.

Reaction of 1 with 3-aminomethylbenzoate: Formation of 2.

A mixture of 2,4-dimethyl-1,3-butadiene-1,4-sultone (0.01 mol) and 3-amino-methylbenzoate (0.01 mol) in a test tube was heated in an oil bath, so that the temperature increases gradually. At 130°C the reaction began spontaneously with evolution of water vapours. The bath temperature was kept at 130°C for 1 h and then elevated to 150°C till evolution of water vapours ceased. The reaction mixture was cooled and the produced mass was treated with dilute hydrochloric acid. The solid formed was filtered off, washed with water and crystallized from methanol (Table 1).

Reaction of 2 with hydrazine hydrate: Formation of 3a.

To a solution of sultam 2 (0.01 mol) in 20 ml ethanol, hydrazine hydrate (0.015 mol) was added. The reaction mixture was refluxed for 6 h. After cooling, the solid formed was filtered off and crystallized from ethanol (Table 1).

Reaction of 2 with aqueous ammonia: Formation of 3b.

The sultam 2 (0.01 mol) was added to aqueous ammonia (20 ml), at room temperature. The reaction mixture was stirred overnight. The

precipitate was filtered off, washed several times with water and crystallized from ethanol (Table 1).

Hydrolysis of 2: Formation of 4.

To a solution of sodium methoxide (0.02 mol of Na metal in 20 ml methanol), **2** (0.01 mol) was added. The mixture was refluxed for 2 h, on cooling and acidification with HCl, the solid formed was filtered off, washed with water and crystallized from ethanol (Table 1).

Reaction of 3a with Aldehydes: Formation of carboxyhydrazide derivatives 5a-c.

To a solution of **3a** (0.01 mol) in 20 ml ethanol, the requisite aldehyde (0.01 mol) was added. The reaction mixture was refluxed for 4 h. After cooling, the solid formed was filtered off and crystallized from ethanol (Table 1).

Formation of 1,3,4-oxadiazole derivatives 6a-c.

Carboxyhydrazides **5a-c** (0.01 mol) were suspended in 10 ml acetic anhydride and the mixture was refluxed for 3 h. The acetic acid and the unreacted acetic anhydride were evaporated under vacuum and the residue was recrystallized from methanol (Table 1).

Reaction of 3a with Isocyanates or Isothiocyanates: Formation of semicarbazide derivatives 7a-d.

To a solution of **3a** (0.01 mol) in 30 ml of dry benzene, the appropriate isocyanate or isothiocyanate (2 ml) was added dropwise. The reaction

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mixture was refluxed for 2 h. After cooling, the solid obtained was filtered off and crystallized from ethanol (Table 1).

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تفاعلات مع السالتون - تخليق مشتقات ٤،٣،١-أكساديازوليل سالتام

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ملخص البحث :

الهدف من هذا البحث هو تخليق بعض المركبات الجديدة التى تحتوى على حلقة السالتام والمتوقع لها تأثير بيولوجى . يتفاعل ٤،٢-ثنائى ميثيل-٣،١-بيوتادين-٤،١-سالتون مع ٢-أمينو ميثيل-بنزوات ويعطى إستر السالتام المقابل ، ويتفاعل الأخير مع الهيدرازين أو الأمونيا يعطى الهيدرازيد أو الأמיד المقابل . التحلل المائى لإستر السالتام بإستخدام محلول من ميثوكسيد الصوديوم ينتج الحمض المقابل . عند تفاعل الهيدرازيد مع البنزالدهيد والسالسالدهيد والأنيزلدهيد تتكون مشتقات الكربوكسى هيدرازيدات الأريلدين المقابلة التى تتحولق بالغليان مع أنهيدريد حمض الخليك لتعطى مشتقات ٤،٣،١-أكساديازول المقابلة التى تحتوى على مجموعة الأستيل . وعند تفاعل الهيدرازيد مع فنيل ، أو باراتوليل أيزوسيانات أو فنيل أيزوسيانات أو أليل أيزوثيوسيانات تكون مشتقات السميكر بازيدات المقابلة . وقد تم إثبات التركيب الكيمائى للمركبات المتكونة بالتحليل الدقيق وطيف الأشعة تحت الحمراء والرنين النووى المغناطيسى والرنين النووى المغناطيسى للكربون-١٣ وطيف الكتلة لبعض المركبات .