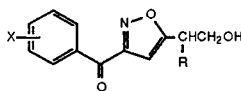


Table I

[5-(2'-Hydroxyalkyl)isoxazol-3-yl]phenylmethanones

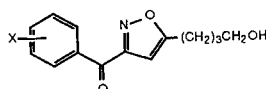


	X	R	Yield, %	Formula	Calcd.		Analysis			N
					C	H	N	C	H	
7a	H	H	67	C ₁₂ H ₁₁ NO ₃	66.35	5.11	6.45	66.49	5.22	6.29
7b	4-CH ₃	H	67	C ₁₃ H ₁₃ NO ₃	67.52	5.67	6.06	67.30	5.69	5.69
7c	4-OCH ₃	H	71	C ₁₃ H ₁₃ NO ₄	63.14	5.31	5.66	62.74	5.45	5.56
7d	4-Cl	H	85 [a]	C ₁₂ H ₁₀ ClNO ₃	57.27	4.01	5.57	57.66	4.18	5.39
7e	4-F	H	37 [b]	C ₁₂ H ₁₀ FNO ₃	61.27	4.29	5.95	61.30	4.47	5.84
7f	2,4-Cl ₂	H	58 [c]	C ₁₂ H ₉ Cl ₂ NO ₃	50.37	3.18	4.89	50.52	3.20	4.71
7g	4-Cl	CH ₃	59	C ₁₃ H ₁₂ ClNO ₃	58.76	4.55	5.27	59.13	4.73	5.15

[a] Mp 59-62°. [b] Mp 42-45°. [c] Mp 78-80°.

Table II

[5-(4'-Hydroxybutyl)isoxazol-3-yl]phenylmethanones

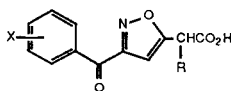


	X	Yield, %	Formula	Calcd.		Analysis			N
				C	H	N	C	H	
7h	H	62	C ₁₄ H ₁₅ NO ₃	68.55	6.16	5.71	68.63	6.19	5.52
7i	4-CH ₃	68	C ₁₅ H ₁₇ NO ₃	69.48	6.61	5.40	69.38	6.61	5.31
7j	4-Cl	78 [d]	C ₁₄ H ₁₃ ClNO ₃	60.11	5.04	5.01	60.14	5.12	4.84
7k	2,4-Cl ₂	78	C ₁₄ H ₁₃ Cl ₂ NO ₃	53.52	4.18	4.46	53.63	4.38	4.20

[d] Mp 48-51°.

Table III

(3-Aroylisoxazol-5-yl)alkanoic Acids



	X	R	Yield, %	Mp°C	Formula	Calcd.		Analysis			N
						C	H	N	C	H	
2a	H	H	43	108-110	C ₁₂ H ₉ NO ₄	62.34	3.92	6.06	62.55	3.95	6.20
2b	4-CH ₃	H	43	105-107	C ₁₃ H ₁₁ NO ₄	63.67	4.52	5.71	63.57	4.49	5.69
2c	4-OCH ₃	H	9	119-121	C ₁₃ H ₁₁ NO ₅	59.76	4.25	5.36	59.49	4.21	5.32
2d	4-Cl	H	32	126-128	C ₁₂ H ₈ ClNO ₄	54.25	3.04	5.27	54.08	3.05	5.23
2e	4-F	H	41	113-115	C ₁₂ H ₈ FNO ₄	57.83	3.24	5.62	57.60	3.34	5.57
2f	2,4-Cl ₂	H	26	108-109	C ₁₂ H ₇ Cl ₂ NO ₄	48.03	2.36	4.67	47.83	2.44	4.59
2g	4-Cl	CH ₃	13	122.5-124.5	C ₁₃ H ₁₀ ClNO ₄	55.83	3.60	5.01	55.46	3.51	4.95

Methodology for chemoselective oxidation of 2-arylethanol to arylacetic acids had not been reported at the time of this investigation. Thus, we set out to perform stepwise oxidation of **7a-g** to the corresponding aldehydes **8** via a recently reported phase transfer catalyzed potassium dichromate procedure [6]. In our hands, none of the expected aldehyde **8a** was obtained under a variety of stoichiometric conditions [7]. Serendipitously, treatment of alcohols **7a-g** in dichloromethane with one molar equivalent of potassium dichromate in 9M sulfuric acid and a catalytic amount of tetra-*n*-butylammonium hydrogen sulfate at room temperature provided the target alkanolic acids **2a-g** directly (see Table III).

Compounds **7h-k** and **2a-g** were less active than reference compounds in antiinflammatory/analgetic screening.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye Unicam SP3-200 spectrophotometer. Nuclear magnetic resonance spectra were taken on a JEOL C-60HL and chemical shifts are given relative to internal tetramethylsilane. Mass spectra were obtained from a Finnigan Model 4000 spectrometer equipped with an INCOS data system. Elemental analysis were performed by Micro-Tech Laboratories, Skokie, Illinois. Thin layer chromatograms were run on silica gel PF-254 plates (E. Merck, AG) and high performance liquid chromatography was carried out with a Waters Prep LC/System 500 using standard silica gel prepacked cartridges.

Arylglyoxyhydroxamyl Chlorides **4a-f**.

Compounds **4a-e** were prepared as previously described [1].

2,4-Dichlorophenylglyoxyhydroxamyl Chloride (**4f**).

This compound was prepared as above. Workup included concentration, trituration with hexane and recrystallization from cyclohexane to give 49% yield of white crystals, mp 100-101°; ir (chloroform): 3530, 1700 cm⁻¹; nmr (deuteriochloroform): δ 7.20-7.60 (m, 2, aromatic H), 8.74 (s, 1, OH); ms: (MH)⁺ m/e 252.

Anal. Calcd. for C₈H₄Cl₂NO₂: C, 38.06; H, 1.60; N, 5.55. Found: C, 38.29; H, 1.61; N, 5.62.

(3-Benzoyl-4,5-dihydro-1,2-oxazol-5-yl)acetonitrile (**5**).

A mixture of phenylglyoxyhydroxamyl chloride (**4a**) (12.0 g, 66 mmoles) and allyl cyanide (26.5 ml, 330 mmoles) was refluxed under nitrogen for 3.5 hours. Concentration and high performance liquid chromatography using ethyl acetate:dichloromethane:hexane (5:45:50) gave 9.2 g (66%) of a light yellow oil, ir (chloroform): 2225, 1655 cm⁻¹; nmr (deuteriochloroform): δ 2.80 (d, 2, J = 10 Hz, CH₂CN), 3.0-4.0 (m, 2, CH₂), 4.80-5.35 (m, 1, CH), 7.20-7.90 (m, 3, aromatic H), 8.10-8.45 (m, 2, aromatic H); ms: M⁺ m/e 214.

Anal. Calcd. for C₁₂H₁₀N₂O₂: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.20; H, 4.83; N, 12.90.

[5-(2'-(1-Hydroxyethyl)isoxazol-3-yl)]phenylmethanone (**7a**).

A solution of **4a** (12.0 g, 66 mmoles) in 3-butyn-1-ol (30 ml, 394 mmoles) was refluxed under nitrogen for 3 hours. Concentration and high performance liquid chromatography using 5% ethyl acetate/dichloromethane as an eluent gave 9.6 g (67%) of an oil; ir (chloroform): 3600, 1665 cm⁻¹; nmr (deuteriochloroform): δ 3.09 (t, 3, J = 10 Hz, CH₂), 3.10 (s, 1, OH), 4.00 (t, 2, J = 10 Hz, CH₂O), 6.76 (s, 1, isoxazole H), 7.40-8.00 (m, 3, aromatic H), 8.25-8.70 (m, 2, aromatic H); ms: M⁺ m/e 217.

Compounds **7b-e** were prepared similarly and details are given in

Table I.

[5-(2'-(1-Hydroxypropyl)isoxazol-3-yl)]-4-chlorophenylmethanone (**7g**).

A solution of **4d** (8.7 g, 40 mmoles) in 2-methyl-3-butyn-1-ol (16.7 g, 200 mmoles) [4] was refluxed under nitrogen for 3 hours. Concentration and high performance liquid chromatography using 5% ethyl acetate/dichloromethane as an eluent gave 6.3 g (59%) of an oil that solidified on standing, mp 49-51°; ir (chloroform): 3600, 1665 cm⁻¹; nmr (deuteriochloroform): δ 1.41 (d, 3, J = 11 Hz, CH₃), 2.25 (bs, 1, OH), 3.31 (sextet, 1, J = 9, 11 Hz, CH), 3.90 (d, 2, J = 9 Hz, CH₂O), 6.76 (s, 1, isoxazole H), 7.60 (d, 2, aromatic H), 8.45 (d, 2, aromatic H); ms: M⁺ m/e 265.

[5-(4'-(1-Hydroxybutyl)isoxazol-3-yl)]phenylmethanone (**7h**).

A solution of **4a** (12.0 g, 66 mmoles) in 5-hexyn-1-ol (30 g, 306 mmoles) was refluxed under nitrogen for 4 hours. Concentration and high performance liquid chromatography using 5% ethyl acetate/dichloromethane as an eluent gave 10.0 g (62%) of an oil, ir (chloroform): 3600, 1660 cm⁻¹; nmr (deuteriochloroform): δ 1.40-2.10 (m, 4, CH₂), 2.23 (s, 1, OH), 2.89 (t, 2, J = 11 Hz, Het-CH₂), 3.68 (t, 2, J = 11 Hz, CH₂O), 6.60 (s, 1, isoxazole H), 7.30-7.90 (m, 3, aromatic H), 8.10-8.55 (m, 2, aromatic H); ms: M⁺ m/e 245.

Compounds **7i-k** were prepared similarly and details are given in Table II.

(3-Benzoylisoxazol-5-yl)acetic Acid (**2a**).

Pulverized potassium dichromate (11.9 g, 41 mmoles) was added to a mixture of **7a** (8.8 g, 41 mmoles), one liter of dichloromethane, 150 ml of 9M sulfuric acid and a few crystals of tetra-*n*-butylammonium hydrogen sulfate. The resulting mixture was stirred at room temperature for 1.5 hours. After settling, the mixture was decanted and the aqueous phase was extracted with dichloromethane. The organic extract was washed with water and brine, and dried (magnesium sulfate). Concentration, followed by trituration with cyclohexane and recrystallization from toluene gave 4.0 g (43%) of a tan solid, mp 108-110°; ir (potassium bromide): 1720, 1660 cm⁻¹; nmr (DMSO-*d*₆): δ 4.14 (s, 2, CH₂), 6.98 (s, 1, isoxazole H), 7.40-7.95 (m, 3, aromatic H), 8.05-8.45 (m, 2, aromatic H), 12.8 (bs, 1, CO₂H); ms: (MH)⁺ m/e 232.

Compounds **2b-e** were prepared similarly and details are given in Table III.

2-[3-(4'-Chlorobenzoyl)isoxazol-5-yl]propionic Acid (**2g**).

This compound was prepared as described above in 13% yield after two recrystallizations from toluene as a white solid, mp 122.5-124.5°; ir (potassium bromide): 1705, 1665 cm⁻¹; nmr (DMSO-*d*₆): δ 1.54 (d, 3, J = 12 Hz, CH₃), 4.09 (q, 1, J = 12 Hz, CH), 6.79 (s, 1, isoxazole H), 7.55 (d, 2, aromatic H), 8.15 (d, 2, aromatic H), 10.10 (bs, 1, CO₂H); ms: (MH)⁺ m/e 280.

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