Synthesis of 3-Arylsulfonylmethyl-1,2,4-oxadiazole-5-carboxylic Acid Derivatives

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Several new 3-arylsulfonylmethyl-1,2,4-oxadiazole-5-carboxylic acid derivatives have been synthesized. A typical example, 3-[(4-chlorophenylsulfonyl)methyl]-1,2,4-oxadiazole-5-carboxylic acid ethyl ester (**2c**), was prepared from the reaction of 2-(4-chlorophenylsulfonyl)acetamide oxime (**1c**) with ethyl oxalyl chloride. The hydrazide derivative (**3f**) showed antihypertensive activity in rats. Various structural modifications to improve activity are discussed.

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Previously, we reported the synthesis of 1,2,4-oxadiazines *via* the reaction of variously substituted acetamide oximes with dimethyl acetylenedicarboxylate (1). During the course of that investigation we had occasion to prepare several arylsulfonylacetamide oximes and to study the products of ring closure with a variety of reagents. The present study deals with the reactions of these amide oximes with ethyl oxalyl chloride to form previously unreported 3-arylsulfonylmethyl-1,2,4-oxadiazole-5-carboxylic acid derivatives. Although several papers have appeared in the literature dealing with the synthesis of 3-aryl-1,2,4-oxadiazole-5-carboxylic acid derivatives (2,3), non specifically describes those that have an arylsulfonylmethyl group at the 3-position of the oxadiazole ring. Some of these novel 1,2,4-oxadiazole derivatives have demonstrated antihypertensive activity in the spontaneous hypertensive rat model. For this reason, we were prompted to study the effect of structural modifications on biological activity and to report the chemistry herein.

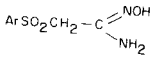
The required arylsulfonylacetamide oxime (**1a-d**) intermediates were prepared from the corresponding arylsulfonyl acetonitriles by reaction with hydroxylamine and are given in Table I. The reaction of these substituted acetamide oximes with ethyl oxalyl chloride gave the corresponding 3-arylsulfonylmethyl-1,2,4-oxadiazole-5-carboxylic acid esters **2a-d** (Table II). In one example, the acetamide oxime (**1d**) was heated under reflux in boiling ethyl oxalyl chloride without solvent. This resulted not only in oxadiazole formation, but also in replacement of the acetyl moiety with an ethyl oxalyl group, thus forming **2d**.

Several of these 1,2,4-oxadiazole-5-carboxylic acid esters when treated with nucleophilic reagents such as ammonia, various amines, hydroxylamine, or hydrazine afforded the corresponding amides, substituted amides, hydroxamic acids or hydrazides. These are shown in Scheme I and Table II.

The most biologically active of these derivatives, 3-[(4-chlorophenylsulfonyl)methyl]-1,2,4-oxadiazole-5-carboxylic acid hydrazide (**3f**), was further modified in an

Table I

Arylsulfonylacetamide Oximes



Compound	Ar	M.p., °C	Recrystallization Solvent	Formula	Analysis, % Calculated C	H	N	Found C	H	N
1a	C_6H_5 (a)	162	(b)							
1b	4-$CH_3C_6H_4$	202-205	Ethanol	$C_9H_{11}N_2O_3S$	47.36	5.30	12.27	47.34	5.27	12.07
1c	4-ClC_6H_4	220-223	Ethanol	$C_8H_9ClN_2O_3S$	38.65	3.65	11.27	38.53	3.65	11.28
1d	4-$CH_3\overset{O}{\overset{\|}{C}}NHC_6H_4$	207-210	Water	$C_{10}H_{13}N_3O_4S$	44.27	4.83	15.49	44.52	4.75	15.36

(a) F. T. Bruderlein, U.S. Patent 3,334,137 (1967), gives m.p. 165-168°. (b) Compound used without recrystallization.

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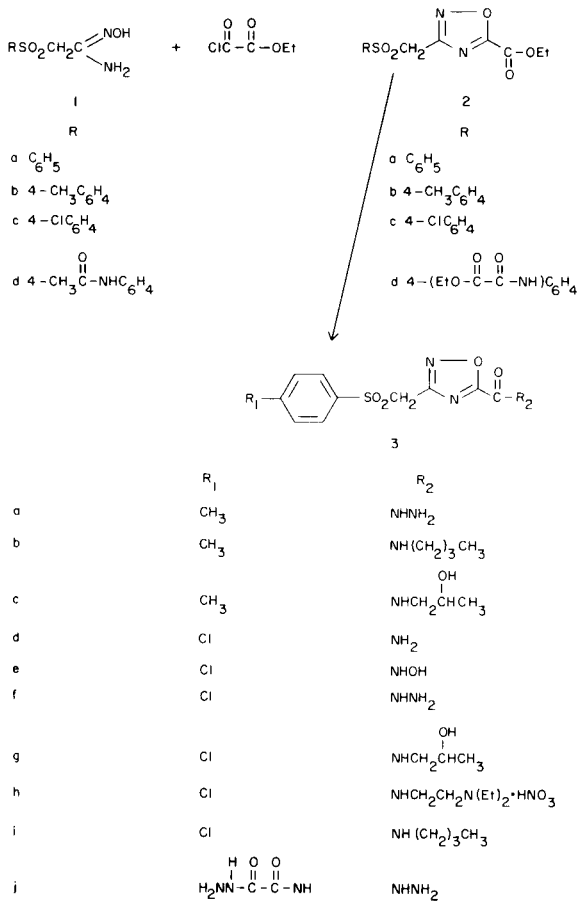
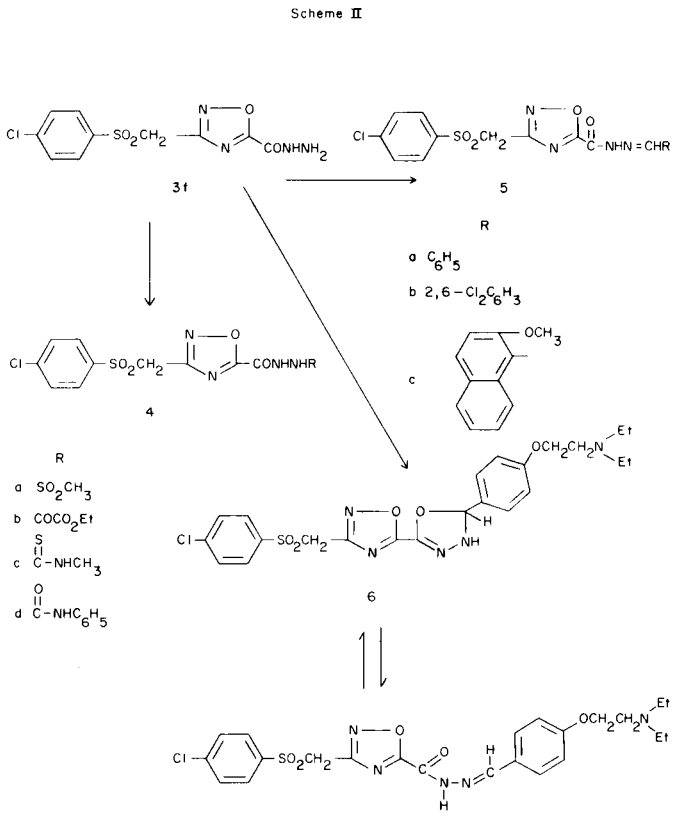
effort to arrive at a compound with a still more favorable profile. For example, the reaction of **3f** with methanesulfonyl chloride afforded the corresponding methanesulfonhydrazide **4a** (Scheme II). The ethyl oxamide derivative **4b** was made by allowing **3f** to react with ethyl oxalyl chloride. Treatment of **3f** with methyl isothiocyanate gave the methylthiocarbamoyl derivative **4c**, while reaction with phenylisocyanate gave the phenylcarbamoyl compound **4d**. Several Schiff base derivatives, **5a-c**, were produced when **3f** was allowed to react with variously substituted aromatic aldehydes. In one of these reactions, when 4-diethylaminoethoxybenzaldehyde was used, the resulting product failed to show a carbonyl absorption in its ir spectrum (potassium bromide). The ir in dimethyl sulfoxide solution, however, revealed the presence of a carbonyl band at 5.90 μ which intensified on standing. These data suggest that the dihydro-1,3,4-oxadiazole **6** is the predominant product in the solid state, while in solution the open-chain or Schiff base form, **7**, is the species that predominates. Examples **5a-c** all appear to exist in the Schiff base form.

None of the above structural modifications, however, was able to enhance the biological profile sufficiently to develop a candidate for clinical consideration.

Scheme I



Scheme II



EXPERIMENTAL

Melting points were determined in capillary tubes (Thomas-Hoover melting point apparatus) and are uncorrected. Ir spectra were obtained in potassium bromide disks using a Perkin-Elmer (Model 21) spectrophotometer.

(4-Chlorophenylsulfonyl)acetamide Oxime (**1c**).

To a solution of 50 g. (0.23 mole) of 4-chlorophenylsulfonylacetonitrile in 1.5 liters of ethanol was added a solution of 16 g. (0.23 mole) of hydroxylamine hydrochloride in 150 ml. of water, followed by the further addition of 14.4 g. (0.12 mole) of sodium carbonate in 150 ml. of water. The reaction mixture was stirred overnight at room temperature. The crude product amounted to 58 g. Recrystallization from ethanol gave 40 g. of product; ir: μ 2.90, 3.00 (NH), 5.93 (C=N), 7.67, 8.60 (SO_2).

3-[(4-Chlorophenylsulfonyl)methyl]-1,2,4-oxadiazole-5-carboxylic Acid Ethyl Ester (**2c**).

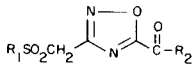
To a stirred solution of 10 g. (0.04 mole) of 4-chlorophenylsulfonyl acetamide in 500 ml. of tetrahydrofuran was added 5.48 g. (0.04 mole) of ethyl oxalyl chloride in 100 ml. of tetrahydrofuran. The reaction mixture was heated under reflux for 2.5 hours and the solvent was removed in a rotary evaporator. The product was collected on a filter and recrystallized from 95% ethanol to give 10 g. of white needles; ir: μ 5.74 (C=O), 7.70 (C-O), 7.55, 8.70 (SO_2).

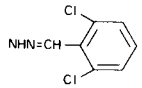
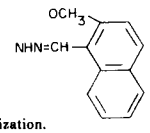
3-[[4-[(Ethoxyoxoacetyl)amino]phenylsulfonyl]methyl]-1,2,4-oxadiazole-5-carboxylic Acid Ethyl Ester (**2d**).

A mixture of 8 g. of *N*-[4-[2-amino-2-(hydroxyamino)ethylsulfonyl]-phenyl]acetamide (**1d**) in 10 ml. of ethyl oxalyl chloride was heated under reflux for 2 hours. After cooling the reaction mixture to room temperature, 25 ml. of ethanol was added and the mixture was heated on a steam bath for a few minutes. The precipitate thus formed amounted to 6.8 g., m.p. 196-204°. Recrystallization from DMF-water gave 3.5 g. of product, m.p. 204-206°; ir: μ 3.0 (NH), 5.8 (broad C=O's), 7.70 (C-O).

Table II

3-Arylsulfonylmethyl-1,2,4-oxadiazole-5-carboxylic Acid Derivatives



Compound No.	R_1	R_2	M.p., °C	Recrystallization Solvent	Formula	Analysis, % Calculated C	H	N	Found C	H	N
2a	C_6H_5	OEt	155-156	Ethanol	$C_{12}H_{12}N_2O_5S$	48.64	4.08	9.45	48.87	4.07	9.38
2b	4-$CH_3C_6H_4$	OEt	160-163	Ethyl Acetate	$C_{13}H_{14}N_2O_5S$	50.31	4.55	9.03	50.07	4.57	9.01
2c	4-ClC_6H_4	OEt	181-184 dec	95% Ethanol	$C_{12}H_{11}ClN_2O_5S$	43.57	3.35	8.47	43.55	3.10	8.48
2d	4-EtOC(=O)-C(=O)-NHC$_6$H$_4$	OEt	204-206	DMF-Water	$C_{16}H_{17}N_3O_6S$	46.71	4.16	10.21	47.03	4.36	10.23
3a	4-$CH_3C_6H_4$	$NHNH_2$	156-158	Ethanol	$C_{11}H_{12}N_2O_4S$	44.59	4.08	18.91	44.55	4.03	19.16
3b	4-$CH_3C_6H_4$	$NH(CH_2)_3CH_3$	76-78	Ethyl Acetate-Petroleum Ether	$C_{17}H_{23}N_3O_4S$	55.87	6.34	11.50	55.94	6.01	11.48
3c	4-$CH_3C_6H_4$	$NHCH_2CHCH_3$ (OH)	130-132	Ethanol	$C_{14}H_{17}N_3O_5S$	49.55	5.05	12.38	49.70	5.06	12.39
3d	4-ClC_6H_4 (a)	NH_2	174-177 dec		$C_{10}H_8Cl_2N_4O_4S$	39.81	2.67	13.93	39.61	2.70	14.03
3e	4-ClC_6H_4 (a)	NHOH	160 dec		$C_{10}H_8ClN_3O_5S$	37.80	2.54	13.23	37.97	2.41	13.42
3f	4-ClC_6H_4	$NHNH_2$	177	Ethanol	$C_{10}H_9ClN_4O_4S$	37.92	2.86	17.69	37.92	2.85	17.96
3g	4-ClC_6H_4 (a)	$NHCH_2CHCH_3$ (OH)	119-122		$C_{13}H_{14}ClN_3O_5S$	43.40	3.92	11.68	43.38	3.95	11.55
3h	4-ClC_6H_4	$NHCH_2CH_2N(Et)_2$	152-153 dec	Ethanol	$C_{16}H_{23}ClN_5O_7S$	41.42	4.78	15.10	41.03	4.56	15.06
3i	4-ClC_6H_4	$NH(CH_2)_5CH_3$	109-111	Petroleum Ether-Ether	$C_{16}H_{20}ClN_3O_4S$	49.80	5.23	10.89	49.66	4.92	10.92
3j	4-(H_2NN-C(=O)-C(=O)-NH)-C_6H_4	$NHNH_2$	253-255	DMF-Ethanol	$C_{12}H_{13}N_7O_6S$	37.60	3.42	25.58	37.91	3.64	25.77
4a	4-ClC_6H_4	$NHNHSO_2CH_3$	198-202	Acetonitrile	$C_{11}H_{11}ClN_4O_6S_2$	33.46	2.81	14.19	33.88	3.03	14.64
4b	4-ClC_6H_4	NHNHC(=O)CO_2Et	161-164	Ethanol	$C_{14}H_{13}ClN_4O_7S$	40.34	3.14	13.44	40.37	2.99	13.53
4c	4-ClC_6H_4	NHNH-C(=S)-NHCH$_3$	195-197	Acetonitrile	$C_{12}H_{12}ClN_5S_2O_4$	36.97	3.10	17.97	37.03	3.06	18.00
4d	4-ClC_6H_4 (a)	NHNH-C(=O)-NHC$_6$H$_5$	210-213		$C_{17}H_{14}ClN_5SO_5$	46.85	3.24	16.07	46.39	2.93	15.85
5a	4-ClC_6H_4	NHN=CHC$_6$H$_5$	189-192	Ethanol	$C_{17}H_{13}ClN_4O_4S$	50.44	3.24	13.84	50.55	3.13	13.80
5b	4-ClC_6H_4 (a)		209-210		$C_{17}H_{11}Cl_3N_4O_4S$	43.10	2.34	11.83	43.03	2.23	11.94
5c	4-ClC_6H_4 (a)		179-182		$C_{22}H_{17}ClN_4O_5S$	54.49	3.54	11.56	54.43	3.35	11.57

(a) Analysis performed without recrystallization.

3-[(4-Chlorophenylsulfonyl)methyl]-1,2,4-oxadiazole-5-carboxamide (**3d**).

To 150 ml. of saturated ethanolic ammonia solution was added 5 g. of **2c**. The reaction mixture was stirred at room temperature for 3 days. The precipitate which formed amounted to 3.8 g. and was analytically pure; ir: μ 2.93, 3.03 (NH), 5.80 (C=O), 7.63, 8.65 (SO_2).

3-[(4-Chlorophenylsulfonyl)methyl]-*N*-hydroxy-1,2,4-oxadiazole-5-carboxamide (**3e**).

To 3.0 g. (0.009 mole) of **2c** in 550 ml. of methanol, was added a methanolic solution of hydroxylamine, prepared by adding 0.66 g. (0.017 mole) of sodium hydroxide to 1.26 g. (0.018 mole) of hydroxylamine hydrochloride in 150 ml. of methanol. The reaction mixture was stirred at room temperature for 4 days. The solvent was removed in a rotary evaporator and the residue was recrystallized several times from water to give 1.3 g. of product, m.p. 160° dec; ir: μ 2.85, 3.00 (OH and NH), 5.85 (C=O), 7.60, 8.65 (SO_2).

3-[(4-Chlorophenylsulfonyl)methyl]-*N*-[2-(diethylamino)ethyl]-1,2,4-oxadiazole-5-carboxamide Nitrate (**3h**).

A solution containing 3 g. (0.009 mole) of **2c** and 1.05 g. (0.009 mole) of 2-diethylaminoethylamine in 250 ml. of ethanol was heated under reflux for 3 hours. The solvent was removed in a rotary evaporator, leaving a viscous oil. To this was added a few drops of conc. nitric acid. The solid product which formed was recrystallized from ethanol to give 3.65 g. of product, m.p. 152-153° dec; ir: μ 2.99 (NH), 5.92 (C=O), 7.24 (NO_3^-), 7.50, 8.60 (SO_2).

3[(4-Chlorophenylsulfonyl)methyl]-1,2,4-oxadiazole-5-carboxylic Acid Hydrazide (**3f**).

To an ice-cooled suspension of 10 g. (0.03 mole) of **2c** in 250 ml. of ethanol was added slowly 5 ml. of 95% hydrazine (0.15 mole). The reaction mixture was stirred in an ice bath for 5 hours and then overnight at room temperature. The product was removed by filtration and recrystallized from ethanol to afford 8 g. of product, m.p. 177°; ir: μ 3.05, 3.17, 3.25 ($NHNH_2$), 5.87 (C=O), 7.5, 8.63 (SO_2).

3-[(4-Chlorophenylsulfonyl)methyl]-1,2,4-oxadiazole-5-carboxylic Acid 2-(Methylsulfonylhydrazide) (**4a**).

To a solution of 5.0 g. (0.016 mole) of **3f** in 75 ml. of pyridine was added cautiously 1.8 g. (0.016 mole) of methane sulfonyl chloride. The reaction mixture was stirred at room temperature for 3.5 hours and then poured into 1000 ml. of water. The aqueous mixture was neutralized with concentrated hydrochloric acid and chilled in ice. The resulting precipitate was collected and recrystallized from acetonitrile to give 1.2 g. of product, m.p. 198-202°; ir: μ 3.10 (NH), 5.77 (C=O), 7.55, 8.65 (SO_2).

Ethanedioic Acid Ethyl Ester 2-[[[3-(4-Chlorophenylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl]carbonyl]hydrazide (**4b**).

To a solution of 4.0 g. (0.013 mole) of **3f** in 100 ml. of tetrahydrofuran was added 1.72 g. (0.013 mole) of ethyl oxalyl chloride in 25 ml. of tetrahydrofuran. The reaction mixture was heated under reflux for 1 hour. The solvent was removed in a rotary evaporator. The residue was triturated with a few ml. of chloroform and petroleum ether and the solid thus formed was recrystallized from ethanol to give 3.5 g. of product, m.p. 161-164°; ir: μ 3.15 (broad NH), 5.66 (ester C=O), 6.02 (hydrazide C=O's), 7.55, 8.63 (SO_2).

3-[(4-Chlorophenylsulfonyl)methyl]-1,2,4-oxadiazole-5-carboxylic Acid 2-[(Methylamino)thioxomethyl]hydrazide (**4c**).

To a solution of 4 g. (0.013 mole) of **3f** in 150 ml. of ethanol was added 1.0 g. (0.014 mole) of methylisothiocyanate. The reaction mixture was heated under reflux for 5 hours, concentrated in a rotary evaporator, and chilled in ice to yield a white solid. This precipitate was recrystallized from acetonitrile and then from ethanol to give 1.1 g. of product, m.p. 195-197°; ir: μ 3.05, 3.13 (NH), 5.80 (C=O), 7.55, 8.55 (SO_2).

3-[(4-Chlorophenylsulfonyl)methyl]-1,2,4-oxadiazole-5-carboxylic Acid 2-[(Phenylamino)carbonyl]hydrazide (**4d**).

To a solution of 4 g. (0.013 mole) of **3f** in 150 ml. of ethanol was added 1.6 g. (0.014 mole) of phenylisocyanate. Within 15 minutes a solid precipitated out of the solution. The reaction mixture was then heated under reflux for 5 hours and the solid was collected and rinsed with ethanol to afford 2.1 g. of product, m.p. 210-213°; ir: μ 3.09 (NH), 5.93 (hydrazide C=O's), 7.56, 8.71 (SO_2).

3-[(4-Chlorophenylsulfonyl)methyl]1,2,4-oxadiazole-5-carboxylic Acid 2-(Phenylmethylene)hydrazide (**5a**).

To a solution of 1.5 g. (0.0047 mole) of **3f** in 100 ml. of methanol was added 0.5 g. (0.0047 mole) of benzaldehyde. The reaction mixture was heated under reflux for 1 hour and then chilled in ice. The solid which resulted was cooled and recrystallized from ethanol to give 1.0 g. of product, m.p. 189-192°; ir: μ 2.94 (NH), 5.90 (C=O), 7.55, 8.63 (SO_2).

2-[4-[5-[3-[(4-Chlorophenylsulfonyl)methyl]-1,2,4-oxadiazol-5-yl]-2,3-dihydro-1,3,4-oxadiazol-2-yl]phenoxy]-*N,N*-diethylethanamine (**6**).

To a solution of 2.0 g. (0.006 mole) of **3f** in 150 ml. of methanol was added 1.4 g. (0.006 mole) of 4-diethylaminoethoxybenzaldehyde. The reaction mixture was heated under reflux for 1 hour and then chilled. The precipitate was collected and recrystallized from methanol to give 2.3 g. of product, m.p. 131-134° dec; ir: 7.65, 8.55 (SO_2); ir (DMSO): 5.90 (C=O).

Acknowledgment.

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(2) See for example the following references: (a) G. Palazzo and G. Strani, *Gazz. Chim. Ital.*, **90**, 1290 (1960); (b) G. Strani and A. M. Garau, *ibid.*, **93**, 482 (1963); (c) F. Tiemann, *Ber.*, **22**, 3124 (1889); (d) A. Wurm, *ibid.*, **22**, 3130 (1889).

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