Synthesis of 3-[(Aryl)-1,2,4-oxadiazol-5-yl]propionic Acids

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Seven 3,5-disubstituted oxadiazole derivatives, **3a-g**, have been prepared by direct condensation of appropriate benzamidoxime with succinic anhydride. Spectroscopic properties, especially uv, ir and mass spectra confirmed the cyclic 1,2,4-oxadiazole structure. No ring-opened intermediate or side product could be observed. The ^{1}H-nmr assignments of the two CH_2 groups were unequivocally made by acid- and base-induced shifts.

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Introduction.

Various 1,2,4-oxadiazoles have been found to possess biological activity [1]. In fact, three of these compounds, *viz.*, Oxolamine [2,3], Irrigor [3,4], and Libexin [5] are available commercially. Oxolamine as well as Libexin have been employed as antitussive drugs and Irrigor as a coronary vasodilator and local anaesthetic.

We were interested to introduce a 3-carbon side-chain in oxadiazoles in order to see the effect of this group on biological activity. Aryl carboxylic acids are known to have anti-inflammatory properties [6]. It has also been shown that a 3-carbon carboxylic acid side-chain at position 5 in 5-(1-carboxyethyl)-2-(*p*-chlorophenyl)benzoxazole [7] is an anti-inflammatory agent [8]. Recently, it has been demonstrated that 3-(2-benzoxazolyl)propionic acid, when tested in mice, produced anti-inflammatory properties [9]. Thus, it is clear that a side-chain (-CH_2CH_2COOH) attached on carbon of a heterocyclic ring is of great interest. With this idea in view, we decided to: 1) synthesize various 1,2,4-oxadiazoles having -CH_2CH_2COOH side chain at C-5, 2) study the chemistry of these compounds, 3) examine the fragmentation mode by mass spectrometry, and 4) test the pharmacological activity. The present paper describes the synthesis only.

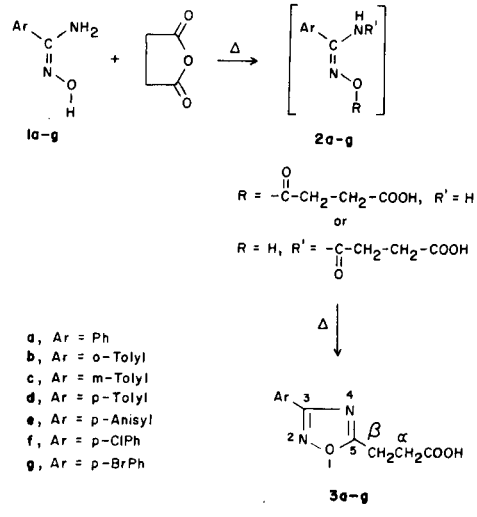

Figure 1

A search of literature revealed that three compounds, **3a** [10], **3d,e** [11], reported in this paper, were prepared about a century ago. However, the other four, **2b,c,f,g**, are new. Synthesis and spectroscopic studies of **3a-g** (Figure 1) are described below.

Table I

Nuclear Magnetic Resonance Spectra of 1,2,4-Oxadiazoles **3a-g** at 100 MHz (in ppm)

Compound	Ar	α-CH_2 [c]	β-CH_2 [c]	CH_3	OCH_3
3a [a]	7.30-7.61 m (3H); 7.83-8.40 m (2H)	3.01	3.28	—	—
3b [a]	7.30-7.53 m (3H); 7.95-8.20 m (1H)	3.03	3.30	2.63	—
3c [a]	7.17-7.42 m (2H); 7.67-8.03 m (2H)	3.00	3.25	2.41	—
3d [a]	[7.35 d (2H); 7.95 d (2H)] [d]	3.00	3.27	2.42	—
3e [a]	[7.09 d (2H); 8.03 d (2H)] [d]	3.00	3.26	—	3.83
3f [b]	[7.46 d (2H); 8.04 d (2H)] [d]	3.00	3.27	—	—
3g [b]	[7.74 d (2H); 8.02 d (2H)] [d]	3.00	3.30	—	—

[a] Solvent deuteriochloroform. [b] Solvent deuteriochloroform + perdeuterioacetone. [c] A_2B_2 system. [d] AA'BB' system having J values of approximately 9.0 Hz.

Results and Discussion.

Synthesis of oxadiazoles, **3a-g**, was effected by fusing an intimate mixture of appropriate benzamidoxime with succinic anhydride (1 equivalent of each) in an oil bath. Crystallization afforded the desired compounds in pure form (24-58% yield). Our initial efforts to run the reaction of **1a** and succinic anhydride in methylene chloride at room temperature failed. Also, no intermediate, either *N*- or *O*-acyl derivative, **2a**, was obtained.

The ultraviolet spectrum of **3a** showed the main absorption at λ max 235 nm. This absorption is similar to 5-methyl-3-phenyl-1,2,4-oxadiazole reported earlier [12]. Hence, it is concluded that **3a**, indeed, possesses a 1,2,4-oxadiazole skeleton. The spectrum of **3b** was identical. Compounds **3c** and **3d** displayed bathochromic shifts and both absorbed at 242 nm. Oxadiazole **3e** had significant dislocation towards longer wavelength (λ max 256 nm). Substances **3f** and **3g** produced λ max at 246 and 250 nm respectively.

The infrared spectra of **3a-g** had characteristic -OH absorption of a carboxylic acid. A strong band due to C=O appeared in the range of 1700-1720 cm^{-1} in all the compounds indicating that these oxadiazoles exist as dimers. Other vibrations, for example, C=N and C=C were observed at 1620-1560 cm^{-1}.

The 60 MHz nmr spectrum of **3a** provided a multiplet at δ 2.78-3.43 for both methylene groups which is almost identical with the coupling pattern of β-iodopropionic acid. The α- and β-protons of -CH_2 groups linked to the carboxylic function of the latter are reported [13] to absorb at δ 3.07 and 3.30 respectively. The 100 MHz nmr spectrum of **3a** gave two triplet-like patterns centered at δ 3.01 (2H) and 3.28 (2H).

In order to differentiate the two methylene groups, we have compared the chemical shifts of CH_2 protons of propionic acid and 5-ethyl-3-phenyl-1,2,4-oxadiazole [14]. The former and the latter presented the CH_2 quartets at δ 2.41 and 2.94 respectively. It is then clear that the heterocyclic ring possesses greater electron-withdrawing effect than -COOH function and this effect is transmitted to the adjacent carbon as is evidenced by the absorption of CH_3 protons of ethyl group at δ 1.42 compared to methyl signal of propionic acid which appears at δ 1.16. Thus, it is safe to assume that the two protons at lower field in **3a** are due to CH_2 attached to C-5 and the other two at higher field are due to CH_2 linked with carboxylic acid group. Table I lists the chemical shifts of various protons of compounds **3a-g**. Further confirmation of this assignment was obtained by running the ^1H nmr spectrum of **3a** in methanol-d_4 and gradually adding small quantity of methanolic potassium hydroxide solution and measuring the spectrum each time. This way, the CH_2 group at δ 3.01 showed a continuous upfield shift reaching a maximum of 15 Hz; the lower field methylene function did not move. On the other hand, measurement of the spectrum in deuteriochloroform followed by the addition of trifluoroacetic acid caused the CH_2 signal at δ 3.28 to move 3.5 Hz downfield without affecting the position of the other methylene group. These observations are in complete agreement with our previous assignment since formation of carboxylate ion should affect the methylene group attached to -COOH group whereas protonation of the heterocyclic ring will apparently cause the CH_2 group connected to it to dislocate downfield.

EXPERIMENTAL

Melting points are uncorrected. Elemental analyses were performed by Dr. Riva Moscovici, Instituto de Química, Universidade de São Paulo. Ultraviolet spectra were measured on Beckman DB-G instrument using 95% ethanol as solvent and infrared on Perkin-Elmer model 237B spectrophotometer with potassium bromide pellets. The nmr spectra were obtained either on Varian A-60, EM 390, or XL-100 instruments using tetramethylsilane as internal standard. Plates coated with silica gel G were employed for tlc and ethyl acetate as the solvent for the development. The spots exhibited faint color when exposed to iodine vapors.

Benzamidoximes **1a-g**.

Benzamidoximes **1a-g**, were prepared according to the procedure reported earlier [15].

3-[(3-Aryl)-1,2,4-oxadiazol-5-yl]propionic Acids **3a-g**.

A test tube containing an intimate mixture of the desired benzamidoxime (7.0 mmoles) and succinic anhydride (7.0 mmoles) was immersed in an oil bath maintained at 120° (unless otherwise specified) and kept at this temperature for about half an hour and then taken out of the oil bath. After cooling the solid was crystallized to obtain the pure procuct. In some cases, chromatography on silica gel helped to purifiy the substance. The data on individual compounds are given below.

3-[(3-Phenyl)-1,2,4-oxadiazol-5-yl]propionic Acid (**3a**).

Repeated crystallizations from ethanol-water provided **3a** in 55% yield, mp 118-120°, lit [10] mp 120°. No yield was furnished in the literature; ir (potassium bromide): 3400-2000, 1700, 1600, 1575, 1560, 1535, 890 cm^{-1}; uv (ethanol): λ max 235 (ε = 14600), 275 (1721), 284 nm (872); ms: (70 eV) m/e 218 (50%, M^+), 173 (60), 119 (100), 118 (20), 103 (39), 91 (46), 77 (21), 55 (81).

3-[(3-*o*-Tolyl)-1,2,4-oxadiazol-5-yl]propionic Acid (**3b**).

Here the oil bath temperature was 140°. Crystallization from chloroform-*n*-hexane provided crystals, mp 103-104°. The yield was 25%; ir (potassium bromide): 3400-2000, 1700, 1590, 1560, 1530, 900 cm^{-1}; uv (ethanol): λ max 235 (ε = 10213), 275 (2340), 285 nm (1490); ms: (70 eV) m/e 232 (1%, M^+), 187 (68), 159 (19), 133 (50), 131 (72), 119 (19), 118 (100), 117 (35), 116 (42), 105 (19), 104 (31), 91 (32), 55 (30).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$ (232): C, 62.07; H, 5.21; N, 12.06. Found: C, 61.88; H, 5.14; N, 11.78.

3-[(3-*m*-Tolyl)-1,2,4-oxadiazol-5-yl]propionic Acid (**3c**).

Crystallization from ethanol-water yielded **3c** in 53% yield, mp 98-100°; ir (potassium bromide): 3300-2000, 1710, 1615, 1600, 1585, 910 cm^{-1} uv (ethanol): λ max 242 (ε = 13353), 280 (1089), 288 nm (870); ms: (70 eV) m/e 232 (38%, M^+), 187 (33), 133 (100), 132 (43), 131 (4), 119 (7), 117 (26), 104 (17), 91 (23), 55 (72).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$ (232): C, 62.07; H, 5.21; N, 12.06. Found: C, 61.86; H, 4.99; N, 12.34.

3-[(3-*p*-Tolyl)-1,2,4-oxadiazol-5-yl]propionic Acid (**3d**).

In this case, the bath temperature was 135°. Recrystallization from

ethanol-water furnished the desired product in 54% yield, mp 139-140°; lit [11] mp 138.5°; ir (potassium bromide): 3400-2000, 1700, 1620, 1595, 1570, 1560, 890 cm^{-1}; uv (ethanol): λ max 244 (ε = 15151), 273 (657), 285 nm (444); ms: (70 eV) m/e 232 (43%, M^+), 187 (28), 133 (100), 132 (65), 131 (5), 117 (43), 116 (30), 104 (15), 91 (24), 55 (74).

3-[(3-*p*-Anisyl)-1,2,4-oxadiazol-5-yl]propionic Acid (**3e**).

The reaction product, after crystallization from chloroform, afforded pure **3e** in 37% yield and melted at 138-139°; lit [11] reported mp 140-141°; ir (potassium bromide): 3300-2000, 1715, 1605, 1580, 1570, 1540, 910 cm^{-1}; uv (ethanol): λ max 256 (ε = 18331), 284 inf (3666), 290 nm (2372); ms: (70 eV) m/e 248 (43%, M^+), 203 (4), 149 (67), 148 (32), 135 (5), 133 (100), 132 (6), 55 (47).

3-[(3-*p*-Chloropenyl)-1,2,4-oxadiazol-5-yl]propionic Acid (**3f**).

The bath temperature was 130°. The yield, in this reaction, was 58% after crystallization from ethanol-water. The compound melted at 145-146°; ir (potassium bromide): 3400-2000, 1710, 1600, 1595, 1570, 1560, 910 cm^{-1}; uv (ethanol): λ max 246 (ε = 22045), 276 (2046), 286 nm (1364); ms: (70 eV) m/e 252 (20%, M^+), 207 (25), 153 (47), 152 (11), 139 (33), 137 (100), 125 (15), 111 (6), 55 (47).

Anal. Calcd. for $C_{11}H_9ClN_2O_3$ (252): C, 52.26; H, 3.59; N, 11.08. Found: C, 52.44; H, 3.71; N, 11.53.

3-[(3-*p*-Bromophenyl)-1,2,4-oxadiazol-5-yl]propionic Acid (**3g**).

The reaction was conducted at 135°. The yield here was 40% after various crystallizations from chloroform. The substance melted at 149-150°; ir (potassium bromide): 3400-2000, 1720, 1600, 1570, 1560, 1540, 910 cm^{-1}; uv (ethanol): λ max 250 (ε = 20772), 280 (2671), 292.5 nm (1484); ms: (70 eV) 296 (19%, M^+), 251 (21), 197 (35), 196 (10), 183 (51), 181 (53), 155 (4), 55 (100).

Anal. Calcd. for $C_{11}H_9BrN_2O_3$ (296): C, 44.44; H, 3.05; N, 9.42. Found: C, 43.85; H, 3.11; N, 9.10.

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