Synthesis of 5-Aryl-2-oxazolepropionic Acids and Analogs. Antiinflammatory Agents

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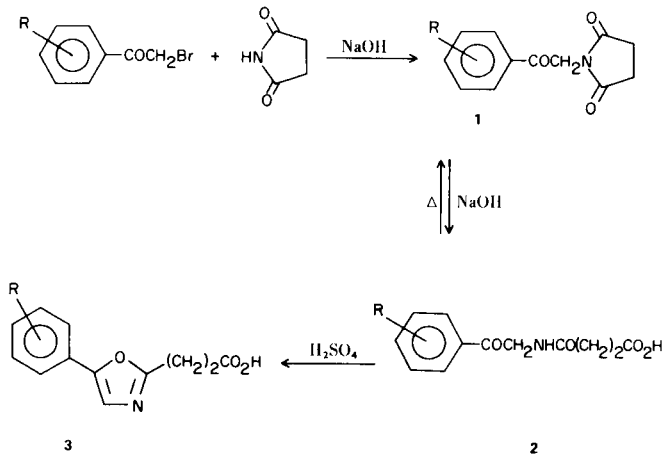
Condensation of 2-bromoacetophenones with sodium succinimide gave *N*-phenacylsuccinimides (**1**) which were opened with sodium hydroxide to *N*-phenacylsuccinamic acids (**2**). The latter were cyclized to 5-aryl-2-oxazolepropionic acids (**3**) in sulfuric acid. Similar cyclization of *N*-phenacylphthalamic acid (**5**) and succinic acid 2-benzoylhydrazide (**7**) gave *o*-(5-phenyl-2-oxazolyl)benzoic acid (**6**) and 5-phenyl-1,3,4-oxadiazole-2-propionic acid (**8**). The succinamic acids **2** and the phthalamic acid **5** were observed to recyclize to the corresponding imides (**1** and **4**) on heating, and the succinic acid hydrazide **7** was similarly cyclized to *N*-benzamidosuccinimide (**9**) with acetic anhydride. Antiinflammatory screening data are reported for **3**, **6** and **8**.

We have previously described the preparation of 5-aryl-2-furanpropionic acids as potential antiinflammatory agents (1). In this paper we report the synthesis and antiinflammatory activity of some analogous oxazoles (**3** and **6**) and an 1,3,4-oxadiazole (**8**).

RESULTS AND DISCUSSION

5-Aryl-2-oxazolepropionic acids (**3**) were obtained by the route shown in Scheme I. Condensation of 2-bromoacetophenones in ethanol or dimethylformamide with the sodium salt of succinimide in water gave *N*-phenacylsuccinimides (**1**). Using available 2-haloacetophenones, this procedure is more convenient than the Friedel-Crafts acylation of benzene with 2,5-dioxo-1-pyrrolidineacetyl chloride previously reported (2,3) for the preparation of **1a**.

SCHEME I

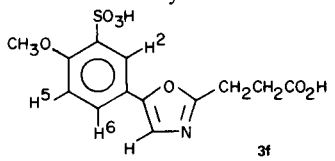


a R = H
b R = *p*-F
c R = *p*-Cl
d R = *p*-Br
e R = *p*-OCH_3
f R = 3-SO_3H-4-OCH_3

Ring-cleavage of imides **1** with aqueous sodium hydroxide gave *N*-phenacylsuccinamic acids (**2**). We also prepared **2c** in higher overall yield without isolation of imide **1c**. Sheehan and Laubach (3) have reported the synthesis of **2a**, but isolated and characterized it only as the 2,4-dinitrophenylhydrazone. Preparation of the methyl ester of **2a** by condensation of 2-aminoacetophenone with methyl 3-chloroformylpropionate, but without purification or characterization, has been disclosed recently (4).

We observed that the melting points of succinamic acids **2c** and **2e** varied several degrees depending on the duration of heating, and that the cooled and resolidified sample of **2c** remelted about 20° lower with gas evolution. By heating **2c** above its melting point until gas evolution stopped, we then found the pyrolysis product to be the imide **1c** formed by recyclization of the succinamic acid.

Robinson-Gabriel cyclization (5) of α-acylamino ketones **2** in concentrated sulfuric acid gave the 5-aryl-2-oxazolepropionic acids (**3**). The preparation of **3a** by a similar cyclization of the methyl ester of **2a** followed by hydrolysis of the ester has been disclosed recently (4). In performing these cyclizations we allowed the reaction temperatures to rise spontaneously without cooling. Under these conditions the reactive methoxy compound **2e** gave the sulfonated aryloxazole **3f**, isolated and characterized as the hemihydrate and monohydrate.



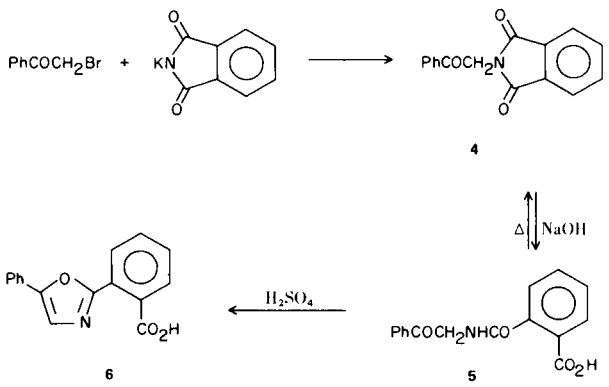
3f

The sulfonic acid group in **3f** was exposed by electrometric titration ($pK'_a < 1$ in 50% methanol) and its position was clearly displayed by the proton magnetic resonance spectrum (dimethylsulfoxide solution). In the unsubstituted compound **3a**, the five phenyl hydrogens appear as a multiplet in the range δ 7.8-7.3 ppm. In **3f**, the phenyl 2-H, deshielded by the *ortho* sulfonic acid and split by the *meta* 6-H, appears downfield as a doublet centered at δ 8.05 ppm. ($J_{2,6}$ = 2.2 Hz.). The 5-H, shielded by the *ortho* methoxy and split by the *ortho* 6-H, appears upfield as a doublet centered at δ 7.14 ppm. ($J_{5,6}$ = 8.5 Hz.). The 6-H, split by both the *ortho* 5-H and the *meta* 2-H, appears as a pair of doublets centered at δ 7.72 ppm. In both **3a** and **3f**, the oxazole H appears as a singlet at δ 7.55 ppm. The four protons in **3f** monohydrate arising from the carboxyl and sulfonic acid groups and the water molecule all appear as a sharp singlet at δ 8.79 ppm., while the single carboxyl proton in **3a** gives a broad signal at δ 12.1 ppm. The infrared absorption spectrum of **3f** in potassium bromide does not show an oxazole ring vibration band in the 1550 cm^{-1} region which is present in the spectra of the other **3**. Instead, a new band appears at 1649-cm^{-1} which we consider to be the oxazole vibration, increased in frequency by the *-I* effect of the sulfonic acid group.

An analog of **3a** in which the propionic acid group is replaced by an *o*-carboxyphenyl group was prepared by a similar series of reactions indicated in Scheme II. *N*-Phenacylphthalimide (**4**), obtained by simplification of the published (6-8) procedure, was converted to *N*-phenacylphthalamic acid (**5**) with aqueous sodium hydroxide. Other workers (8-10) have reported the successful preparation of anhydrous and presumably pure **5** by essentially the same method. Goedeckemeyer (8) obtained analytically (C, H) pure material by crystallization from acetic acid. This apparently is not the solvent of choice, however, because Drefahl and Fischer (9) have since demonstrated that *N*-phenacylphthalamic acids are readily cyclized to the phthalimides by brief boiling in glacial acetic acid. We found that when **5** was dried under reduced pressure at 60-70° after filtration from an aqueous slurry, partial recyclization to **4** occurred as indicated by the appearance of imide absorption (1770 cm^{-1}) and a reduction in the intensity of the amide bands (1530, 1642 and 3380 cm^{-1}) in the infrared absorption spectrum of the product. Because of this instability we elected to obtain **5** by drying the material to constant weight at room temperature, a procedure which gave the monohydrate. Ultimately, cyclization of **5** monohydrate in concentrated sulfuric acid gave *o*-(5-phenyl-2-oxazoyl) benzoic acid (**6**).

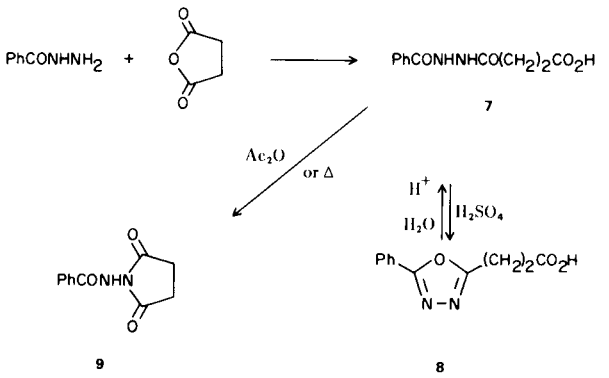
The 1,3,4-oxadiazole analog of **3a** was obtained as shown in Scheme III. Succinic acid 2-benzoylhydrazide (**7**) was prepared by simplification of a published (11)

SCHEME II



procedure and cyclized in concentrated sulfuric acid to 5-phenyl-1,3,4-oxadiazole-2-propionic acid (**8**). Huisgen and co-workers (11) have previously isolated **8** as one of the products formed by fusion of 5-phenyltetrazole with succinic anhydride, and reported failure of attempts to cyclize **7** to **8** using polyphosphoric acid, phosphorus pentoxide and thionyl chloride. We found that **8** was quite susceptible to acid hydrolysis, as indicated by partial reopening of the ring to **7** when the diluted sulfuric acid solution was not kept cold.

SCHEME III



The cyclodehydration of diacylhydrazines to 1,3,4-oxadiazoles has also been effected with acetic anhydride (12). Solution of the succinic acid hydrazide **7** in hot acetic anhydride, however, gave *N*-benzamidosuccinimide (**9**) rather than **8**. Activation of the carboxyl carbonyl by formation of the mixed anhydride presumably initiates this cyclization. Huisgen and co-workers (11) have observed that when **7** is heated above its melting point it gives a pyrolysis product, m.p. 219-220°, which they did not purify or characterize. We suggest that this product is probably **9** because of the coincidence of its melting point with that we observed for **9** (225.5-226°), and the analogous pyrolytic behavior of **2c** and **5** discussed above.

Following are preliminary screening estimates of anti-inflammatory activity, expressed as the minimum effective dose in mg./kg. required to delay the appearance of ultraviolet light-induced erythema on the skin of depilated albino guinea pigs; the compounds were administered by gavage as an aqueous solution of the sodium salt (13,14): **3a**, 50; **-b**, 100; **-c**, 25; **-d**, 12.5; **-f**, > 100; **6**, > 100; **8**, > 100.

EXPERIMENTAL

The ethanol used was 3A denatured, the petroleum ether was low boiling (distillation range about 30-60°). Melting points were observed in open capillary tubes in a calibrated Thomas-Hoover apparatus and the values were recorded without correction. Uv absorption spectra were recorded on a Cary Model 11 spectrophotometer with methanol as solvent; the *p*H was adjusted by addition of 5 *N* hydrochloric acid or 12 *N* potassium hydroxide. Ir absorption spectra were recorded on a Beckman IR7 or -9 spectrophotometer with samples in potassium bromide disks. Nmr spectra were recorded on a Varian A-60 spectrometer with dimethyl sulfoxide-d_6 as solvent, sample concentration 15% w/v, and tetramethylsilane as internal standard. Dissociation constants were determined by electrometric titration in 50% aqueous methanol.

N-Phenacylsuccinimide (**1a**).

To a stirred, cold solution of 8.8 g. (0.22 mole) of sodium hydroxide and 21.8 g. (0.220 mole) of succinimide in 200 ml. of water was added 39.8 g. (0.200 mole) of 2-bromoacetophenone. Ethanol (three 50-ml. portions) was added while the mixture was heated slowly to 50°, and the resulting solution was kept at 50-55° for 2 hours during which a precipitate formed. The slurry was chilled to 5°, and the solid was collected, washed with cold water and dried to give 26.5 g. (61%) of product, m.p. 133-136°. Recrystallization from 200 ml. of ethanol gave 22.5 g. of **1a**, m.p. 145° [lit. (2,3) m.p. 143-144°].

N-(*p*-Fluorophenacyl)succinimide (**1b**).

A cold solution of 10.0 g. (0.25 mole) of sodium hydroxide and 24.8 g. (0.250 mole) of succinimide in 30 ml. of water was added in 4 minutes to a stirred solution of 49.3 g. (0.227) mole of 2-bromo-4′-fluoroacetophenone in 200 ml. of dimethylformamide, during which the reaction temperature rose to 58°. After 2 hours at ambient temperature, this solution was added in a slow stream with stirring to 1 l. of water containing sufficient ice to keep the temperature below 10°. The mixture was chilled for a few minutes and the precipitate was collected, washed with water and dried to give 45.1 g. (85%) of product, m.p. 147-152°. Crystallization of 10.0 g. from 100 ml. of 95% ethanol gave 8.9 g. of **1b**, m.p. 153-154°; ir 1699 (ketone C=O), and 1707, 1714 and 1780 cm^{-1} (imide C=O).

Anal. Calcd. for $C_{12}H_{10}FNO_3$: C, 61.3; H, 4.3; F, 8.1; N, 6.0. Found: C, 61.6, 61.8; H, 4.4, 4.6; F, 7.9, 8.2; N, 5.8, 5.8.

N-(*p*-Chlorophenacyl)succinimide (**1c**).

A cold solution of 16.9 g. (0.42 mole) of sodium hydroxide and 41.7 g. (0.421 mole) of succinimide in 50 ml. of water was added in one portion to a stirred slurry of 98.2 g. (0.421 mole) of 2-bromo-4′-chloroacetophenone in 500 ml. of ethanol. The mixture was heated to reflux over a period of 3.3 hours and the resulting solution was refluxed for 1.2 hours during which the *p*H (measured on wet test paper) fell from 9 to 6. The solution was kept overnight at room temperature and the crystalline precipitate obtained was collected, washed with 95% ethanol and dried to give 35.2 g. (33%) of product, m.p. 147-148.5°. The chilled filtrate gave a second crop of 11.7 g. (11%), m.p. 146.5-148°.

Recrystallization of the second crop from 100 ml. of 95% ethanol gave 10.6 g. of **1c**, m.p. 148-149.5°; ir 1698 (ketone C=O), and 1710 and 1780 cm^{-1} (imide C=O).

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.3; H, 4.0; Cl, 14.1; N, 5.6. Found: C, 57.2; H, 4.1; Cl, 14.1, 14.4; N, 5.2, 5.2.

A 0.1-g. sample of *N*-(*p*-chlorophenacyl)succinamic acid (**2c**, m.p. 180-182.5°) was heated in an oil bath from 25° to 188° in 24 minutes, the melt was held at 181° to 192° until gas evolution had essentially stopped (25 minutes), then kept at 100° under reduced pressure for 0.5 hour. A sample of the melt was insoluble in cold 1 *N* sodium hydroxide. The bulk of the material was crystallized from 95% ethanol to give **1c**, m.p. 146-148°, identical by m.m.p. and ir with **1c** prepared above.

N-(*p*-Bromophenacyl)succinimide (**1d**).

Using essentially the same procedure described for the preparation of **1c**, 101.6 g. (0.365 mole) of 2,4′-dibromoacetophenone in 500 ml. of ethanol was allowed to react with a solution of 15.4 g. (0.39 mole) of sodium hydroxide and 38.1 g. (0.384 mole) of succinimide in 50 ml. of water. The chilled reaction mixture gave 45.9 g. (42%) of product, m.p. 165-169°. Recrystallization from 1300 ml. of methanol gave 31.9 g. of **1d**, m.p. 171-172.5°; ir 1700 (ketone C=O), and 1713, 1774 and 1780 cm^{-1} (imide C=O).

Anal. Calcd. for $C_{12}H_{10}BrNO_3$: C, 48.7; H, 3.4; Br, 27.0; N, 4.7. Found: C, 48.7; H, 3.6; Br, 26.7; N, 4.7.

The methanol filtrate gave a second crop of 5.5 g., m.p. 168.5-170°.

N-(*p*-Methoxyphenacyl)succinimide (**1e**).

Using essentially the same procedure described for the preparation of **1b**, 49.5 g. (0.216 mole) of 2-bromo-4′-methoxyacetophenone in 100 ml. of dimethylformamide was allowed to react with a solution of 9.5 g. (0.24 mole) of sodium hydroxide and 23.6 g. (0.238 mole) of succinimide in 30 ml. of water. After 23 hours, the reaction solution was poured into 500 ml. of cold water and the mixture was extracted with chloroform (200 and 100 ml.). The extract was washed with water (two 100-ml. portions), dried over sodium sulfate and concentrated to give 50.5 g. (95%) of product as an oil which solidified on cooling. Crystallization from 350 ml. of 95% ethanol (charcoal) gave 31.0 g. of **1e**, m.p. 91-93°; ir 1689 (ketone C=O), and 1710 and 1783 cm^{-1} (imide C=O).

Anal. Calcd. for $C_{13}H_{13}NO_4$: C, 63.2; H, 5.3; N, 5.7. Found: C, 63.3; H, 5.6; N, 5.8.

N-Phenacylsuccinamic Acid (**2a**).

To a solution of 2 g. (0.05 mole) of sodium hydroxide in 50 ml. of water was added 10.9 g. (0.050 mole) of *N*-phenacylsuccinimide (**1a**, m.p. 143-145°) and the mixture was shaken and heated to 60-70°. The solution obtained after a few minutes was cooled and acidified with 5 ml. (0.06 mole) of concentrated hydrochloric acid. The crystalline precipitate was collected, washed with water and dried to give 12 g. (> 100%) of product. Recrystallization from 50 ml. of ethanol gave 11 g. (93%) of **2a**, m.p. 149-151°; ir 1518 (amide II), 1637 (amide I), 1677 (ketone C=O), 1718 (carboxyl C=O), and 3380 cm^{-1} (N-H).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.3; H, 5.6. Found: C, 61.3; H, 5.7.

N-(*p*-Fluorophenacyl)succinamic Acid (**2b**).

A suspension of 35.1 g. (0.149 mole) of *N*-(*p*-fluorophenacyl)-succinimide (**1b**, m.p. 147-152°) in 164 ml. (0.164 mole) of 1 *N* sodium hydroxide was stirred for 3 days. The solution obtained was decanted from a gummy, undissolved material and filtered, then added dropwise with stirring to a solution of 181 ml. (0.181 mole) of 1 *N* hydrochloric acid and 181 ml. of water. The precipitate was collected, washed with water and dried to give 26.8 g. (71%) of product, m.p. 165-167°. Crystallization of 10.0 g. from 100 ml. of 95% ethanol gave 7.8 g. of **2b**, m.p. 168-169.5°; ir 1533 (amide II), 1647 (amide I), 1699 (ketone and carboxyl C=O), and 3335 cm^{-1} (N-H).

Anal. Calcd. for $C_{12}H_{12}FNO_4$: C, 56.9; H, 4.8; F, 7.5; N, 5.5. Found: C, 57.0, 56.9; H, 5.2, 4.9; F, 7.4, 7.5; N, 5.6, 5.4.

N-(*p*-Chlorophenacyl)succinamic Acid (**2c**).

Using essentially the same procedure described for the preparation of **2b**, 35.2 g. (0.140 mole) of *N*-(*p*-chlorophenacyl)succinimide (**1c**, m.p. 147-148.5°) was stirred in 147 ml. (0.147 mole) of 1 *N* sodium hydroxide for 17.5 hours to give 35.2 g. (93%) of product, m.p. 176-179°. Crystallization of 15.0 g. from 200 ml. of 95% ethanol gave 12.8 g. of **2c**, m.p. 180-182.5°; ir 1531 (amide II), 1635 (amide I), 1690 (ketone C=O), 1725 (carboxyl C=O), and 3380 cm^{-1} (N-H).

Anal. Calcd. for $C_{12}H_{12}ClNO_4$: C, 53.4; H, 4.5; Cl, 13.2; N, 5.2. Found: C, 53.5; H, 4.3; Cl, 13.1, 13.2; N, 4.9, 5.1.

Using essentially the same procedure described for the preparation of **1c**, 87.8 g. (0.376 mole) of 2-bromo-4'-chloroacetophenone in 500 ml. of ethanol was allowed to react with a solution of 16.6 g. (0.42 mole) of sodium hydroxide and 41.0 g. (0.414 mole) of succinimide in 50 ml. of water. To the reaction solution at 60° was added 15.0 g. (0.38 mole) of sodium hydroxide. After the latter had dissolved, the solution was stirred at ambient temperature for 1 hour and concentrated. The solution of the residue in about 750 ml. of water was washed with ether (three 100-ml. portions), heated and aerated to remove ether, chilled to 10° and acidified by slow addition of 32 ml. (0.39 mole) of concentrated hydrochloric acid. After 3 hours, the precipitate was collected, washed with water and dried to give 71.6 g. (71%) of **2c**. (The overall yield of **2c** when **1c** was isolated was 41%.)

The m.p. of pure **2c** was observed to be higher (182-184°) when the sample was inserted at 175° rather than at room temperature and the resolidified material melted *ca.* 160° with gas evolution. When the melt was then heated to 190° for a few minutes until gas evolution stopped, the resolidified sample melted *ca.* 140°. This observation prompted the experiment described above under preparation of **1c** in which **2c** was thermally recyclized.

N-(*p*-Bromophenacyl)succinamic Acid (**2d**).

Using essentially the same procedure described for the preparation of **2b**, 21.8 g. (0.074 mole) of *N*-(*p*-bromophenacyl)succinimide (**1d**, m.p. 171-172.5°) was stirred in 77 ml. (0.077 mole) of 1 *N* sodium hydroxide for 2 hours to give 22.3 g. (97%) of product, m.p. 179-182°. Crystallization of 10.0 g. from 150 ml. of 95% ethanol-150 ml. of water gave 9.1 g. of **2d**, m.p. 183-185°; ir 1556 (amide II), 1651 (amide I), 1699 (ketone and carboxyl C=O), and 3310 cm^{-1} (N-H).

Anal. Calcd. for $C_{12}H_{12}BrNO_4$: C, 45.9; H, 3.9; Br, 25.4; N, 4.5. Found: C, 45.8; H, 3.9; Br, 25.5; N, 4.4, 4.2.

N-(*p*-Methoxyphenacyl)succinamic Acid (**2e**).

Using essentially the same procedure described for the preparation of **2b**, 24.7 g. (0.100 mole) of *N*-(*p*-methoxyphenacyl)succinimide (**1e**, m.p. 91-93°) was stirred in 110 ml. (0.110 mole) of 1 *N* sodium hydroxide for 6 hours to give 25.2 g. (95%) of product, m.p. 151.5-155°, with some solid remaining to about 165° when inserted at room temperature; m.p. 154-156.5° when inserted at 140°. Crystallization of 8.1 g. from 150 ml. of 95% ethanol gave 7.1 g. of **2e**, m.p. 164-168°; ir 1509 (amide II) (slightly weaker and narrower band at 1520 assigned to Ph), 1669 (amide I), 1684, 1700 and 1720 (ketone and carboxyl C=O), and 3385 cm^{-1} (N-H).

Anal. Calcd. for $C_{13}H_{15}NO_5$: C, 58.9; H, 5.7; N, 5.3. Found: C, 59.0, 58.8; H, 5.5, 5.5; N, 4.9, 5.0;

5-Phenyl-2-oxazolepropionic Acid (**3a**).

A solution of 6.4 g. (0.027 mole) of *N*-phenacylsuccinamic acid (**2a**, m.p. 144.5-149°) in 32 ml. of concentrated sulfuric acid was kept at room temperature for 3.5 hours and poured into 650 ml. of water. The suspension obtained was kept at room temperature for 3 days, and the crystalline precipitate was collected, washed with water and dried to give 4.5 g. (76%) of **3a**, m.p. 148-150° [lit. (4) m.p. 148-149°]; mixed with **2a**, m.p. 123-140°; pK_a' 5.1; uv max neutral 265 (ϵ, 21,350) and 271 (ϵ, 21,100), acidic 263 (ϵ, 19,500), basic 266 (ϵ, 21,100) and 272 mμ (ϵ, 20,950); ir 1559 (oxazole ring), and 1714 and 1723 cm^{-1} (carboxyl C=O); nmr δ 12.1 (broad s, 1, CO_2H), 7.8-7.3 (m, 5, Ph H), 7.55 (s, 1, oxazole H), and 2.93 ppm (m, 4, CH_2CH_2).

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.3; H, 5.1; N, 6.5. Found: C, 66.3; H, 5.0; N, 6.4.

5-(*p*-Fluorophenyl)-2-oxazolepropionic Acid (**3b**).

Over a period of 8 minutes, 16.7 g. (0.066 mole) of *N*-(*p*-fluorophenacyl)succinamic acid (**2b**, m.p. 165-167°) was added with stirring to 42 ml. of concentrated sulfuric acid during which the temperature rose to 42°. The dark solution was stirred at room temperature for 16 hours, then poured slowly with stirring into 420 ml. of water while ice was added to keep the temperature below 10° (final volume 800 ml.). The precipitate obtained was collected, washed with water and dried to give 10.1 g. (65%) of product, m.p. 137-139.5°. Crystallization from 100 ml. of ethyl acetate-25 ml. of petroleum ether gave 6.7 g. of **3b**, m.p. 141-142°; ir 1561 (oxazole ring), and 1710 sh. and 1718 cm^{-1} (carboxyl C=O).

Anal. Calcd. for $C_{12}H_{10}FNO_3$: C, 61.3; H, 4.3; F, 8.1; N, 6.0. Found: C, 61.0; H, 4.3; F, 8.0, 8.2; N, 6.0.

5-(*p*-Chlorophenyl)-2-oxazolepropionic Acid (**3c**).

Using essentially the same procedure described for the preparation of **3b**, 20.1 g. (0.075 mole) of *N*-(*p*-chlorophenacyl)succinamic acid (**2c**, m.p. 176-179°) was stirred in 50 ml. of concentrated sulfuric acid (maximum temperature, 38°) for 25 hours to give 17.6 g. (94%) of product, m.p. 131-134°. Crystallization from 150 ml. of ethyl acetate (charcoal)-35 ml. of petroleum ether gave 10.8 g. of **3c**, m.p. 135-136°; ir 1552 (oxazole ring), and 1700 sh. and 1710 cm^{-1} (carboxyl C=O).

Anal. Calcd. for $C_{12}H_{10}ClNO_3$: C, 57.3; H, 4.0; Cl, 14.1; N, 5.6. Found: C, 57.4; H, 4.1; Cl, 14.4; N, 5.4, 5.4.

When this cyclization was allowed to proceed for only 2.5 hours the material recovered was almost half unreacted **2c** (by ir).

5-(*p*-Bromophenyl)-2-oxazolepropionic Acid (**3d**).

Using essentially the same procedure described for the preparation of **3b**, 17.4 g. (0.055 mole) of *N*-(*p*-bromophenacyl)succinamic acid (**2d**, m.p. 176-182°) was stirred in 44 ml. of concentrated sulfuric acid (maximum temperature, 38°) for 23 hours to give 16 g. (98%) of product, m.p. 156.5-158°. Crystallization from 200 ml. of ethyl acetate (charcoal)-50 ml. of petroleum ether gave

9.0 g. of **3d**, m.p. 158.5-160°; ir 1551 (oxazole ring), and 1700 sh. and 1709 cm^{-1} (carboxyl C=O).

Anal. Calcd. for $C_{12}H_{10}BrNO_3$: C, 48.7; H, 3.4; Br, 27.0; N, 4.7. Found: C, 48.9; H, 3.6; Br, 27.0; N, 4.6.

5-(4-Methoxy-3-sulfophenyl)-2-oxazolepropionic Acid (**3f**) Hemihydrate and Monohydrate.

Using essentially the same procedure described for the preparation of **3b**, 17.0 g. (0.064 mole) of *N*-(*p*-methoxyphenacyl)succinamic acid (**2e**, m.p. 151.5-155°) was stirred in 42.5 ml. of concentrated sulfuric acid (maximum temperature, 50°) for 21 hours. The clear, dark aqueous solution subsequently obtained (volume 700 ml.) was chilled for 2 hours to give a crystalline precipitate. The solid was collected, washed with cold water and dried under reduced pressure at 60° to give 20.9 g. (97%) of product (hemihydrate), m.p. 260° (dec.). Recrystallization from 550 ml. of water and drying under reduced pressure at 85° gave 17.7 g. of **3f** hemihydrate, m.p. 264.5° (dec.); $pK'_a < 1$ and 5.4; uv max neutral 216 (ϵ, 19,500) and 274 (ϵ, 24,800), acidic 215 (ϵ, 20,350) and 280 (ϵ, 22,250), basic 274 mμ (ϵ, 24,800); ir 619, 1032 and 1185 (sulfonic acid), 1649 (oxazole ring), 1727 (carboxyl C=O), and 3420 cm^{-1} (water); nmr (monohydrate) δ 8.79 (sharp s, 4, SO_3H, CO_2H and H_2O), 8.05 (d, 1, $J_{2,6}$ = 2.2 Hz., Ph 2-H), 7.72 (dd, 1, $J_{5,6}$ = 8.5 Hz., Ph 6-H), 7.55 (s, 1, oxazole H), 7.14 (d, 1, Ph 5-H), 3.84 (s, 3, CH_3O), and 2.95 ppm (m, 4, CH_2CH_2).

Anal. Calcd. for $C_{13}H_{13}NO_7S \cdot 0.5H_2O$: C, 46.4; H, 4.2; N, 4.2; S, 9.5; H_2O, 2.7. Found: C, 46.1, 46.3; H, 4.3, 4.1; N, 4.3, 4.2; S, 9.6, 9.7; H_2O, 2.4, 2.6.

Calcd. for $C_{13}H_{13}NO_7S \cdot H_2O$: H_2O, 5.2. Found: H_2O, 5.4.

N-Phenacylphthalimide (**4**).

To a stirred solution of 99.7 g. (0.50 mole) of 2-bromoacetophenone in 400 ml. of dimethylformamide was added 100 g. (0.54 mole) of potassium phthalimide in portions over 5 minutes, during which the temperature rose to 61°. After 45 minutes, the solution was poured slowly with stirring into 2 l. of water while ice was added to keep the temperature below 10° (final volume 3.5 l.). The precipitate obtained was collected, washed with water and dried to give 134.3 g. (> 100%) of product, m.p. 160-165°. Crystallization from 400 ml. of glacial acetic acid gave 118.3 g. (89%) of **4**, m.p. 166.5-167.5° [lit. (6,8) m.p. 165-167°, 167°]; ir 1701 (ketone C=O), and 1720 and 1770 cm^{-1} (imide C=O).

N-Phenacylphthalamic Acid (**5**) Monohydrate.

A suspension of 26.5 g. (0.100 mole) of *N*-phenacylphthalimide (**4**, m.p. 166.5-167.5°) in 110 ml. (0.110 mole) of 1 *N* sodium hydroxide was stirred for 6 days (3 days was also sufficient). The solution obtained was filtered and added at a rapid dropwise rate with stirring to a solution of 121 ml. (0.121 mole) of 1 *N* hydrochloric acid and 121 ml. of water. The precipitate was collected, washed with water and dried to constant weight at room temperature under reduced pressure over calcium chloride to give 27.6 g. (92%) of **5** monohydrate, softens 100°, m.p. 148-150° (effervescence) [lit. (8-10) for presumably pure anhydrous material m.p. 160°, 160-160.5°]; ir 1530 (amide II), 1642 (amide I), 1691 (ketone C=O), 1717 sh. (carboxyl C=O), and 3380 cm^{-1} (N-H).

Anal. Calcd. for $C_{16}H_{13}NO_4 \cdot H_2O$: C, 63.8; H, 5.0; N, 4.7; H_2O, 6.0. Found: C, 63.8; H, 5.0; N, 4.6; H_2O, 5.8.

When **5** was dried at 60-70° under reduced pressure partial cyclization to **4** occurred, as evidenced by appearance of the imide bands and reduction of the intensity of the amide bands in the ir spectrum of the product.

o-(5-Phenyl-2-oxazolyl)benzoic Acid (**6**).

Using essentially the same procedure described for the preparation of **3b**, 26.2 g. (0.087 mole) of *N*-phenacylphthalamic acid (**5**) monohydrate (m.p. 149-150°) was stirred in 65.5 ml. of concentrated sulfuric acid (maximum temperature, 45°) for 24 hours to give 22.1 g. (96%) of product, m.p. 185-192°. Crystallization of this material, combined with 1.6 g. from a previous run, from 400 ml. of methanol-200 ml. of water gave 20.5 g. of **6**, m.p. 191.5-193.5°; ir 1551 (oxazole ring) and 1708 cm^{-1} (carboxyl C=O).

Anal. Calcd. for $C_{16}H_{11}NO_3$: C, 72.4; H, 4.2; N, 5.3. Found: C, 72.6, 72.2; H, 4.0, 4.2; N, 5.2, 5.3.

Succinic Acid 2-Benzoylhydrazide (**7**).

A mixture of 101.3 g. (0.745 mole) of benzoic acid hydrazide and 74.5 g. (0.745 mole) of succinic anhydride in 350 ml. of acetone was heated to boiling giving a solution from which a crystalline precipitate began to separate almost immediately. The mixture was refluxed for 15 minutes and kept at room temperature for 2.5 days. The precipitate was collected, washed with acetone and dried to give 146.5 g. (83%) of **7**, m.p. 179-179.5° (effervescence) [lit. (11,15) m.p. variable 165-173°, 175°]; ir 1616, 1622 sh. and 1677 (diacyl-hydrazine C=O), 1725 (carboxyl C=O), and 3205 cm^{-1} (N-H).

Anal. Calcd. for $C_{11}H_{12}N_2O_4$: C, 55.9; H, 5.1; N, 11.9. Found: C, 55.6; H, 5.0; N, 11.5, 11.6.

5-Phenyl-1,3,4-oxadiazole-2-propionic Acid (**8**).

To 5 ml. of stirred concentrated sulfuric acid was rapidly added 1.0 g. (0.004 mole) of succinic acid 2-benzoylhydrazide (**7**) giving, after 10 minutes, a colorless solution which was stirred at room temperature for 65 hours. The solution was poured into 25 ml. of water and ice, the mixture was extracted with dichloromethane (50 and 25 ml.), and the extract was washed with saturated sodium chloride solution until neutral (three 10-ml. portions), dried over sodium sulfate and concentrated. Crystallization of the residue from 10 ml. of ethyl acetate-10 ml. of cyclohexane gave 0.4 g. (43%) of **8**, m.p. 139-140.5° [lit. (11) m.p. 138-140°]; ir 1559 (oxadiazole ring) and 1732 cm^{-1} (carboxyl C=O).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.6; H, 4.6; N, 12.8. Found: C, 60.8, 60.7; H, 4.7, 4.9; N, 13.0.

A subsequent run in which 10.4 g. (0.044 mole) of **7** was stirred in 25 ml. of concentrated sulfuric acid (maximum temperature, 45°) for 16.5 hours gave 5.5 g. (58%) of **8**, m.p. 138.5-140°; In a small preliminary run, dilution of the sulfuric acid solution without ice cooling caused partial hydrolysis of the product back to **7** as evidenced by the appearance of hydrazide bands in the ir spectrum of the crude product.

N-Benzamidosuccinimide (**9**).

A suspension of 1.0 g. (0.004 mole) of succinic acid 2-benzoylhydrazide (**7**) in 5 ml. of acetic anhydride was stirred in a water bath at 80° for 40 minutes during which the solid gradually dissolved. The solution was allowed to cool and the resulting slurry was diluted with 10 ml. of ether. The solid was collected, washed with ether and dried to give 0.6 g. (65%) of **9**, m.p. 225.5-226°; ir 1525 (amide II), 1657 (amide I), 1735 (broad) and 1793 (imide C=O), and 3150 cm^{-1} (N-H); nmr δ 11.05 (broad s, 1, NH), 8.1-7.4 (m, 5, Ph H), and 2.85 ppm (s, 4, CH_2CH_2).

Anal. Calcd. for $C_{11}H_{10}N_2O_3$: C, 60.6; H, 4.6; N, 12.8. Found: C, 60.8; H, 4.8; N, 13.0.

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