acid was quickly added to the reaction mixture. The product was subsequently isolated by dilution of this mixture with 100 mL of 15% (w/v) aqueous sodium chloride and extraction with 4:1 (v/v) ether–dichloromethane. The organic layer was washed in succession with 1:1 (v/v) 2 M aqueous hydrochloric acid–saturated brine (2 × 100 mL) and saturated brine (1 × 100 mL). The product was then isolated from the organic extract in the usual manner and purified by evaporative distillation [bp 80–100 °C (bath temperature) (0.20 mm)], affording 408 mg of a colorless oil shown by ^{1}H NMR and VPC analyses (retention times: **3a** > **5a** > **8a**) to contain diester **5a**, Dieckmann cyclization product **8a**, and unreacted starting material in a ratio of 3.0:4.5:2.5. Chromatography of this distillate on Florisil (20 mL, elution with hexane–2% ether) afforded 124 mg (21%, uncorrected for recovered starting material) of purified diester **5a** as an undetermined mixture of stereoisomers: ^{1}H NMR δ 3.10–3.40 (m, 2 CHC=O), 2.05–2.45 (m, 4 H), 1.47 (s, 2 C(CH$_3$)$_3$). Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.45; H, 9.03. The structural identity of **5a** was further confirmed by its saponification using 3:1 (v/v) ethylene glycol–20% aqueous potassium hydroxide at reflux for 2.5 h. Acidification of the cooled reaction mixture, followed by extraction with 4:1 (v/v) ether–ethyl acetate, afforded a white, crystalline solid (mp 110–125 °C), which was subsequently purified by recrystallization from benzene: mp of *trans*-diacid **6a** (57% overall yield based on diester **5a**) 128–130 °C (lit.[4] mp 127–129 °C).

Oxidative Cyclization of Di-*tert*-butyl Pimelate (3b).[10] A procedure identical with that described above for the preparation of diester **5a** was used with the following modifications: (a) The quantities of diisopropylamine (1.00 mL, 7.13 mmol), *n*-butyllithium (7.0 mmol), and anhydrous cupric chloride (1.01 g, 7.5 mmol) were increased relative to the starting diester (644 mg, 2.36 mmol). (b) After addition of cupric chloride to the reaction mixture, it was allowed to warm to 0 °C over a period of 30 min and stirred for an additional 60 min at 0 °C. Evaporative distillation [bp 80–90 °C (bath temperature) (0.30 mm)] of the crude product afforded 495 mg (78%, if solely diester **5b**) of a colorless oil shown by ^{1}H NMR and VPC analyses (oven temperature 200 °C, flow 15 mL/min) to be a mixture consisting of >70% diester **5b** (1:1 mixture of cis:trans stereoisomers; retention times 4.68 and 4.42 min, respectively), <2% Dieckmann cyclization product (**8b**; retention time 3.57 min), and 28% starting diester (**3b**; retention time 5.34 min). Since the chromatographic separation of this mixture proved to be troublesome, verification of the obtention of a cyclopentanoid product (**5b**) was achieved by the transesterification process described below to afford the known[11] dimethyl ester **4b**.

Dimethyl 1,2-Cyclopentanedicarboxylate (4b). The distilled mixture (495 mg) of products obtained in the cyclization described above was heated for 40 h in 4.0 mL of a 1:1 (v/v) mixture of refluxing glacial acetic acid–2 M aqueous hydrochloric acid to effect hydrolysis of the *tert*-butyl ester moiety. At this point, the heat source was removed, and 5 mL of toluene was added to the reaction flask. The mixture was then concentrated to a volume of approximately 2 mL by distillation at atmospheric pressure. This latter procedure (i.e., addition of toluene and subsequent distillation) was repeated two additional times, leaving behind a suspension of the solid diacid (**6b** contaminated with **1b**) in toluene. After addition of 0.25 mL (6.13 mmol) of methyl alcohol, 1.00 mL (8.13 mmol) of 2,2-dimethoxypropane, and a catalytic amount (17 mg) of *p*-toluenesulfonic acid monohydrate, the mixture was stirred at room temperature for 20 h. Dilution of the mixture with 20 mL of 15% (w/v) aqueous sodium chloride and extraction with 3:1 (v/v) ether–dichloromethane, followed by washing the organic layer with 3:1 (v/v) brine–1 M aqueous sodium hydroxide (2 × 20 mL), afforded 406 mg of a yellow oil after the usual isolation procedure. Evaporative distillation [bp 90–110 °C (bath temperature) (0.35 mm) [lit.[11] bp 119–120 °C (bath temperature) (16 mm)]], followed by chromatography on silica gel (Baker Analyzed, 40–140 mesh, 15 mL, elution with hexane–3% ether), afforded 215 mg (1.15 mmol, 49% overall yield based on acyclic diester **3b**) of diester **4b**,[12] homogeneous by TLC and VPC analyses: ^{1}H NMR δ 3.73 (s, 6 H, 2 OCH$_3$), 2.95–3.38 (complex m, 2 H, 2 CHC=O), 1.55–2.40 (complex m, 6 H).

Registry No. **1a**, 124-04-9; **3a**, 20270-53-5; **3b**, 55623-59-1; *trans*-**4b**, 941-75-3; *cis*-**5a**, 108836-33-5; *trans*-**5a**, 108836-34-6; *cis*-**5b**, 108836-35-7; *trans*-**5b**, 108836-36-8; *trans*-**6a**, 1124-13-6; *trans*-**6b**, 1461-97-8; **8a**, 84109-76-2.

(10) Diester **3b**[7] was prepared from pimelic acid by a procedure identical with that described for the preparation of di-*tert*-butyl adipate (**3a**).

(11) Ingold, C. K.; Mohrhenn, H. G. G. *J. Chem. Soc.* **1935**, *138*, 1482.

(12) Diester **4b** can be assumed to possess the trans configuration in view of the vigorous reaction conditions used to hydrolyze diesters **5b** (1:1 cis:trans mixture). Further confirmation of the identity of **4b** was obtained by its saponification to afford diacid **6b**. The IR spectrum and melting point of the latter were identical with those exhibited by an authentic sample[6] of *trans*-1,2-cyclopentanedicarboxylic acid.

Aldehyde-Promoted Decomposition of 1-(Alkylthio)-2-alkylisoindoles

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Primary amines undergo facile condensation with *o*-phthalaldehyde (OPA) in the presence of alkanethiols to generate 1-(alkylthio)-2-alkylisoindoles **1**.[1] This reaction is of considerable analytical importance and is widely used for derivatization of primary amines prior to liquid chromatographic analysis. Thiol coreagents most frequently employed for this purpose are 2-mercaptoethanol (2-ME) or ethanethiol (ET). Both of these thiols lead to formation of products whose stability is highly variable, with in situ half-lives ranging from a few minutes to several hours.[2] Excess OPA in the reaction mixture has been shown to exert a significant destabilizing effect,[2-4] and derivative loss in the presence of excess OPA follows pseudo-first-order kinetics with

$$k_{app} = k_0 + k_{OPA}[OPA]$$

where k_0 is the first-order rate constant for OPA-independent loss and k_{OPA} is the second-order term for the OPA-dependent process. Under typical analytical conditions, the latter term predominates and derivative stability is dictated by the OPA-dependent process. Considerable speculation has arisen concerning the nature of the reactions leading to decomposition of these derivatives and, in particular, apparent differences between those derived from 2-ME and ET.[1,3,4] In our earlier studies we demonstrated strong parallels between the OPA-dependent decomposition of 2-ME and ET-derived isoindoles[2] and suggested at that time that the most probable sequence in both cases was one initiated by electrophilic attact at C(3) of the isoindole. Subsequent findings appear to substantiate this hypothesis.

We have found isoindoles of type **1a** and **1b** to be quite susceptible to decomposition by aldehydes in general, with OPA representing a special case. In a study of reactivity of **1a** and **1b** toward para-substituted benzaldehydes, rate constants for both isoindoles correlated well with Hammett σ_p constants (Figure 1), yielding ρ values of 1.30 (r = 0.9969) and 1.44 (r = 0.9720) for **1a** and **1b**, respectively.

(1) Simons, S. S.; Johnson, D. F. *J. Am. Chem. Soc.* **1976**, *98*, 7098–7099.

(2) Jacobs, W. A.; Leburg, M. W.; Madaj, E. J. *Anal. Biochem.* **1986**, *156*, 334–340.

(3) Nakamura, H.; Matsumoto, A.; Tamura, Z. *Anal. Lett.* **1982**, *15*, 1393–1410.

(4) Stobaugh, J. F.; Repta, A. J.; Sternson, L. A.; Garren, K. W. *Anal. Biochem.* **1983**, *135*, 495–504.

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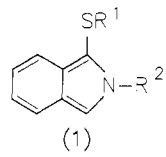
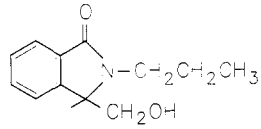


(1)

	R^1	R^2
1a	$-CH_2CH_2OH$	$-CH_3$
1b	$-CH_2CH_3$	$-CH_3$
1c	$-CH_2CH_2OH$	$-CH_2CH_2CH_3$
1d	$-CH_2CH_2OH$	$-CH_2CH_2CH_2CH_3$

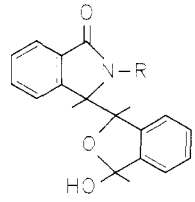
The positive slope in both of the Hammett plots indicates that the reaction is strongly favored as the aldehyde becomes more electron-deficient. Aliphatic aldehydes, such as formaldehyde, show behavior similar to that displayed by aromatic aldehydes. α-Keto aldehydes are especially reactive, and decomposition of **1a** and **1b** by phenylglyoxal and pyruvic aldehyde proceeds too rapidly to permit chromatographic monitoring.

Preparative reactions were carried out in aqueous/methanolic media buffered to pH 9.6 with sodium carbonate, conditions that parallel those used for analytical derivatizations. Reaction of isoindole **1c** with excess formaldehyde resulted in formation of 2,3-dihydro-3-(hydroxymethyl)-2-(1-propyl)-1*H*-isoindol-1-one (**2**) in 53%



(2)

isolated yield. Reaction of **1a** with excess OPA led to isolation of 3-(1,3-dihydro-3-hydroxy-1-isobenzofuranyl)-2,3-dihydro-2-methyl-1*H*-isoindol-1-one (**3a**) in 47% yield. **3b** was isolated in 44% yield from reaction of **1d** with OPA. Authentic samples of **3a** and **3b** were prepared by a literature procedure.[6]



(3)

	R
3a	$-CH_3$
3b	$-CH_2CH_2CH_2CH_3$

In contrast to the 1-[(hydroxyethyl)thio]isoindoles, 1-(ethylthio)isoindoles did not lead to formation of isolable products upon reaction with either formaldehyde or OPA. These derivatives (as well as those based on other simple alkanethiols) differed also in the formation of a semistable, electrochemically oxidizable intermediate, observed as a transient peak during chromatographic monitoring of reaction mixtures.[5] The intermediate differed for each aldehyde employed, strongly indicating incorporation of the aldehyde moiety. Appearance and decay of the intermediate from reaction of **1b** with OPA fit a simple sequential first-order model (Figure 2), i.e.

$$\mathbf{1b} \xrightarrow[\text{OPA}]{k_{\text{OPA}}} \text{I} \xrightarrow{k_{\text{I}}} \text{product(s)}$$

$$[\text{I}] = \frac{k'_{\text{OPA}}[\mathbf{1b}]}{k_{\text{I}} - k'_{\text{OPA}}}(e^{-k'_{\text{OPA}}t} - e^{-k_{\text{I}}t})$$

No evidence for a similar intermediate was observed during decomposition of any 2-ME derived isoindoles.

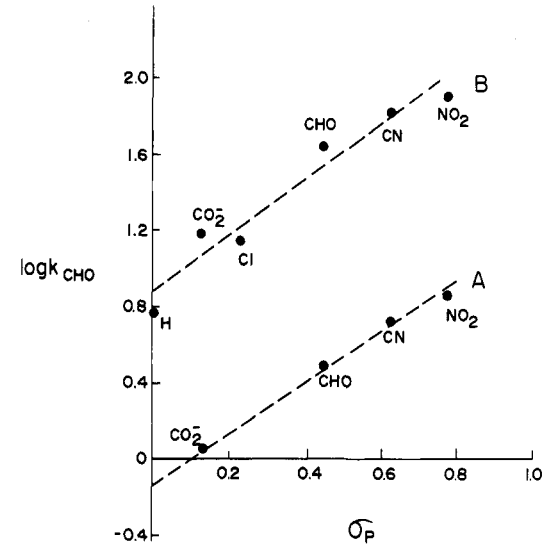


Figure 1. Hammett plots for reaction of **1a** (B) and **1b** (A) with para-substituted benzaldehydes.

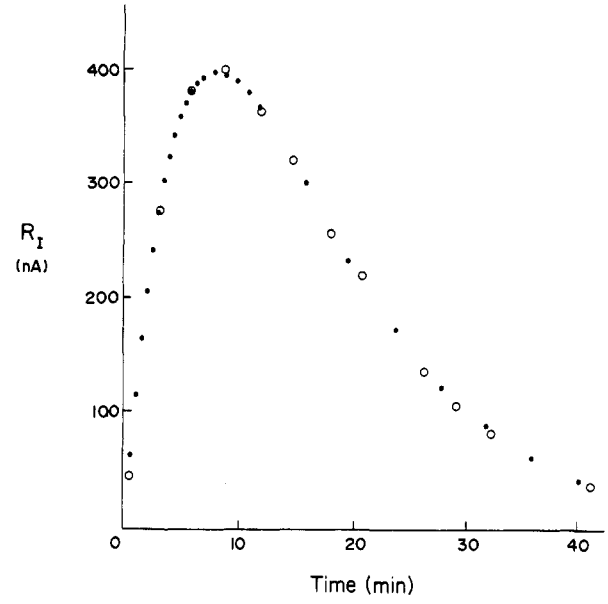
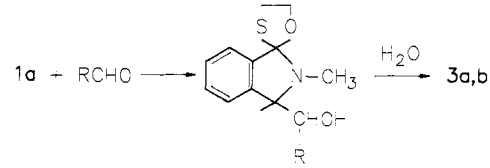


Figure 2. Observed (○) vs. calculated (●) values for the peak height of the intermediate formed during reaction of **1b** with OPA.[7]

Scheme I



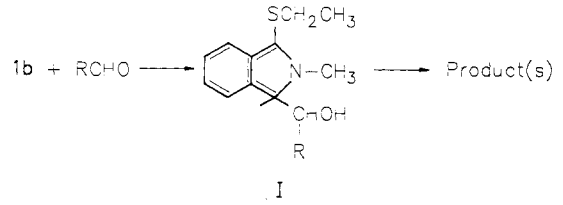
4

(5) Reactions were routinely monitored by reverse phase liquid chromatography/electrochemistry using a glassy carbon electrode poised at +0.75 V vs. Ag/AgCl.

(6) DoMinh, T.; Johnson, A. L.; Jones, J. E.; Senise, P. P., Jr. *J. Org. Chem.* **1977**, *42*, 4217–4221.

(7) k_{I} was obtained from kinetic runs by following the loss of intermediate after the concentration of **1b** was less than 2–5% of its starting value. The value for k_{I} obtained in this manner was 0.114 ± 0.006 min^{-1}.

Scheme II



I

Our interpretation of these observations is summarized in Schemes I and II for isoindoles of type **1a** and **1b**, respectively. In both cases, the sequence is initiated by attack of the aldehyde at C(3) of the isoindole ring. For isoindoles such as **1a** this results in formation of the rapidly hydrolyzed **4** (nonelectroactive) and ultimately **3a**. **1b** and similar isoindoles are suggested to undergo a normal substitution resulting in formation of I (the proposed electroactive intermediate), which undergoes a slower deocmposition to mixed products, probably largely polymeric.

Experimental Section

Chemicals. All thiols, amines, and aldehydes were obtained from Aldrich Chemical Co. Glass-distilled methanol and acetonitrile were from Burdick and Jackson; other solvents were J. T. Baker reagent grade. Buffer components were from J. T. Baker or Mallinkrodt (all reagent grade or better). Deionized water was prepared with a Barnstead Nanopure system.

Liquid Chromatography. Reaction mixtures were routinely monitored on a Bioanalytical Systems, Inc. LC-304 liquid chromatography fitted with a 0.46 × cm C-18 column (MF 6030). For detection, a standard TL-5A thin layer amperometric transducer operated at an applied potential of 0.75 V vs. Ag/AgCl was employed. Isoindole derivatives were chromatographed by using acetate buffered (0.1 M, pH 5) mobile phases of water/acetonitrile.

Kinetic Studies. Isoindoles were generated from stoichiometric quantities of reagents as follows: 150 μL each of 5 mM solutions of OPA, thiol, and amine were mixed and incubated 5 min at 25 °C, after which they were diluted with 5.6 mL of a solution of the corresponding aldehyde. The concentration of aldehyde was normally determined by its solubility, but in most cases represented 100–150-fold molar excess. All solutions described above were prepared in 25% methanol buffered at pH 9.6 with 0.1 M sodium carbonate. Loss of isoindole and formation of the electrochemically active intermediate were monitored by chromatographic analysis of aliquots at timed intervals. Second-order rate constants were obtained by dividing the apparent pseudo-first-order constant by [RCHO].

Formaldehyde-Promoted Degradation of 1-[(2-Hydroxyethyl)thio]-2-(1-propyl)isoindole (1c). Isoindole **1c** was generated in situ by the addition of *n*-propylamine (220 μL) to a solution of *o*-phthalaldehyde (367 mg) and 2-mercaptoethanol (210 μL) in methanol (50 mL) at 0 °C. This was then added over 35 min to a stirred solution of formaldehyde prepared by adding 10 mL of a 0.5 M sodium carbonate solution (pH 9.6) to 15 mL of methanol followed by addition of 37% formaldehyde solution to give a total volume of 50 mL (the formaldehyde solution was kept at room temperature for the duration of the addition of isoindole).

After the completion of the addition of **1c**, the solution was stirred 2 h and then kept overnight at −20 °C. Methanol was removed by evaporation and the aqueous suspension was extracted with chloroform. The chloroform extracts were combined and dried over $MgSO_4$, filtered, and evaporated to give 1.28 g of a yellow oil; 0.64 g of this material was chromatographed in three portions over silica gel (230–400 mesh, 1.5 × 30 cm column size) using CH_2Cl_2/CH_3OH (18/1, v/v) to give a white solid (148.1 mg, 53%). This was crystallized from ether–methanol (ca. 10/1, v/v) and identified as 2,3-dihydro-3-(hydroxymethyl)-2-(1-propyl)-1*H*-isoindol-1-one (**2**): mp 115–116 °C; NMR ($CDCl_3$) 7.81 (d, J = 7.1 Hz, 1), 7.53 (m, 3), 4.32 (m, 1), 4.06 (m, 2), 3.90 (m, 1), 3.29 (m, 1), 1.70 (m, 2), 1.60 (s, 1), 3.95 (t, J = 7.3 Hz, 3); IR (KBr) 3390 (OH), 2850, 2900, 2940 (CH), 1660 (amide C=O), 1410, 1045, 710, 680 cm^{-1}; CIMS (70 eV, CH_4), m/z (rel intensity) 206 (100, M + 1); high resolution mass spectrum, calcd for $C_{12}H_{15}NO_2$ 205.11027, found 205.11008.

OPA-Promoted Degradation of 1-[(2-Hydroxyethyl)thio]-2-methylisoindole (1a). A solution of **1a** was prepared at 0 °C in methanol (5 mL) from OPA (100.7 mg), 2-hydroxyethanethiol (53 μL), and methylamine (64 μL of a 40% aqueous solution). This was added over 50 min to a stirred solution of OPA (567.3 mg) in a mixture of methanol (5 mL) and 0.1 M aqueous sodium carbonate (pH 9.6, 5 mL) at room temperature. Stirring was continued 15 min and the mixture was stored at −20 °C overnight. The solid was isolated (102.1 mg, 47%). The melting range of this materal was 212–213 °C (lit.[6] mp 220–222 °C), but after recrystallization from methanol, the compound melted at 208–210 °C. Repeated recrystallization did not change this. However, TLC (4 solvent systems) behavior as well as NMR, IR, and CIMS were identical with those of an authentic sample of **3a** prepared by the literature procedure.[6]

OPA-Promoted Degradation of 1-[(2-Hydroxyethyl)thio]-2-(1-butyl)isoindole (1d). The procedure above was repeated with **1d**. The crude **3b** was isolated in 44% yield. After two recrystallizations from acetone–methanol the compound had a melting point of 176–178 °C (lit.[6] mp 177–179°C) and was identified as **3b** by comparison with an authentic sample (NMR, IR). In the formation of both **3a** and **3b** TLC showed more product present in the reaction mixture, but this was not isolated due to the large quantities of other materials present (e.g., excess OPA, minor side products).

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A One-Step Preparation of α-Azido Sulfones from Nitro Compounds

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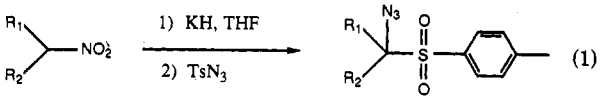
Activated azides are versatile reagents for diazo group transfer to a variety of active methylene compounds[1] including α-nitro ketones and nitro esters.[2] Arenesulfonyl azides have also been noted as azide donors to organometallic nucleophiles.[3,4] We disclose in this paper an unusual reaction (eq 1) between isolated nitronates and toluenesulfonyl azide leading to the formation of α-azido sulfones **2**, a functional group combination often available only with difficulty via other methods.[5]



(1)

1 2

As shown in Table I, a preliminary survey of simple substrates revealed that this reaction is applicable to

(1) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733. Regitz, M. In *The Chemistry of Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: London, 1978; Vol. 2, p 751. Regitz, M.; Maas, G. *Diazo Compounds—Properties and Synthesis*; Academic: Orlando, 1986.
(2) Balli, H.; Low, R. *Tetrahedron Lett.* **1966**, 5821.
(3) Weininger, S. J.; Kohen, S.; Mataka, S.; Koga, N.; Anselme, J.-P. *J. Org. Chem.* **1974**, *39*, 1591.
(4) Smith, P. A. S.; Rowe, C. D.; Bruner, L. B. *J. Org. Chem.* **1969**, *34*, 3430.
(5) (a) Oxidation of azido sulfides: Böhme, H.; Morf, D. *Chem. Ber.* **1957**, *90*, 446. (b) $S_{RN}1$ reaction of α-nitro azides with sulfinates: Al-Khalil, S. I.; Bowman, W. R. *Tetrahedron Lett.* **1982**, 4513.

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