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Full Paper

The Synthesis of Unsubstituted Cyclic Imides Using Hydroxylamine under Microwave Irradiation†

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Abstract: Unsubstituted cyclic imides were synthesized from a series of cyclic anhydrides, hydroxylamine hydrochloride ($NH_2OH{\cdot}HCl$), and 4-*N*,*N*-dimethylamino-pyridine (DMAP, base catalyst) under microwave irradiation in monomode and multimode microwaves. This novel microwave synthesis produced high yields of the unsubstituted cyclic imides for both the monomode (61 - 81%) and multimode (84 - 97%) microwaves.

Keywords: Hydroxylamine·HCl; unsubstituted cyclic imides; DMAP; microwaves.

Introduction

The unsubstituted cyclic imide is an important functionality which has been found to maintain significant biological activity [1-3]. The synthesis of unsubstituted cyclic imides either by conventional methods or microwave irradiation is often carried out under harsh conditions thereby increasing byproduct formation [4]. Currently, there are several conventional and microwave techniques to produce unsubstituted cyclic imides. Many conventional syntheses of unsubstituted

cyclic imides use the reaction of cyclic anhydrides with reactants including ammonia, urea, formamide, and lithium nitride [5-7]. Other conventional reactions catalyze the cyclization of acid-amide functionalities forming unsubstituted cyclic imides. These catalysts include carbonyldiimidazole (CDI), DMAP, and $AlCl_3$ [8, 9]. Additional microwave syntheses use the reaction of cyclic anhydrides with urea or thiourea, formamide, benzonitrile, cyanate, thiocyanate, DMAP/ammonium chloride, and ammonium acetate [10-15].

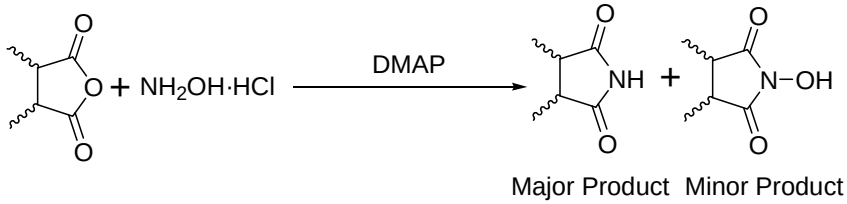
The application of microwave technology in many conventional syntheses offers many advantages including increased product yields and decreased reaction times [16-19]. We wish to report the synthesis of a series of unsubstituted cyclic imides using cyclic anhydrides, $NH_2OH{\cdot}HCl$, and DMAP via a novel microwave technique. This novel microwave synthesis produced unsubstituted cyclic imides in good yields within minutes.

Results and Discussion

Microwave Synthesis

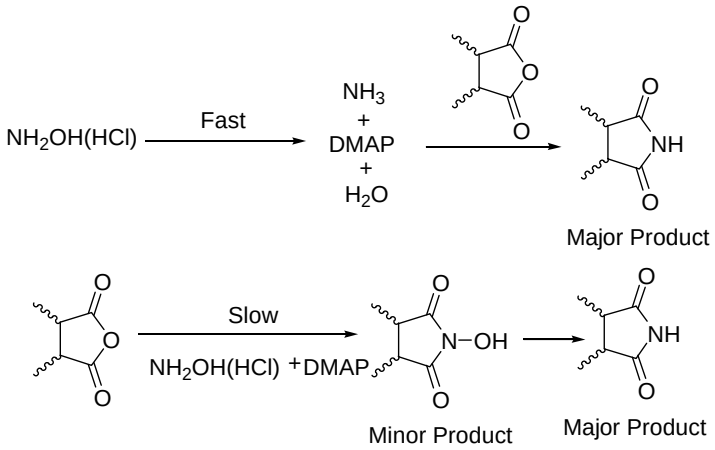
The novel syntheses were conducted under microwave irradiation using hydroxylamine hydrochloride, DMAP, and an array of cyclic anhydrides yielding the corresponding unsubstituted cyclic imide. (Scheme 1) [20]. Although modifications of several experimental parameters gave moderate yields of the *N*-hydroxy cyclic imides (~30 percent), repeated studies found that the unsubstituted cyclic imides were the major products. Increased *N*-hydroxy cyclic imides yields were identified at lower temperatures and shorter reaction times. These results contradict Sugamoto *et al*., whoreported that *N*-hydroxy cyclic imides were synthesized in high yield under similar conditions [20]. The current data supports research done by Consonni *et al*., which found that cyclic *N*-hydroxyimides are converted to unsubstituted cyclic imides under basic conditions [21]. Application of this novel microwave technique can be used to synthesize many biologically important molecules including that of streptimidone, a glutarimide antibiotic [22].

Scheme 1. The Synthesis of Unsubstituted Cyclic Imides



Whereas this novel microwave synthesis produced high yields of the unsubstituted cyclic imides, no definite mechanism has been identified. One possible mechanism for unsubstituted cyclic imide formation is the breakdown of hydroxylamine·HCl into ammonia and water (Scheme 2). Ammonia production then promotes unsubstituted cyclic imide formation. A second possibility is the conversion of cyclic *N*-hydroximide to the unsubstituted cyclic imide. Unsubstituted cyclic imides formation appears to be enhanced by the addition of a base catalyst and additional heating.

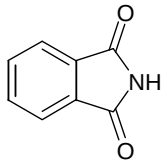
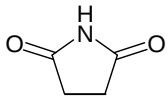
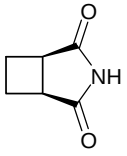
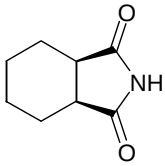
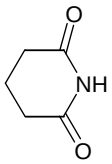
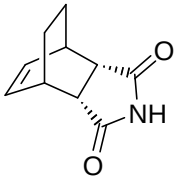
Scheme 2. Possible Mechanisms for the Hydroxylamine and Cyclic Anhydride Synthesis



Monomode Microwave Synthesis

The monomode microwave synthesis furnished unsubstituted cyclic imides using hydroxylamine as a source for nitrogen, DMAP, and cyclic anhydrides for the cyclic carbon backbone. The microwave synthesis was done at 150 ˚C over 5 minutes with a maximum energy output of 300W, producing between 61 and 81 isolated percent yields.

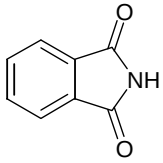
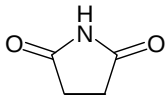
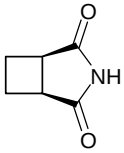
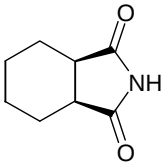
Table 1. Monomode Synthesis of Unsubstituted Cyclic Imides using $NH_2OH(HCl)$/ DMAP.

$NH_2OH(HCl)$/ DMAP (CEM Discover)				
Entry	**Imides**	**Time (min)**	**Temp (^oC)**	**Yield (%)**
1		5	150	70
2		5	150	71
3		5	150	61
4		5	150	61
5		5	150	61
6		5	150	81

Multimode Microwave Synthesis

A series of multimode microwave reactions were used to identify a cost effective alternative to the more expensive monomode synthesis. This technique used similar reaction conditions and anhydrides to that of the monomode microwave syntheses. The reaction times ranged from 1 to 3 minutes at full power until the material melted and started to vigorously bubble. Isolated percent yields were between 84 and 97 percent.

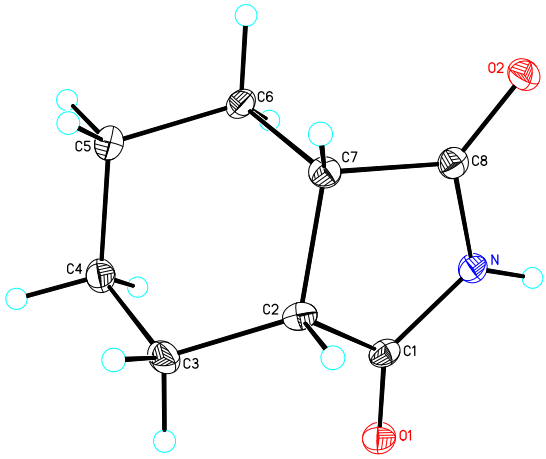
Table 2. Multimode Synthesis of Unsubstituted Imides Using NH_2OH and DMAP.

NH_2OH and DMAP (Multimode)			
Entry	Imides	Time (min)	Yield (%)
1		2.68	97
2		1.82	96
3		1.20	96
4		1.57	84

Unsubstituted cyclic imides were produced in good yields in both the multimode and monomode microwaves. Slightly higher isolated yields were found in the multimode reactions compared to the monomode result. This variation may stem from energy output differences for the multimode (1100 W) and the monomode (300 W) microwaves.

Crystals isolated from this and previous unsubstituted cyclic imide syntheses were analyzed by single crystal X-ray diffraction generating good structural data for the desired cyclic imide products [23]. Specifically, the unsubstituted cyclic imide 3a,4,5,6,7,7a-hexahydro-1H-isoindole-1,3(2H)-dione (**4**, Figure 1) was characterized by X-ray diffraction studies [24]. The crystal structure of this compound has previously been reported by Wang and co-workers [25]. Our unpublished crystal data found an unsubstituted cyclic imide bound in the *cis* position of a well defined cyclohexane ring (R factor = 0.0393).

Figure 1. Molecular Diagram of 3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione (**4**) [24].



Experimental

General

The monomode microwave reactions were carried out in a CEM Discover Microwave. Multimode microwave reactions were done in a Kennmore Microwave Oven (Household) Output: 1100 Watts (Frequency: 2450 MHz). All Gas Chromatograph Mass Spectrometry (GC-MS) was performed using a Shimadzu GC-17A and GCMS-QP5050A Labsolutions system. All reagents were purchased from Aldrich Chemical Company and were used without further purification. Since two different methods are described in this article *Method 1* will refer to synthesis carried out under monomode conditions, while, *Method 2* will refer to synthesis under multimode conditions. Only the GCMS data is given, however unsubstituted cyclic imides data matched that reported earlier [15].

Phthalimide (**1**): *Method 1*. Phthalic anhydride (0.20 g, 1.35 mmol), $NH_2OH{\cdot}HCl$ (0.09 g, 1.30 mmol), and DMAP (0.04 g, 0.33 mmol) were thoroughly mixed in a CEM vial with a stirrer. This was capped and heated in a CEM Discover microwave for 5 minutes at 150 ^oC. This was rapidly cooled to room temperature yielding a dark brown solid. The reaction mixture was dissolved in AcOEt (4 mL) and was washed with distilled water (2 x 2 mL). The organic layer was concentrated to obtain a white solid (0.14 g, 70%); MS m/z 147 (M^+) 104, 76, 50.

Phthalimide (**1**): *Method 2.* Phthalic anhydride (1.0 g, 6.75 mmol), $NH_2OH{\cdot}HCl$ (0.54 g, 7.7 mmol), and DMAP (0.08 g, 0.65 mmol) were mixed in an 8 mL Teflon capped vial. The mixture was allowed to heat for 4 minutes and 11 seconds at 30 percent power in the multimode microwave and then cooled to room temperature. The sample was dissolved in acetone and flash chromatographed using silica (~30 g) with pure acetone as the mobile phase to obtain a yellow solid. Yield: 0.96 g (97%); MS m/z 147 (M^+) 104, 76, 50.

Succinimide (**2**): *Method 1*. Succinic anhydride (0.20 g, 2.00 mmol), $NH_2OH{\cdot}HCl$ (0.14 g, 2.0 mmol), and DMAP (0.04 g, 0.33 mmol) were thoroughly mixed in a CEM vial with a stirrer. This was capped

and heated in a CEM Discover microwave for 5 minutes at 150 ˚C. This was rapidly cooled to room temperature yielding a dark brown solid. The reaction mixture was dissolved in AcOEt (4 mL) and was washed with distilled water (2 x 2 mL). The organic layer was concentrated to obtain a white solid (0.14 g, 71%); MS m/z 99 (M^+) 56.

Succinimide (**2**): *Method 2*. Succinic anhydride (1.0 g, 10 mmol), $NH_2OH{\cdot}HCl$ (0.80 g, 11 mmol), and DMAP (0.12 g, 0.98 mmol) were mixed in an 8 mL Teflon capped vial. The mixture was allowed to heat for 1 minute 49 seconds at full power in the multimode microwave and then cooled to room temperature. The sample was dissolved in acetone and flash chromatographed using silica (~30 g) with pure acetone as the mobile phase to obtain a yellow solid (0.95 g, 96%); MS m/z 99 (M^+) 56.

cis-1,2-Cyclobutanedicarboximide (**3**): *Method 1. cis*-1,2-Cyclobutanedicarboxylic acid anhydride (0.20 g, 1.59 mmol), $NH_2OH{\cdot}HCl$) (0.11 g, 1.58 mmol), and DMAP (0.04 g, 0.33 mmol) were thoroughly mixed in a CEM vial with a stirrer. This was capped and heated in a CEM Discover microwave for 5 minutes at 150 ˚C. This was rapidly cooled to room temperature yielding a white solid. The reaction mixture was dissolved in AcOEt (4 mL) and was washed with distilled water (2 x 2 mL). The organic layer was concentrated to obtain a white solid (0.12 g, 61%); MS m/z 125 (M^+) 82, 54.

cis-1,2-Cyclobutanedicarboximide (**3**): *Method 2. cis*-1,2-Cyclobutanedicarboxylic acid anhydride (1.0 g, 7.9 mmol), $NH_2OH{\cdot}HCl$ (0.63 g, 9.1 mmol), and DMAP (0.10 g, 0.82 mmol) were mixed in an 8 mL Teflon capped vial. The mixture was allowed to heat for 1 minute 12 seconds at full power in the multimode microwave and then cooled to room temperature. The sample was dissolved in acetone and flash chromatographed using silica (~30 g) with pure acetone as the mobile phase to obtain a light brown solid, (0.95 g, 96%); MS m/z 125 (M^+) 82, 54.

3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione (**4**): Method 1. *cis*-1,2-Cyclohexanedicarboxylic acid anhydride (0.20 g, 1.30 mmol), $NH_2OH{\cdot}HCl$ (0.09 g, 1.29 mmol), and DMAP (0.04 g, 0.33 mmol) were thoroughly mixed in a CEM vial with a stirrer. This was capped and heated in a CEM Discover microwave for 5 minutes at 150 ˚C. This was rapidly cooled to room temperature yielding a white solid. The reaction mixture was dissolved in AcOEt (4 mL) and was washed with distilled water (2 x 2 mL). The organic layer was concentrated to obtain a white solid (0.12 g, 61%); MS m/z 153 (M^+) 125, 99, 82, 67, 54, 41.

3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione (**4**): Method 2. *cis*-1,2-Cyclohexanedicarboxylic acid anhydride (1.0 g, 6.5 mmol), $NH_2OH{\cdot}HCl$ (0.51 g, 7.3 mmol), and DMAP (0.08 g, 0.65 mmol) were mixed in an 8 mL Teflon capped vial. The mixture was allowed to heat for 1 minute 49 seconds at full power in the multimode microwave and then cooled to room temperature. The sample was dissolved in acetone and flash chromatographed using silica (~30 g) with pure acetone as the mobile phase to obtain a white solid (0.83 g, 84%); MS m/z 153 (M^+) 125, 99, 82, 67, 54, 41.

Glutarimide (**5**): *Method 1.* Glutaric anhydride (0.20 g, 1.75 mmol), $NH_2OH{\cdot}HCl$ (0.12 g, 1.73 mmol), and DMAP (0.04 g, 0.33 mmol) were thoroughly mixed in a CEM vial with a stirrer. This was capped and heated in a CEM Discover microwave for 5 minutes at 150 ˚C. This was rapidly cooled to room temperature yielding a dark brown solid. The reaction mixture was dissolved in AcOEt (4 mL) and was washed with distilled water (2 x 2 mL). The organic layer was concentrated to obtain a light brown solid (0.12 g, 61%); MS m/z 113 (M^+) 70, 42.

3a,4,7,7a-Tetrahydro-4,7-ethano-1H-isoindole-1,3(2H)-dione (**6**): *Method 1.* cis-Bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic acid anhydride (0.10 g, 0.56 mmol), $NH_2OH{\cdot}HCl$ (0.05 g, 0.72 mmol) and DMAP (0.02 g, 0.16 mmol) were mixed thoroughly in a CEM-sealed vial with a magnetic stirrer. The mixture was heated for 5 min at 150 ˚C in a CEM Discover microwave powered at 150 W. The sample was then cooled rapidly to 40 ˚C. The reaction mixture was dissolved in AcOEt (4 mL) and was washed with distilled water (2 x 2 mL). The organic layer was concentrated to obtain a light brown solid (0.08 g, 81 %); MS m/z 177 (M^+) 149, 99, 78, 51.

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Sample Availability: Samples of the compounds are commerically available.

Supporting Data

Table 1. Crystal Data for 3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione.

Identification code	3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione	
Empirical formula	$C_8H_{11}NO_2$	
Formula weight	153.18	
Temperature	203(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_1\,2_1\,2_1$	
Unit cell dimensions	a = 6.7185(4) Å	α= 90°
	b = 7.8339(4) Å	β= 90°
	c = 14.2861(10) Å	γ = 90°
Volume	751.91(8) $Å^3$	
Z	4	
Density (calculated)	1.353 Mg/m^3	
Absorption coefficient	0.098 mm^{-1}	
F(000)	328	
Crystal size	0.65 x 0.55 x 0.35 mm^3	
Theta range for data collection	4.91 to 32.46°.	
Index ranges	$-4<=h<=9$, $-9<=k<=11$, $-20<=l<=18$	
Reflections collected	5210	
Independent reflections	2427 [$R_{(int)}$ = 0.0317]	
Completeness to theta = 25.00°	99.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.90324	
Refinement method	Full-matrix least-squares on F_2	
Data / restraints / parameters	2427 / 0 / 100	
Goodness-of-fit on F2	0.873	
Final R indices [I>2sigma(I)]	R_1 = 0.0393, wR_2 = 0.0772	
R indices (all data)	R_1 = 0.0674, wR_2 = 0.0821	
Absolute structure parameter	-1.2(9)	
Largest diff. peak and hole	0.248 and -0.202 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 104) and equivalent isotropic displacement parameters ($Å^2 x\ 10^3$) for 3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atoms	**x**	**y**	**z**	**U(eq)**
O(1)	14804(1)	4204(1)	1252(1)	36(1)
O(2)	9681(1)	1315(1)	2592(1)	36(1)
N	12075(1)	3090(1)	2005(1)	28(1)
C(1)	13916(1)	2996(1)	1573(1)	27(1)
C(2)	14594(1)	1165(1)	1644(1)	27(1)
C(3)	15963(1)	537(1)	866(1)	34(1)
C(4)	14865(1)	35(1)	-21(1)	34(1)
C(5)	13199(1)	-1214(1)	201(1)	33(1)
C(6)	11673(1)	-391(1)	850(1)	28(1)
C(7)	12617(1)	196(1)	1778(1)	27(1)
C(8)	11271(1)	1519(1)	2197(1)	27(1)

Table 3. Bond lengths [Å] for 3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione.

Bonds	Lengths
O(1)-C(1)	1.2089(7)
O(2)-C(8)	1.2185(9)
N-C(8)	1.3718(8)
N-C(1)	1.3840(9)
N-H(0A)	0.8700
C(1)-C(2)	1.5091(8)
C(2)-C(3)	1.5241(10)
C(2)-C(7)	1.5419(9)
C(2)-H(2A)	0.9900
C(3)-C(4)	1.5179(10)
C(3)-H(3A)	0.9800
C(3)-H(3B)	0.9800
C(4)-C(5)	1.5208(10)
C(4)-H(4A)	0.9800
C(4)-H(4B)	0.9800
C(5)-C(6)	1.5246(10)
C(5)-H(5A)	0.9800
C(5)-H(5B)	0.9800
C(6)-C(7)	1.5401(10)
C(6)-H(6A)	0.9800
C(6)-H(6B)	0.9800
C(7)-C(8)	1.5000(10)
C(7)-H(7A)	0.9900

Table 4. Bond Angles [°] for 3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione.

Atoms	Angles
C(8)-N-C(1)	113.19(5)
C(8)-N-H(0A)	123.4
C(1)-N-H(0A)	123.4
O(1)-C(1)-N	124.68(6)
O(1)-C(1)-C(2)	128.35(6)
N-C(1)-C(2)	106.88(5)
C(1)-C(2)-C(3)	116.13(5)
C(1)-C(2)-C(7)	102.49(5)
C(3)-C(2)-C(7)	116.87(5)
C(1)-C(2)-H(2A)	106.9
C(3)-C(2)-H(2A)	106.9
C(7)-C(2)-H(2A)	106.9
C(4)-C(3)-C(2)	113.50(6)
C(4)-C(3)-H(3A)	108.9
C(2)-C(3)-H(3A)	108.9
C(4)-C(3)-H(3B)	108.9
C(2)-C(3)-H(3B)	108.9
H(3A)-C(3)-H(3B)	107.7
C(3)-C(4)-C(5)	110.48(6)
C(3)-C(4)-H(4A)	109.6
C(5)-C(4)-H(4A)	109.6
C(3)-C(4)-H(4B)	109.6
C(5)-C(4)-H(4B)	109.6
H(4A)-C(4)-H(4B)	108.1
C(4)-C(5)-C(6)	110.47(6)
C(4)-C(5)-H(5A)	109.6
C(6)-C(5)-H(5A)	109.6
C(4)-C(5)-H(5B)	109.6
C(6)-C(5)-H(5B)	109.6
H(5A)-C(5)-H(5B)	108.1
C(5)-C(6)-C(7)	111.88(6)
C(5)-C(6)-H(6A)	109.2
C(7)-C(6)-H(6A)	109.2
C(5)-C(6)-H(6B)	109.2
C(7)-C(6)-H(6B)	109.2
H(6A)-C(6)-H(6B)	107.9
C(8)-C(7)-C(6)	107.52(6)
C(8)-C(7)-C(2)	103.25(5)
C(6)-C(7)-C(2)	113.23(6)
C(8)-C(7)-H(7A)	110.8
C(6)-C(7)-H(7A)	110.8
C(2)-C(7)-H(7A)	110.8
O(2)-C(8)-N	123.75(6)
O(2)-C(8)-C(7)	128.51(6)
N-C(8)-C(7)	107.61(6)

Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters (Å2x 103) for eb1a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	42(1)	28(1)	39(1)	1(1)	7(1)	-8(1)
O(2)	38(1)	28(1)	42(1)	-1(1)	14(1)	-4(1)
N	32(1)	20(1)	33(1)	-1(1)	4(1)	-1(1)
C(1)	31(1)	26(1)	23(1)	0(1)	-4(1)	-5(1)
C(2)	25(1)	24(1)	31(1)	2(1)	-5(1)	-3(1)
C(3)	25(1)	29(1)	47(1)	0(1)	5(1)	4(1)
C(4)	37(1)	30(1)	34(1)	-2(1)	9(1)	1(1)
C(5)	36(1)	29(1)	34(1)	-6(1)	2(1)	2(1)
C(6)	27(1)	23(1)	35(1)	-6(1)	-4(1)	1(1)
C(7)	29(1)	23(1)	28(1)	4(1)	1(1)	0(1)
C(8)	31(1)	27(1)	23(1)	1(1)	-1(1)	-2(1)

Table 6. Hydrogen coordinates ($x10^4$) and isotropic displacement parameters ($Å^2x\ 10^3$) for 3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione.

atom	x	y	z	U(eq)
H(0A)	11488	4048	2141	34
H(2A)	15344	1059	2237	32
H(3A)	16922	1439	716	40
H(3B)	16715	-452	1094	40
H(4A)	15798	-491	-462	40
H(4B)	14308	1057	-317	40
H(5A)	13755	-2233	502	40
H(5B)	12546	-1569	-380	40
H(6A)	10610	-1213	983	34
H(6B)	11075	595	535	34
H(7A)	12791	780	2211	32

Table 7. Torsion angles [°] for for 3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione.

Torsional Atoms	Atoms
C(8)-N-C(1)-O(1)	171.80(6)
C(8)-N-C(1)-C(2)	-11.56(7)
O(1)-C(1)-C(2)-C(3)	-32.24(10)
N-C(1)-C(2)-C(3)	151.28(6)
O(1)-C(1)-C(2)-C(7)	-160.86(7)
N-C(1)-C(2)-C(7)	22.66(7)
C(1)-C(2)-C(3)-C(4)	-80.77(7)
C(7)-C(2)-C(3)-C(4)	40.46(8)
C(2)-C(3)-C(4)-C(5)	-52.03(7)
C(3)-C(4)-C(5)-C(6)	61.99(7)
C(4)-C(5)-C(6)-C(7)	-59.17(7)
C(5)-C(6)-C(7)-C(8)	159.28(5)
C(5)-C(6)-C(7)-C(2)	45.88(7)
C(1)-C(2)-C(7)-C(8)	-24.88(6)
C(3)-C(2)-C(7)-C(8)	-153.05(6)
C(1)-C(2)-C(7)-C(6)	91.07(6)
C(3)-C(2)-C(7)-C(6)	-37.09(8)
C(1)-N-C(8)-O(2)	178.41(6)
C(1)-N-C(8)-C(7)	-5.39(7)
C(6)-C(7)-C(8)-O(2)	75.38(9)
C(2)-C(7)-C(8)-O(2)	-164.68(7)
C(6)-C(7)-C(8)-N	-100.59(6)
C(2)-C(7)-C(8)-N	19.36(7)

Symmetry transformations used to generate equivalent atoms:

Table 8. Hydrogen bonds for 3a,4,5,6,7,7a-Hexahydro-1H-isoindole-1,3(2H)-dione [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N-H(0A)...O(2)#1	0.87	1.98	2.8472(7)	175.8

Symmetry transformations used to generate equivalent atoms:
#1 *-x+2,y+1/2,-z+1/2*