Synthesis and ^{1}H NMR Spectra of Some 1-Aryl-2,5-pyrrolidinediones [1]

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Three 1-aryl-2,5 pyrrolidinediones, two of which are novel, were prepared by reaction of the requisite primary aromatic amines with succinic anhydride, followed by treatment with acetic anhydride. The ^{1}H nmr spectra for the derivatives in which aryl is 1-naphthyl and 1-anthracenyl exhibit 32-line multiplets for the four aliphatic hydrogens, indicating that all four are in different environments. Examination of molecular models demonstrates that the pyrrolidinedione and aryl ring systems cannot be coplanar and that rotation about the nitrogen-aryl bond is restricted. Molecular mechanics calculations reveal that a dihedral angle of 50-65° for the two ring systems results in the minimum steric interaction energy.

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1-(3,5-Dichlorophenyl)-2,5-pyrrolidinedione, **1a**, also commonly called *N*-(3,5-dichlorophenyl)succinimide (NDPS), has potentially useful fungicidal activity [3,4]. However, agricultural use of the compound is restricted due to its demonstrated nephrotoxicity [5].

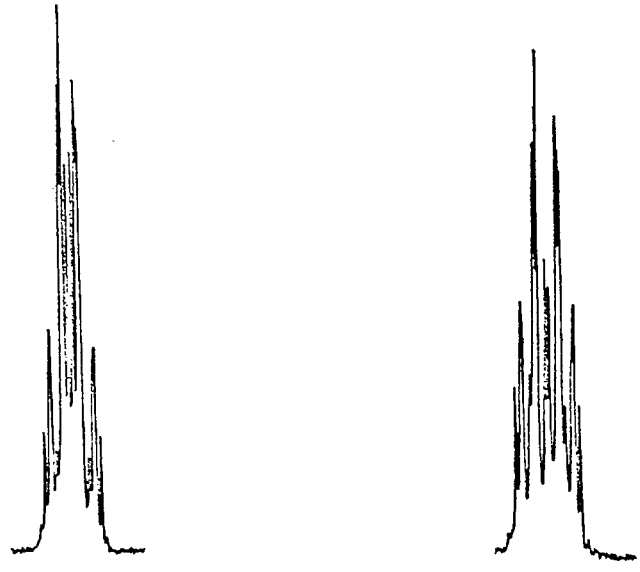
As part of an effort to develop a model for chemical-induced nephrotoxicity, systematic variation in the structure of NDPS has been undertaken. One aspect of the study is to assess the effect of increasing the size of the aryl portion and varying the position of its connection to nitrogen, **1b-d** [6].

Preparation of NDPS is accomplished easily as indicated [4] (reactions 1 and 2). Application to **1b-d** appeared feasible, the requisite primary aromatic amines being available for purchase or by reduction of the corresponding nitro compounds [7] (reaction 3). There is no published reference to the anthracenyl derivatives **1c** and **1d**. 1-(1-Naphthyl)-2,5-pyrrolidinedione, **1b**, has reportedly been prepared from 1-aminonaphthalene using three different procedures.

Heating 1-aminonaphthalene with succinic acid at 190° yields **1b** [8,9]. However, the method used for making NDPS (reactions 1 and 2) is superior.

There is an assertion that boiling 1-aminonaphthalene with a fivefold excess of diethyl succinate forms **1b** [10]. All efforts to reproduce this outcome were unsuccessful; tlc examination of the solutions invariably revealed only 1-aminonaphthalene and no **1b**. There is no apparent explanation for the result reported; others have referred to the unreactivity of primary aromatic amines toward esters [11].

There is a relatively recent claim that heating an acetic acid solution of 1-aminonaphthalene and succinic anhydride to reflux for 30 minutes gives **1b** [12], although the procedure cited [13] is for preparation of phthalimides. As expected, the result is actually formation of the corresponding succinamic acid **2** (Ar = 1-naphthyl).



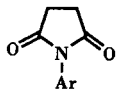
1-(1-naphthyl)-2,5-pyrrolidinedione

1-(1-anthracenyl)-2,5-pyrrolidinedione

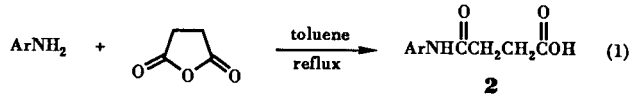
Figure 1. NMR spectra of 2,5-pyrrolidinedione ring hydrogens.

It was concluded that the best route to **1b-d** was use of reactions **1** and **2**. The products thus prepared were recrystallized from ethanol and further purified *via* column chromatography. The resulting materials yielded single spots when examined by tlc. Elemental analyses and ir spectra were satisfactory. The ^{1}H nmr spectra, however, were not entirely as expected.

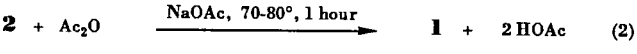
Superficial considerations led to the assumption that the aliphatic hydrogens of the 2,5-pyrrolidinedione ring should give rise to a singlet. Indeed, for **1d** a 4 H singlet was observed at δ 3.14. On the other hand, **1b** and **1c** both exhibited complex but symmetrical multiplets centered at



1a, Ar = 3,5-dichlorophenyl
1b, Ar = 1-naphthyl
1c, Ar = 1-anthracenyl
1d, Ar = 9-anthracenyl



(1)



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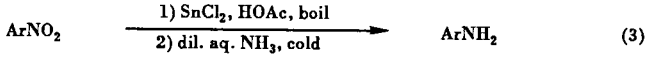

(3)

δ 2.93 and δ 3.01, respectively (Figure 1). In these molecules, which are obviously less symmetrical than **1d**, it is evident that non-equivalence of the aliphatic hydrogens is induced.

The non-equivalence is explained on the basis that the 2,5-pyrrolidinedione ring and the aryl substituents cannot be coplanar and rotation about the nitrogen-aryl bond is restricted. Examination of molecular models reveals overlapping van der Waals radii for oxygen and the C(8) hydrogen of the naphthyl substituent of **1b** (Figure 2). Molecular mechanics calculations indicate a rotational

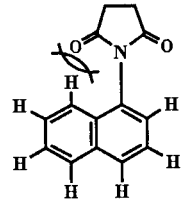

Figure 2. Overlapping van der Waals radii for oxygen and the naphthyl C(8) hydrogen in 1-(1-naphthyl)-2,5-pyrrolidinedione.

barrier of about 350 kcal/mole and that a dihedral angle of approximately 50° for the two ring systems in **1b** results in the minimum steric interaction energy (Figure 3). Thus, all four aliphatic hydrogens are in different environments, resulting in a 32-line multiplet. Similar considerations apply to **1c**.

The compounds **1c** and **1d** are novel, as are their corresponding succinamic acid precursors **2**. However, the latter were not characterized thoroughly and were promptly treated as in reaction 2.

This investigation clearly demonstrates that reactions 1 and 2 provide the preferred method for synthesis of 1-aryl-2,5-pyrrolidinediones.

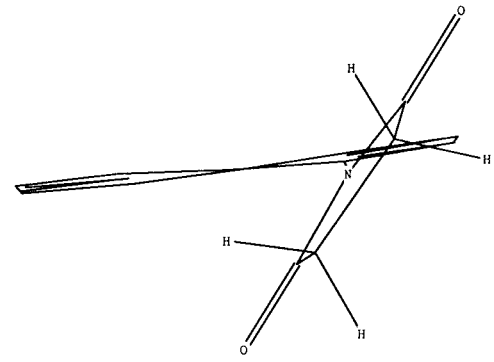

Figure 3. Conformation of 1-(1-naphthyl)-2,5-pyrrolidinedione with minimum steric interaction energy viewed along the naphthyl C(1)-nitrogen bond axis.

EXPERIMENTAL

Melting points were determined using a Mel-temp device and are uncorrected. The ir spectra were obtained with a Nicolet 20DXB spectrophotometer using the DRIFTS technique. The ^{1}H nmr spectra were recorded using a Varian XL-200 spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, GA.

Molecular mechanics calculations were performed using the program PCMODEL PI (Version 3.3) [14], available from Serena Software, Box 3076, Bloomington, IN 47402-3076.

Solvents and routine reagents such as acids and bases (Fisher Scientific), diethyl succinate (Matheson, Coleman and Bell), and succinic anhydride (Sigma and Aldrich) were used as received. All other starting materials were obtained from Aldrich and used as received. 9-Aminoanthracene, the precursor to **1d**, was prepared by reduction of 9-nitroanthracene with tin(II) chloride followed by treatment with dilute aqueous ammonia [7].

Attempted Reaction of 1-Aminonaphthalene with Diethyl Succinate.

1-Aminonaphthalene (2.90 g, 0.020 mole) was placed in a 100-ml flask with a Teflon-coated magnetic stirring bar. Diethyl succinate (16.6 ml, 0.100 mole) was added with stirring. A Dean-Stark trap was installed and the solution was heated to reflux four hours. There was no evidence of reaction, and no distillate was collected. After cooling, examination of the solution by tlc revealed a single spot due to 1-aminonaphthalene and no **1b**.

Reaction of 1-Aminonaphthalene with Succinic Anhydride in Acetic Acid Heated to Reflux.

1-Aminonaphthalene (5.00 g, 0.035 mole) was placed in a 250-ml flask with a Teflon-coated magnetic stirring bar. Glacial acetic acid (30 ml) was added with stirring, resulting in a deep purple solution. A slurry of succinic anhydride (5.00 g, 0.050 mole) in glacial acetic acid (20 ml) was added, with an additional 10 ml of acetic acid being used to assure quantitative transfer. After the addition, a lavender solid formed which dissolved on heating. The solution was heated to reflux for 30 minutes, then cooled and allowed to remain at room temperature for seven days. Crystallization began by the end of two days and was essentially complete after five days. The crystalline material was collected by vacuum filtration, washed with several small portions of

glacial acetic acid, and dried in air, 2.22 g, mp 156-163°. Examination by tlc revealed a single spot with R_f identical to that for authentic **2** (Ar = 1-naphthyl); the yield was 26%.

1-Aryl-2,5-pyrrolidinediones **1b-d**.

Preparation was according to the general method of Fujinami *et al.* [4]. If necessary, final products were purified by column chromatography using 60-270 mesh silica gel (Universal Scientific); columns were packed using ethyl acetate, while elution was accomplished using either 100% chloroform or 1:1 chloroform:-ethyl acetate. All products exhibited single spots when examined by tlc.

1-(1-Naphthyl)-2,5-pyrrolidinedione (**1b**) was prepared using 1-aminonaphthalene (5.00 g, 0.035 mole) and succinic anhydride (3.49 g, 0.035 mole) dissolved in 200 ml toluene and heated to reflux. After cooling the *N*-(1-naphthyl)succinamic acid was collected by vacuum filtration and dried, 7.81 g (92%). The succinamic acid (0.032 mole) was heated with acetic anhydride (200 ml, 0.44 mole) and sodium acetate (0.88 g, 0.011 mole). Pouring the mixture into 400 ml cold water caused the product to separate as an oil. Trituration produced a pale purple solid. Recrystallization from absolute ethanol yielded pure **1b**, 3.75 g (52%), mp 147-149° (lit 152° [8,9]); ir: 1698 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.7-3.1 (symmetrical m, 4 H), 7.3-8.1 (m, 7 H).

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.56; H, 4.93; N, 6.19.

1-(1-Anthracenyl)-2,5-pyrrolidinedione (**1c**) was prepared using 1-aminoanthracene (5.00 g, 0.026 mole) and succinic anhydride (2.59 g, 0.026 mole) dissolved in 200 ml toluene and heated to reflux. After cooling the *N*-(1-anthracenyl)succinamic acid was collected by vacuum filtration and dried, 7.10 g (93%). The succinamic acid (0.024 mole) was heated with acetic anhydride (100 ml, 0.33 mole) and sodium acetate (0.66 g, 0.008 mole). The mixture was poured into 300 ml water. The precipitated **1c** was recrystallized from absolute ethanol, 4.44 g (67%). This material was purified further by column chromatography, mp 248-250°; ir: 1706 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 2.8-3.2 (symmetrical m, 4 H), 7.3-7.7 (m, 4 H), 8.0-8.3 (m, 3 H), 8.5 (s, 1 H), 8.7 (s, 1 H).

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.40; H, 4.83; N, 5.03.

1-(9-Anthracenyl)-2,5-pyrrolidinedione (**1d**) was prepared using 9-aminoanthracene (4.01 g, 0.21 mole) and succinic anhydride (2.08 g, 0.21 mole) dissolved in 200 ml toluene and heated to reflux. After cooling the pale yellow *N*-(9-anthracenyl)succinamic acid was collected and dried, 3.42 g (56%). The succinamic acid (0.012 mole) was heated with acetic anhydride (100 ml, 0.16 mole) and sodium acetate (0.33 g, 0.004 mole). The mixture was poured into an equal volume of cold water. Collection of the precipitate and recrystallization from absolute ethanol provided **1d**, 3.00 g (61%). This material was further purified by column chromatography, mp 261-263°; ir: 1722 cm^{-1}; ^1H nmr (dimethyl sulfoxide-d_6): δ 3.14 (s, 4 H), 7.5-7.7 (m, 4 H), 7.8-8.0 (m, 2 H), 8.1-8.3 (m, 2 H), 8.8 (s, 1 H).

Anal. Calcd. for $C_{18}H_{13}NO_2$: C, 78.53; H, 4.76; N, 5.09. Found: C, 78.62; H, 4.81; N, 5.03.

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REFERENCES AND NOTES

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[14] W. C. Still, MODEL program (VAX version 1.1); modified by K. Steliou; adapted to the IBM-PC by M. M. Midland; further modified by K. E. Gilbert and J. J. Gajewski.