

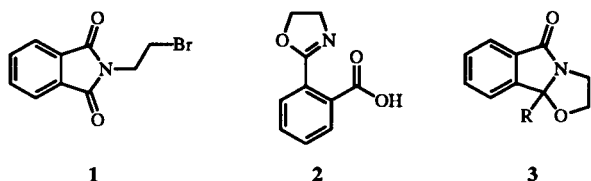
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The titled compounds were prepared by reacting *N*-(2-bromoethyl)phthalimide with enolates of phenylacetic acid esters. 2,3-Dihydrooxazolo[2,3-*a*]isoindolones are believed to be intermediates in the process. An X-ray crystallographic analysis was conducted on one of the compounds.

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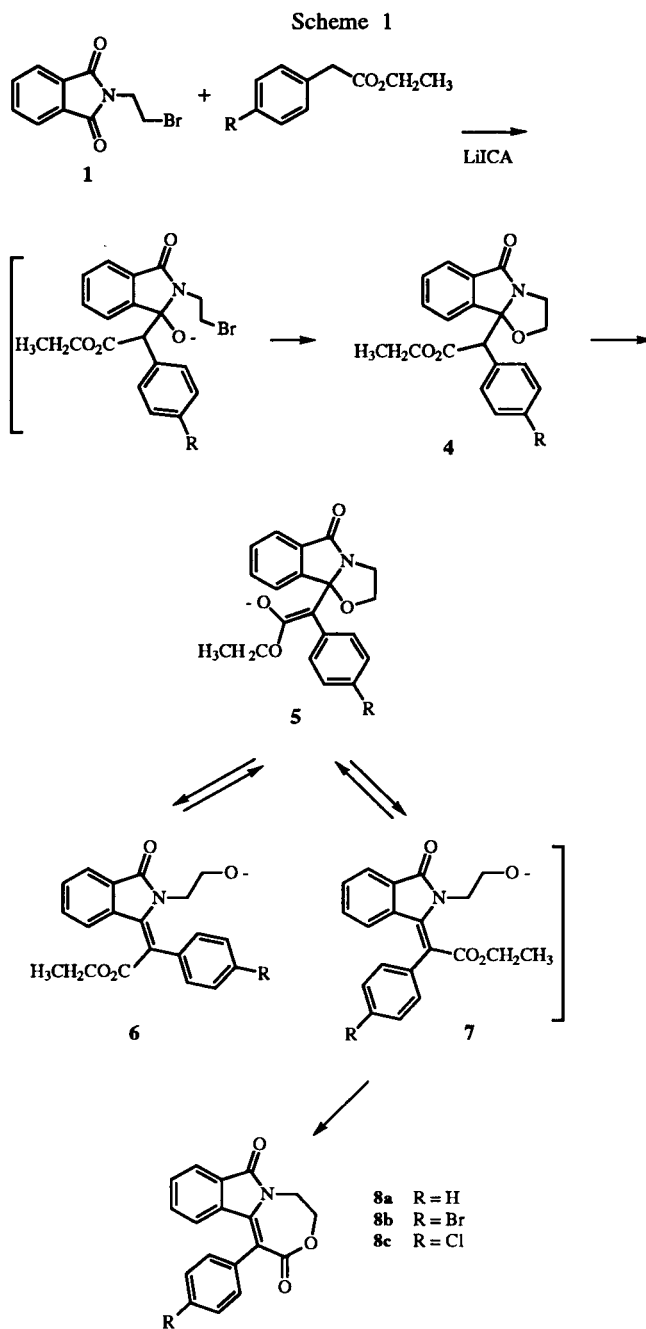
N-(2-Bromoethyl)phthalimide **1** exhibits a proclivity to react with nucleophiles by way of the imide carbonyl. For example, reaction with potassium hydroxide leads to the oxazoline **2** [1] whereas reaction with lithium phenylacetylide [2], aryllithium [3] and arylmagnesium reagents [4] affords 2,3-dihydrooxazolo[2,3-*a*]isoindolones **3**. Such isoindolones also formed with diethyl sodium phosphonate [5].



The reaction of *N*-(2-bromoethyl)phthalimide with ester enolates has received less attention. Using the lithium enolate of methyl butyrate, generated with lithium diisopropylamine, Naruto *et al* [6] obtained **3** in 20% yield as a mixture of diastereomers, one of which was isolated in pure form. More recently, De Kimpe *et al* [7] identified the product from the reaction of the enolate of methyl isobutyrate and **1** as an isoindolone.

We investigated the course of the reaction of *N*-(2-bromoethyl)phthalimide with the enolates of ethyl phenylacetates. These ester enolates were generated by the method of Rathke and Lindert [8] which utilizes lithium *N*-isopropylcyclohexylamine. Thus, a tetrahydrofuran solution of ethyl phenylacetate was added to this base in tetrahydrofuran at -78° , followed by cannula transfer of this solution to *N*-(2-bromoethyl)phthalimide in dimethyl sulphoxide at ambient temperature. After several hours, addition of this solution to water yielded a solid which crystallized nicely from ethanol.

Its infrared spectrum exhibited strong absorptions at 1718 and 1695 cm^{-1} , consistent with ester and lactam functionalities, respectively, as would be expected for isoindolone **3**. However, hydrogen resonances associated with an ethyl moiety were absent in the proton nmr spectrum. Of the higher field resonances, δ 5.84-5.87, a doublet, integrated for one hydrogen, and δ 4.71-4.73 and δ 4.32-4.34, both



multiplets, integrated for two protons each. No protons were exchangeable with deuterium oxide. The latter two chemical shifts could be interpreted simplistically as being in accord with methylenes next to oxygen and nitrogen, respectively. However, De Kimpe *et al* [7] have shown that the ring methylene hydrogens of the dihydrooxazolo[2,3-*a*]isoindoles are not equivalent, one hydrogen appearing at the higher field and one at the lower. The multiplicity we observed suggested methylene protons which were not equivalent. With elemental and mass spectral analysis supporting $C_{17}H_{13}NO_3$, we concluded that the product was a lactone. The course of the reaction is speculated in Scheme 1 where the anticipated 2,3 dihydrooxazolo[2,3-*a*]isoindole **4** is an intermediate enroute to the lactone **8**.

Of these lactones, only **8a** formed a crystal suitable for X-ray crystallographic analysis [9] which firmly established its structure, a thermal ellipsoid plot of which is shown in Figure 1. The fused 5- and 6-membered rings of the isoindole form a nearly rigorously planar motif. The root mean square fit to the plane is 0.018 Å. The seven-membered ring is puckered with the maximum deviation from the ring plane being 1.1 Å for atom C3. The phenyl ring at atom C5 makes an angle of 77° with the ring plane. The hydrogen on atom C14 is virtually centered over the C5 phenyl and this shielding results in an unusually high nmr resonance at δ 5.84-5.87. In Table I is a summary of

crystal data, data collection parameters, and structure refinement statistics. Table II is a list of non-hydrogen atom positions and equivalent isotropic temperature factors. Tables III, IV, and V list the bond lengths, valence angles, and torsion angles, respectively.

Table I
Data Collection Summary for **8a**.

Empirical Formula	$C_{18}H_{13}NO_3$
Crystal Color and Habit	transparent prism
Crystal Size	0.40 x 0.20 x 0.12 mm ³
Crystal System	Monoclinic
Space Group	$P2_1/c$
Unit Cell Dimensions	a = 9.600 (1) Å b = 15.787 (1) Å c = 9.510 (1) Å $\beta = 102.366 (7)^\circ$
Volume	1407.9 (2) Å ³
Z	4
Formula Weight	291.3
Dm	1.44 g/cm ³
Dx	1.37 g/cm ³
Linear Absorption	
Coefficient (μ)	0.770 mm ⁻¹
F (000)	608
Diffractometer Used	Siemens P4/RA
Radiation	CuK α ($\lambda = 1.54178$ Å)
Monochromator	graphite crystal, incident beam
Temperature	21°C
2 θ Range	2.0 to 108.5°
Scan Type	$\theta/2\theta$
Scan Speed	2.00 to 60.00°/min. in ω
Scan Range (ω)	1.00° plus α_1/α_2 separation
Standard Reflections	6 measured every 250 reflections
Index Ranges	-10 $\leq h \leq 10$, -16 $\leq k \leq 16$ -10 $\leq l \leq 0$
Reflections Collected	3896
Independent Reflections	1720
R (merge)	2.72%
Observed Reflections	1586
Absorption Correction	Analytical
Min./Max. Transmission	0.8297/ 0.9156
Crystal Structure Solution	Direct Methods
Refinement Method	Full-Matrix Least-Squares
Quantity Minimized	$\Sigma w (F_o - F_c)^2$
Extinction Correction	$F^* = F_c [1 + 0.002\chi F_c^2 / \sin(2\theta)]^{-1/4}$
Hydrogen Atoms	Riding model, fixed Uiso
Weighting Scheme	$w^{-1} = \sigma^2(F) + 0.0008F^2$
No. of Non-hydrogen Atoms	22
Total No. of Atoms	35
Number of Parameters Refined	200
Final R Indices (obs. data)	R = 3.98%, wR = 7.69%
R Indices (all data)	R = 4.24%, wR = 7.85%
Goodness-of-Fit	2.11
Largest and Mean Δ/σ	0.005, 0.001
Data-to-Parameter Ratio	7.9:1
Largest Difference Peak	0.15 e ⁻ /Å ³
Largest Difference Hole	-0.18 e ⁻ /Å ³

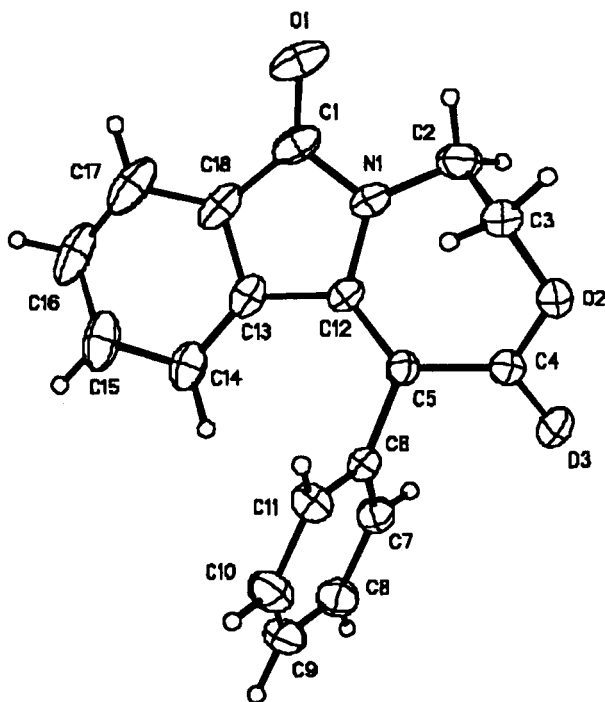


Figure 1. Molecular Structure of **8a**. Thermal ellipsoids envelop 25% of the normal probability density of the non hydrogen atoms. Spheres representing hydrogen atoms are of arbitrary diameter.

Table II

Fractional Atomic Coordinates and Equivalent Isotropic Temperature Factors for **8a**. Standard deviations in parentheses refer to the least significant digits

Atom	x	y	z	Beq [a]
O1	0.2845 (2)	0.9152 (1)	-0.2401 (2)	7.40 (6)
O2	0.4046 (1)	0.7821 (1)	0.2638 (1)	5.27 (5)
O3	0.5781 (2)	0.8340 (1)	0.4235 (2)	6.10 (5)
N1	0.4176 (2)	0.8801 (1)	-0.0168 (2)	4.59 (5)
C1	0.3992 (3)	0.9080 (1)	-0.1557 (2)	5.46 (7)
C2	0.2985 (2)	0.8445 (2)	0.0350 (3)	5.71 (7)
C3	0.3399 (2)	0.7648 (1)	0.1167 (2)	5.00 (7)
C4	0.5324 (2)	0.8207 (1)	0.2989 (2)	4.36 (6)
C5	0.6142 (2)	0.8435 (1)	0.1868 (2)	3.84 (5)
C6	0.7703 (2)	0.8347 (1)	0.2410 (2)	3.90 (6)
C7	0.8478 (2)	0.8935 (1)	0.3351 (2)	4.92 (6)
C8	0.9934 (2)	0.8845 (2)	0.3789 (3)	5.94 (8)
C9	1.0630 (2)	0.8193 (2)	0.3301 (3)	6.06 (8)
C10	0.9864 (3)	0.7585 (2)	0.2396 (3)	6.07 (8)
C11	0.8406 (2)	0.7667 (1)	0.1960 (2)	4.93 (6)
C12	0.5618 (2)	0.8724 (1)	0.0523 (2)	3.90 (5)
C13	0.6421 (3)	0.9045 (1)	-0.0533 (2)	4.59 (6)
C14	0.7874 (3)	0.9172 (1)	-0.0461 (3)	5.80 (8)
C15	0.8259 (4)	0.9498 (2)	-0.1709 (3)	7.5 (1)
C16	0.7273 (5)	0.9674 (2)	-0.2937 (3)	8.6 (1)
C17	0.5856 (4)	0.9566 (2)	-0.2994 (3)	8.0 (1)
C18	0.5428 (3)	0.9251 (1)	-0.1770 (2)	5.57 (8)

[a] Beq, or equivalent isotropic temperature factor, is one-third of the trace of the orthogonalized U_{ij} tensor, multiplied by $8\pi^2$.

Table III

Bond Distances for **8a**. Standard deviations in parentheses refer to the least significant digits.

Atom	Atom	Distance (Å)	Atom	Atom	Distance (Å)
O1	C1	1.221 (3)	C6	C11	1.384 (3)
O2	C3	1.430 (3)	C7	C8	1.378 (3)
O2	C4	1.346 (2)	C8	C9	1.361 (4)
O3	C4	1.191 (3)	C9	C10	1.390 (4)
N1	C1	1.368 (3)	C10	C11	1.378 (3)
N1	C2	1.451 (3)	C12	C13	1.480 (3)
N1	C12	1.405 (2)	C13	C14	1.397 (3)
C1	C18	1.461 (3)	C13	C18	1.386 (3)
C2	C3	1.487 (3)	C14	C15	1.413 (4)
C4	C5	1.497 (3)	C15	C16	1.365 (5)
C5	C6	1.483 (3)	C16	C17	1.360 (5)
C5	C12	1.349 (3)	C17	C18	1.405 (4)
C6	C7	1.389 (3)			

As depicted in Scheme 1, initial addition of the enolate of ethyl phenylacetate to the imide carbonyl would be expected to give diastereomeric isoindolones **4**. Enolization of each diastereomer, presumably by consumption of another equivalent of the enolate of ethyl phenylacetate, would result in loss of alkoxide and the formation of the unsaturated esters, *E*-**6** and *Z*-**7**, of which only the latter can lactonize. However, the conversion of **6** to **7** by Michael addition of the alkoxide followed by elimination could, in principle, be continuously prompted by the removal of **7** through lactonization to **8**. While the enhanced acidity of

Table IV

Valence Angles for **8a**. Standard deviations in parentheses refer to the least significant digits.

Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
C3	O2	C4	120.7 (2)	C6	C7	C8	119.7 (2)
C1	N1	C2	120.3 (2)	C7	C8	C9	121.0 (2)
C1	N1	C12	112.9 (2)	C8	C9	C10	120.0 (2)
C2	N1	C12	125.2 (2)	C9	C10	C11	119.3 (2)
O1	C1	N1	125.2 (2)	C6	C11	C10	120.8 (2)
O1	C1	C18	129.5 (2)	N1	C12	C5	127.0 (2)
N1	C1	C18	105.3 (2)	N1	C12	C13	104.9 (2)
N1	C2	C3	111.3 (2)	C5	C12	C13	128.0 (2)
O2	C3	C2	111.2 (2)	C12	C13	C14	132.5 (2)
O2	C4	O3	116.7 (2)	C12	C13	C18	107.0 (2)
O2	C4	C5	121.4 (2)	C14	C13	C18	120.4 (2)
O3	C4	C5	121.9 (2)	C13	C14	C15	116.7 (2)
C4	C5	C6	112.0 (2)	C14	C15	C16	122.3 (3)
C4	C5	C12	127.6 (2)	C15	C16	C17	120.9 (3)
C6	C5	C12	120.3 (2)	C16	C17	C18	118.6 (3)
C5	C6	C7	121.6 (2)	C1	C18	C13	109.7 (2)
C5	C6	C11	119.3 (2)	C1	C18	C17	129.2 (2)
C7	C6	C11	119.2 (2)	C13	C18	C17	121.1 (2)

Table V

Torsion Angles for **8a**. The sign convention of Klyne and Prelog [a] is used. Standard deviations in parentheses refer to the least significant digits.

Atom	Atom	Atom	Atom	Angle (°)
C4	O2	C3	C2	-67.1 (2)
C3	O2	C4	O3	178.9 (2)
C3	O2	C4	C5	-2.8 (3)
C2	N1	C1	O1	9.1 (3)
C2	N1	C1	C18	-170.4 (2)
C12	N1	C1	O1	175.8 (2)
C12	N1	C1	C18	-3.7 (2)
C1	N1	C2	C3	134.0 (2)
C12	N1	C2	C3	-30.9 (3)
C1	N1	C12	C5	-177.3 (2)
C1	N1	C12	C13	3.9 (2)
C2	N1	C12	C5	-11.4 (3)
C2	N1	C12	C13	169.8 (2)
O1	C1	C18	C13	-177.5 (2)
O1	C1	C18	C17	1.9 (5)
N1	C1	C18	C13	2.0 (3)
N1	C1	C18	C17	-178.7 (3)
N1	C2	C3	O2	84.6 (2)
O2	C4	C5	C6	-144.9 (2)
O2	C4	C5	C12	37.7 (3)
O3	C4	C5	C6	33.4 (3)
O3	C4	C5	C12	-144.1 (2)
C4	C5	C6	C7	-75.0 (2)
C4	C5	C6	C11	105.4 (2)
C12	C5	C6	C7	102.6 (2)
C12	C5	C6	C11	-76.9 (2)
C4	C5	C12	N1	-6.3 (3)
C4	C5	C12	C13	172.2 (2)
C6	C5	C12	N1	176.5 (2)
C6	C5	C12	C13	-5.0 (3)
C5	C6	C7	C8	-177.8 (2)
C11	C6	C7	C8	1.7 (3)
C5	C6	C11	C10	177.3 (2)
C7	C6	C11	C10	-2.2 (3)
C6	C7	C8	C9	0.8 (3)
C7	C8	C9	C10	-2.8 (4)

Table V (continued)

Atom	Atom	Atom	Atom	Angle(°)
O3	C4	C5	C12	-144.1 (2)
C4	C5	C6	C7	-75.0 (2)
C4	C5	C6	C11	105.4 (2)
C12	C5	C6	C7	102.6 (2)
C12	C5	C6	C11	-76.9 (2)
C4	C5	C12	N1	-6.3 (3)
C4	C5	C12	C13	172.2 (2)
C6	C5	C12	N1	176.5 (2)
C6	C5	C12	C13	-5.0 (3)
C5	C6	C7	C8	-177.8 (2)
C11	C6	C7	C8	1.7 (3)
C5	C6	C11	C10	177.3 (2)
C7	C6	C11	C10	-2.2 (3)
C6	C7	C8	C9	0.8 (3)
C7	C8	C9	C10	-2.8 (4)
C8	C9	C10	C11	2.3 (4)
C9	C10	C11	C6	0.2 (3)
N1	C12	C13	C14	176.2 (2)
N1	C12	C13	C18	-2.5 (2)
C5	C12	C13	C14	-2.6 (4)
C5	C12	C13	C18	178.8 (2)
C12	C13	C14	C15	-179.9 (2)
C18	C13	C14	C15	-1.4 (3)
C12	C13	C18	C1	0.3 (2)
C12	C13	C18	C17	-179.1 (2)
C14	C13	C18	C1	-178.5 (2)
C14	C13	C18	C17	2.1 (4)
C13	C14	C15	C16	-0.7 (4)
C14	C15	C16	C17	2.1 (5)
C15	C16	C17	C18	-1.4 (5)
C16	C17	C18	C1	-180.0 (3)
C16	C17	C18	C13	-0.7 (4)

[a] W. Klyne and V. Prelog, *Experientia*, **16**, 521 (1960).

these phenylacetates is a factor in this process, the solvent mixture of dimethyl sulphoxide and tetrahydrofuran may also be important.

EXPERIMENTAL

4,5-dihydro-1-phenyl[1,4]oxazepino[5,4-*a*]isoindole-2,7-dione (**8a**).

Under nitrogen, *N*-isopropylcyclohexylamine, 5.64 g (0.04 mole), in 40 ml of dry tetrahydrofuran was placed in a dry 250 ml 3-necked flask equipped with a condenser, addition funnel and magnetic stirring bar and was cooled to -76° (Dry Ice-acetone). *n*-Butyllithium, 17.4 ml (0.04 mole), was added using a syringe. After one hour, ethyl phenylacetate, 6.56 g (0.04 mole), in 20 ml of tetrahydrofuran was added dropwise from the addition funnel over 10 minutes. After one hour, this cold solution was transferred by cannula under nitrogen pressure to another 3-necked flask equipped with a septum, magnetic stirring bar, nitrogen inlet, and containing 10.16 g (0.04 mole) of *N*-(2-bromoethyl)phthalimide in 40 ml of dry dimethyl sulphoxide at ambient temperature. After 2.5 hours the contents were added to 600 ml of water resulting in a solid which was collected by filtration, triturated with ether and air dried to give 5.2 g. This material was dissolved in 350 ml of hot ethanol, filtered, concentrated to 100 ml and left at ambient temperature to deposit a solid which was dried in a drying pistol at 65° and 0.01 mm Hg to yield 4.80 g (83% based on the consumption of two equivalents of

the lithium enolate of ethyl phenylacetate), mp 190-192°, tlc (silica gel, ether) indicated a homogeneous material, Rf 0.32; ir (Nujol): 1718 (s), 1695 (s) cm⁻¹; ¹H nmr (300 MHz, deuteriochloroform): δ 4.32-4.34 (m, 2H), 4.71-4.73 (m, 2H), 5.84-5.87 (d, 1H), 7.17-7.51 (m, 7H), 7.81-7.84 (d, 1H); ms: m/z 292 (M+H)⁺.

Anal. Calcd. for C₁₈H₁₃NO₃: C, 74.21; H, 4.49; N, 4.80. Found: C, 74.24; H, 4.63; N, 4.56.

1-(4-Bromophenyl)-4,5-dihydro[1,4]oxazepino[5,4-*a*]isoindole-2,7-dione (**8b**).

Using the same procedure as for **8a**, methyl 4-bromophenylacetate, 9.16 g (0.04 mole) was converted to its enolate and reacted with *N*-(2-bromoethyl)phthalimide. On adding the contents of the reaction flask to 600 ml of water after 2.5 hours, an oil separated. After stirring overnight the oil partially solidified. The supernatant was decanted and the oily residue was triturated with ether to get 2.65 g of a solid. This material was dissolved in 450 ml of hot ethanol, filtered, concentrated to 150 ml, whereupon a solid just started to separate, and was then left at ambient temperature. The resulting "cotton-like" solid was dried in a drying pistol at 65° and 0.01 mm Hg to yield 2.00 g, mp 223.5-225°; ir (Nujol): 1718 (s), 1695 (s) cm⁻¹; ¹H nmr (300 MHz, deuteriochloroform): δ 4.32-4.35 (m, 2H), 4.70-4.73 (m, 2H), 6.02-6.05 (d, 1H), 7.25-7.65 (m, 6H), 7.84-7.86 (d, 1H).

Anal. Calcd. for C₁₈H₁₁BrNO₃: C, 58.39; H, 3.27; N, 3.78. Found: C, 58.25; H, 3.45; N, 3.49.

1-(4-Chlorophenyl)-4,5-dihydro[1,4]oxazepino[5,4-*a*]isoindole-2,7-dione (**8c**).

Using the same procedure as for **8a**, methyl 4-chlorophenylacetate, 7.38 g (0.04 mole) was converted to its enolate and reacted with *N*-(2-bromoethyl)phthalimide. After one hour the contents of the reaction flask was added to 600 ml of water, and a solid slowly separated. An ether titration gave 1.80 g of material. This was dissolved in 350 ml of hot ethanol, filtered, concentrated to 100 ml when a solid just started to separate, and was then left at ambient temperature. The resulting pale yellow solid was dried in a drying pistol at 65° and 0.01 mm Hg to yield 1.60 g, mp 222-223°; ir (Nujol): 1721 (s), 1686 (s) cm⁻¹; ¹H nmr (300 MHz, deuteriochloroform): δ 4.32-4.34 (m, 2H), 4.70-4.73 (m, 2H), 6.01-6.04 (d, 1H), 7.26-7.51 (m, 6H), 7.84-7.86 (d, 1H).

Anal. Calcd. for C₁₈H₁₁ClNO₃: C, 66.36; H, 3.71; N, 4.38. Found: C, 66.34; H, 3.82; N, 4.08.

Single Crystal X-ray Diffraction of **8a**.

Single crystals suitable for X-ray diffraction experiments were obtained by cooling a saturated solution of **8a** in ethanol slowly from 67° to room temperature. A prismatic crystal of approximate dimensions 0.40 x 0.20 x 0.12 mm³ was harvested, attached to a glass fiber with epoxy glue, and mounted on a Siemens P4 diffractometer. The diffractometer was equipped with a rotating anode generator operated at 45 kV and 90 mA, Cu target, 0.3 x 3 mm² fine focus, graphite crystal monochromator, and FSD detector. Twenty-five reflections for which 23° ≤ 2θ ≤ 54° were found by random search and indexed with reference to a primitive monoclinic unit cell. Lattice parameters were determined by non-linear least squares based on the setting angles of the indexed reflections. Integrated intensities were measured in one hemisphere of reciprocal space using the θ/2θ scan technique. Intensities were corrected for Lorentz and polarization effects. Crystal faces were indexed, and the perpendicular distance from each face to an arbitrary origin was

measured. These data were used to calculate an analytical absorption correction. A correction for secondary extinction was applied during structure refinement. The structure was solved by direct methods. All twenty-two non-hydrogen atoms were revealed in the E-map of the correct solution. The structure was refined against the structure amplitudes (F-values) by non-linear full-matrix least squares. Data for which $F < 4\sigma(F)$, about 8% of the total, were considered unobserved and were excluded. The positions of non-hydrogen atoms were refined with no restrictions, and the temperature factors of these atoms were refined anisotropically. Thirteen hydrogen atoms were inserted at idealized positions relative to neighboring non-hydrogen atoms. The C-H bond length was 0.96 Å and the isotropic temperature factor assigned to each hydrogen was 10% higher than the equivalent isotropic temperature factor of the atom to which each was attached. Hydrogen positions were refined using the riding model and hydrogen temperature factors were held fixed. Structure refinement converged at $R(F) = 4.0\%$ and $R_w(F^2) = 7.7\%$ for 1586 observed data. The final difference Fourier map was featureless and the final difference electron density did not exceed $0.20 e/\text{Å}^3$ in absolute value.

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