Synthesis and Some Reactions of Naphth[1,2-*d*]oxazole-5-sulfonic Acids

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Naphth[1,2-*d*]oxazole-5-sulfonic acid (**1**) has been prepared by the fusion of 4-amino-3-hydroxynaphthalene-1-sulfonic acid with formamide. Interaction of **1** with a number of arenesulfonyl chlorides, aryloxyacetyl chlorides, 1-naphthyloxyacetyl chloride, and chloroacetyl chloride gave 2-(arylsulfonyl)-, 2-(aryloxyacetyl)-, 2-(1-naphthyloxyacetyl)- and 2-(chloroacetyl)naphth[1,2-*d*]oxazole-5-sulfonic acids (**2**, **3**, **4** and **5**), respectively. The corresponding sulfonyl chloride of **2** was condensed with amines giving the expected 2-(arylsulfonyl)-naphth[1,2-*d*]oxazole-5-sulfonamides (**6**). Interaction of **5** with hydrazine gave 2-hydrazinoacetyl and disubstituted hydrazine derivatives **7** and **8**. Condensation of **7** with aromatic aldehydes yielded substituted hydrazonoacetyl derivatives **9**. Two moles of **5** react with one mole of hydroquinone in dry acetone in the presence of anhydrous potassium carbonate and potassium iodide gave 1,4-bis[5-sulfonaphth[1,2-*d*]oxazol-2-ylcarbonylmethoxy]benzene (**10**).

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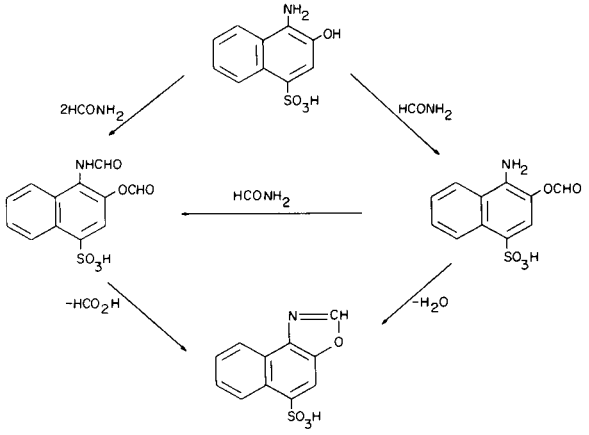
Napththoxazoles, being condensed oxazoles, are of considerable importance in the fields of dyestuffs, photosensitizers, optical brightners and for biological assays (1-3). Moreover, the importance of sulfones, phenoxyacetic acids and sulfonamides in medicine is known (4). The present investigation is a continuation of our previous work (5,6) on the synthesis of condensed oxazoles and an attempt to synthesize the parent naphth[1,2-*d*]oxazole-5-sulfonic acid and its different derivatives. Thus, the parent compound was synthesized by fusion of 4-amino-3-hydroxynaphthalene-1-sulfonic acid with formamide. The reaction scheme may be represented as follows:



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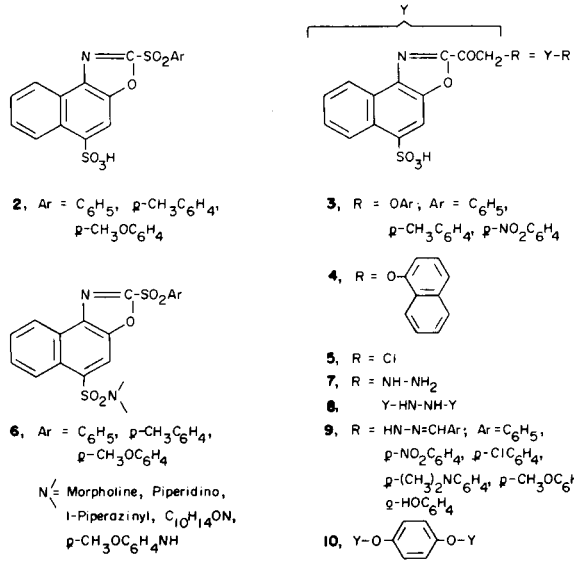
The structure of **1** was confirmed by analytical and spectroscopic data. The ir spectrum showed absorption bands at 1590, 1220 and 1200 cm^{-1} attributable to the oxazole ring structure and 1210-1150 cm^{-1} for the sulfo group (7).

With respect to the fragmentation pattern of 2*H*-naphth[1,2-*d*]oxazole-5-sulfonic acid (**1**), the molecular ion is not indicated in the spectrum probably due to desulfonation of this product prior to electron impact (8). The molecular ion loses SO_3 to give an ion of m/e 169 (100%) which represents the base peak. This ion loses CO (9) followed by ring expansion then elimination of HCN (10) to give an ion of m/e 114 (27.5%).

The proton of oxazoles is quite active (6) and this is shown by the coupling reaction of 5*H*-oxazolo[4,5-*b*]-phenoxazine with benzene diazonium chloride in neutral medium. The resulting azo dye was found to lack the oxazole proton as indicated by the nmr spectrum. Consequently, the parent naphth[1,2-*d*]oxazole-5-sulfonic acid was allowed to interact with a number of arenesulfonyl chlorides, aryloxyacetyl chlorides, 1-naphthyloxyacetyl chloride and chloroacetyl chloride to give 2-(arylsulfonyl)-(**2**), 2-(aryloxyacetyl)- (**3**), 2-(1-naphthyloxyacetyl)- (**4**), and 2-(chloroacetyl)naphth[1,2-*d*]oxazole-5-sulfonic acids (**5**).



2-(Arylsulfonyl)naphth[1,2-*d*]oxazole-5-sulfonic acids (**2**) were converted to the corresponding sulfonyl chlorides

Table I

2-(Arylsulfonyl)naphth[1,2-*d*]oxazole-5-sulfonic Acids (**2**)

Compound No.	Ar	Mp °C	Molecular Formula	Analysis % (Calcd./Found) C	H	N	S
2a	C_6H_5	192	$C_{17}H_{11}NO_6S_2$	52.44	2.82	3.59	16.45
				52.60	3.01	3.61	16.46
2b	*p*-$CH_3C_6H_4$	172	$C_{18}H_{13}NO_6S_2$	53.59	3.22	3.47	15.88
				53.79	3.49	3.45	15.85
2c	*p*-$CH_3OC_6H_4$	142	$C_{18}H_{13}NO_7S_2$	51.55	3.10	3.34	15.27
				51.80	3.33	3.39	15.29

Table II

2-(Aryloxyacetyl)naphth[1,2-*d*]oxazole-5-sulfonic Acids (**3**)

Compound No.	Ar	Mp °C	Yield %	Molecular Formula	Analysis % (Calcd./Found) C	H	N	S
3a	C_6H_5	180	72	$C_{19}H_{13}NO_6S$	59.53	3.39	3.65	8.35
					59.43	3.55	3.62	8.20
3b	*p*-$CH_3C_6H_4$	188	75	$C_{20}H_{15}NO_6S$	60.45	3.77	3.52	8.06
					60.22	3.58	3.47	8.00
3c	*p*-$NO_2C_6H_4$	122	80	$C_{19}H_{12}N_2O_8S$	53.27	2.80	6.54	7.47
					53.13	3.00	6.57	7.50

Table III

2-(Arylsulfonyl)naphth[1,2-*d*]oxazole-5-sulfonamides (**6**)

Ar	N<	Mp °C	Yield %	Molecular Formula	Analysis % (Calcd./Found) C	H	N	S
C_6H_5	Morpholino	166	85	$C_{21}H_{18}N_2O_6S_2$	55.02	3.93	6.11	13.97
					55.15	4.01	6.09	13.95
C_6H_5	Piperidino	154	75	$C_{22}H_{20}N_2O_5S_2$	57.89	4.38	6.14	14.03
					57.77	4.30	6.12	14.05
C_6H_5	1-Piperazinyl	320	72	$C_{21}H_{19}N_3O_5S_2$	55.14	4.15	9.19	14.00
					55.25	4.17	9.14	14.03
C_6H_5	$C_{10}H_{14}ON$ (a)	214	70	$C_{27}H_{24}N_2O_6S_2$	60.44	4.47	5.22	11.94
					60.34	4.51	5.17	11.89
C_6H_5	*p*-$CH_3OC_6H_4NH$	174	80	$C_{24}H_{18}N_2O_6S_2$	58.29	3.64	5.66	12.95
					58.31	3.72	5.69	12.92
p-$CH_3C_6H_4$	Morpholino	160	80	$C_{22}H_{20}N_2O_6S_2$	55.93	4.23	5.93	13.55
					56.05	4.32	5.91	13.59
p-$CH_3C_6H_4$	Piperidino	196	68	$C_{23}H_{22}N_2O_5S_2$	58.72	4.68	5.95	13.61
					58.70	4.65	5.95	13.62
p-$CH_3C_6H_4$	1-Piperazinyl	290	82	$C_{22}H_{21}N_3O_5S_2$	56.05	4.45	8.91	13.58
					56.04	4.50	8.89	13.60
p-$CH_3C_6H_4$	$C_{10}H_{14}ON$ (a)	212	70	$C_{28}H_{26}N_2O_6S_2$	61.09	4.72	5.09	11.63
					60.88	4.59	5.05	11.61
p-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4NH$	180	85	$C_{25}H_{20}N_2O_6S_2$	59.05	3.93	5.51	12.59
					59.00	4.01	5.49	12.56
p-$CH_3OC_6H_4$	Morpholino	174	79	$C_{22}H_{20}N_2O_7S_2$	54.09	4.09	5.73	13.11
					53.90	4.15	5.70	13.08
p-$CH_3OC_6H_4$	Piperidino	208	73	$C_{23}H_{22}N_2O_6S_2$	56.79	4.52	5.76	13.16
					56.73	4.55	5.75	13.19
p-$CH_3OC_6H_4$	1-Piperazinyl	280	75	$C_{22}H_{21}N_3O_6S_2$	54.20	4.31	8.62	13.14
					54.10	4.23	8.63	13.10
p-$CH_3OC_6H_4$	$C_{10}H_{14}ON$ (a)	138	70	$C_{28}H_{26}N_2O_7S_2$	59.36	4.59	4.94	11.30
					59.33	4.61	4.92	11.26
p-$CH_3OC_6H_4$	*p*-$CH_3OC_6H_4NH$	192	78	$C_{25}H_{20}N_2O_7S_2$	57.25	3.81	5.34	12.21
					57.24	3.81	5.40	12.18

(a) $C_6H_5CH(OH)CH(CH_3)N(CH_3)$—

Table IV

Substituted 2-(Hydrazonoacetyl)naphth[1,2-*d*]oxazole-5-sulfonic Acids (**9**)

Ar	Mp °C	Yield %	Molecular Formula	Analysis % (Calcd./Found) C	H	N	S
C_6H_5	140	80	$C_{20}H_{15}N_3O_5S$	58.67	3.66	10.26	7.82
				58.80	3.73	10.28	7.85
p-$NO_2C_6H_4$	230	92	$C_{20}H_{14}N_4O_7S$	52.86	3.08	12.33	7.04
				52.67	2.91	12.30	7.02
p-ClC_6H_4	168	90	$C_{20}H_{14}ClN_3O_5S$	54.11	3.15	9.47	7.21
				54.23	3.01	9.51	7.23
p-$(CH_3)_2NC_6H_4$	266	85	$C_{22}H_{20}N_4O_5S$	58.40	4.42	12.38	7.07
				58.41	4.50	12.42	7.10
p-$CH_3OC_6H_4$	162	79	$C_{21}H_{17}N_3O_6S$	57.40	3.87	9.56	7.28
				57.38	3.90	9.56	7.30
o-HOC_6H_4	182	82	$C_{20}H_{15}N_3O_6S$	56.47	3.52	9.88	7.52
				56.52	3.63	9.85	7.50

with thionyl chloride which in turn condensed with some amines namely, morpholine, piperidine, piperazine, ephedrine and *p*-anisidine in dry benzene giving 2-(arylsulfonyl)naphth[1,2-*d*]oxazole-5-sulfonamides (**6**).

The chemical structure of **2-6** was deduced from their analytical and spectral data. The ir spectra showed besides the foregoing absorption bands, a band at 1320-1340 cm^{-1} assignable to the sulfonyl group for compound **2**, bands at 1700-1680 cm^{-1} (C=O) for compounds **3-5** and 1280 cm^{-1} (phenolic C-O) for compounds **3** and **4** and a band at 1330-1420 cm^{-1} (SO_2N<) for compound **6**.

Interaction of **5** with hydrazine using equimolecular quantities of the two gave 2-(hydrazinoacetyl)naphth-[1,2-*d*]oxazole-5-sulfonic acid (**7**), but using two moles of **5** per mole of hydrazine gave 1,2-bis[5-sulfonaphth[1,2-*d*]-oxazol-2-yl carbonylmethyl]hydrazine (**8**). The structures of **7** and **8** were established on the basis of elemental analysis and spectral data. The ir spectra showed, besides the foregoing absorption bands, a band at 3408 and 3255 cm^{-1} for NH_2 and NH. Compound **7** reacted with various aromatic aldehydes to form substituted 2-(hydrazonoacetyl)naphth[1,2-*d*]oxazole-5-sulfonic acids (**9**) in good yield. The structure of **9** has been established from their correct analytical data and by the consideration of their ir spectra which showed absorption bands at 1700-1680 cm^{-1} (C=O) and 1640-1620 cm^{-1} (C=N).

Two moles of 2-(chloroacetyl)naphth[1,2-*d*]oxazole-5-sulfonic acid (**5**) reacted with one mole of hydroquinone in dry acetone in the presence of anhydrous potassium carbonate and potassium iodide gave 1,4-bis[5-sulfonaphth-[1,2-*d*]oxazol-2-ylcarbonylmethoxy]benzene (**10**).

The structure of **10** was established on the basis of elemental analysis and ir data which showed absorption bands at 1700-1670 cm^{-1} (C=O) and around 1280 cm^{-1} (phenolic C-O).

Antimicrobial Activities.

The antimicrobial activities of the prepared compounds against a variety of microbes were determined. These microorganisms include Gram-positive and Gram-negative bacteria. The bacteria used are *Bacillus subtilis, Staphylococcus aureus, Pseudomones aeruginosa* and *Escherichia coli*. Two different concentrations of each compound were prepared in ethylene glycol (1 mg/ml and 2 mg/ml) and tested by the paper disc technique (11).

The results showed that most of the prepared compounds have a remarkable activity towards the tested organisms. The best results were obtained with compounds **2, 3** and **6** against the mentioned strains of bacteria.

EXPERIMENTAL

All melting points are uncorrected and were obtained on a Kopfler melting point apparatus. Infrared spectra were recorded on a Pye-Unicam ir spectrophotometer SP 200 G. Mass spectrum was measured using an AEI MS 9 mass spectrometer at 70 eV. Sample was introducted through a heated inlet system.

Naphth[1,2-*d*]oxazole-5-sulfonic Acid (**1**) (5,6).

A mixture of 4-amino-3-hydroxynaphthalene-1-sulfonic acid (1 mole) and formamide (3 moles) was heated under an air condenser on a sand bath at 220° for about 1.5 hours. The reaction mixture was cooled then steam distilled. The distillate was cooled thoroughly and the white crystals were collected and dried. Recrystallized from benzene-petroleum ether (40-60°) into colourless needles, mp 68-69°, yield 30%; ms: m/e (relative intensities) 57 (4.0), 61 (1.3), 62 (5.8), 63 (8.2), 64 (2.8), 71 (7.3), 74 (1.7), 75 (2.3), 85 (8.9), 86 (2.2), 87 (4.6), 88 (7.6), 89 (1.0), 113 (11.9), 114 (27.5), 115 (3.1), 140 (5.0), 141 (14.4), 142 (3.3), 169 (100.0), 170 (12.7), 171 (1.0); metastable peaks are found at m/e values of 117.6, 92.2.

Anal. Calcd. for $C_{11}H_7NO_4S$: C, 53.01; H, 2.81; N, 5.62; S, 12.85. Found: C, 52.85; H, 3.05; N, 5.58; S, 12.81.

2-(Arylsulfonyl)naphth[1,2-*d*]oxazole-5-sulfonic Acids (**2**).

A solution of **1** (0.0023 mole) and (0.0023 mole) of arenesulfonyl chloride in 15 ml dry benzene was heated to reflux for 10 hours. Then, the solvent was evaporated under vacuum and cold water was added to the reaction mixture while stirring. The flask was left to stand for about 1 hour, the precipitated solid was filtered, washed with water, with 10% sodium hydrogen carbonate solution and finally with water. The product sulfone was crystallized from ethanol in 75-80% yield. The results are

found in Table I.

2-(Aryloxyacetyl)naphth[1,2-*d*]oxazole-5-sulfonic Acids (**3**).

Aryloxyacetyl chloride (1 mole) dissolved in a mixture of dioxane (10 ml) and triethylamine (1 mole) was refluxed with **1** (1 mole) for 2 hours and the reaction mixture allowed to stand overnight at room temperature. The precipitated triethylamine hydrochloride was filtered, and the filtrate evaporated under *vacuo*. The residue was crystallized from dioxane to give **3** (Table II).

2-(1-Naphthyloxacetyl)naphth[1,2-*d*]oxazole-5-sulfonic Acid (**4**).

The above method was employed using 1-naphthyloxyacetyl chloride. The residue was crystallized from dioxane to give **4** in 70% yield, mp 218°.

Anal. Calcd. for $C_{23}H_{15}NO_6S$: C, 63.74; H, 3.46; N, 3.23; S, 7.39. Found: C, 63.91; H, 3.35; N, 3.15; S, 7.27.

2-(Chloroacetyl)naphth[1,2-*d*]oxazole-5-sulfonic Acid (**5**).

Chloroacetyl chloride (0.01 mole) was added slowly to **1** (0.01 mole) in dry toluene (150 ml), and heated to reflux for 3 hours. Toluene was removed under reduced pressure. The residue was filtered and crystallized from ethanol, yield 80%, mp 200°.

Anal. Calcd. for $C_{13}H_8ClNO_5S$: C, 47.92; H, 2.45; N, 4.30; S, 9.83. Found: C, 48.05; H, 2.65; N, 4.33; S, 9.90.

2-(Arylsulfonyl)naphth[1,2-*d*]oxazole-5-sulfonamides (**6**).

A mixture of **2** (0.017 mole) and thionyl chloride (3 ml) was heated on a water bath for 2 hours. The excess thionyl chloride was removed by applying a gentle suction and the last traces were removed by the addition of a few milliliters of dry benzene and evaporation. The residual sulfonyl chloride was interacted with (0.012 mole) of amines (such as morpholine, piperidine, piperazine, ephedrine and *p*-anisidine) in 15 ml dry benzene under reflux for 3 hours. Benzene was evaporated off, and cold water was added to the residue. The *p*H of the produced mixture was adjusted to around 13.3 using 1% sodium hydroxide solution, to neutralize the ammonium salt formed. The product 2-(arylsolfonyl)naphth[1,2-*d*]oxazole-5-sulfonamides (**6**) were filtered, washed with water, dried and crystallized from dioxane-water. The results are presented in Table III.

2-(Hydrazinoacetyl)naphth[1,2-*d*]oxazole-5-sulfonic Acid (**7**).

A mixture of **5** (0.01 mole) and hydrazine hydrate (99-100%) (0.01 mole) in ethanol (20 ml) was refluxed for 3 hours. The reaction mixture was allowed to cool, diluted with water and crystallized from ethanol, yield 87%, mp 194°.

Anal. Calcd. for $C_{13}H_{11}N_3O_5S$: C, 48.59; H, 3.42; N, 13.08; S, 9.96. Found: C, 48.89; H, 3.23; N, 13.04; S, 9.94.

1,2-Bis[5-sulfonaphth[1,2-*d*]oxazol-2-ylcarbonylmethyl]hydrazine (**8**).

The reaction was carried out as above using **5** (0.02 mole). The product was crystallized from ethanol, yield 84%, mp 220°.

Anal. Calcd. for $C_{26}H_{18}N_4O_{10}S_2$: C, 51.14; H, 2.95; N, 9.18; S, 10.49. Found: C, 51.32; H, 3.16; N, 9.11; S, 10.52.

Substituted 2-(Hydrazonoacetyl)naphth[1,2-*d*]oxazole-5-sulfonic Acids (**9**).

A mixture of equimolecular quantities of **7** and the appropriate aldehyde in galcial acetic acid were refluxed for 3 hours, cooled and poured onto crushed ice, the solid that separated was crystallized from glacial acetic acid (*cf.* Table IV).

1,4-Bis[5-sulfonaphth[1,2-*d*]oxazol-2-ylcarbonylmethoxy]benzene (**10**).

A mixture of **5** (2 moles) in dry acetone, hydroquinone (1 mole) in the presence of anhydrous potassium carbonate (2 moles) and potassium iodide were refluxed for 30 hours and the reaction mixture filtered, the filtrate evaporated and the residue crystallized from ethanol to give **10**, mp 177-178°, yield 77%.

Anal. Calcd. for $C_{32}H_{20}N_2O_{12}S_2$: C, 55.81; H, 2.90; N, 4.06; S, 9.30. Found: C, 55.51; H, 2.78; N, 4.01; S, 9.23.

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