8(*Z,E*): ^{1}H NMR 2.19 (3 H, s), 2.23 (3 H, s), 2.36 (2 H, bq, J = 7.5 Hz), 2.48 (2 H, bq, J = 7.5 Hz), 5.98 (1 H, t, J = 7.5 Hz), 6.10 (1 H, t, J = 7.5 Hz).

Anal. Calcd for $C_{12}H_{12}N_2O_4$: C, 58.06; H, 4.87; N, 11.28. Found: C, 58.14; H, 4.92; N, 11.32.

1,2-Bis(2-acetoxy-2-cyanoethenyl)benzene (13). To a mixture of $Cu_2(CN)_2$ (0.85 g, 9.5 mmol), NaI (1.42 g, 9.5 mmol), and P_2O_5 (0.1 g) in CH_3CN (10 mL) was added a solution of 1,2-benzenediacetyl chloride (11) (1.04 g, 4.5 mmol) in CH_3CN (5 mL) at 0 °C. After stirring for 2 h at rt (for the ^{1}H NMR data for intermediate cyanide 12 see ref 21 for the hydrolysis of 13), AcCl (0.85 g, 10.8 mmol) and pyridine (0.86 g, 10.8 mmol) were added successively. After 3 days the precipitated solids were removed and the AcCN solution of the filtrate was concentrated under vacuum and worked up with a mixture of water and AcOEt. Purification on a silica gel column afforded crystalline 13 in 34% yield. 13(*E,E*): mp 140–142 °C; ^{1}H NMR 2.22 (6 H, s), 6.90 (2 H, s), 7.42 (2 H, m), 7.55 (2 H, m); ^{13}C NMR 20.27 (CH_3), 113.89 (CN), 121.70 (=CH), 129.65, 129.70, 130.01, 130.11 (two sets of aromatic =CH, one set each of aromatic =C and olefinic =C), 166.78 (CO); IR (KBr) 2220, 1790, 1650, 1200, 1160 cm^{-1}; UV λ_{max} (EtOH) 251 (14 000), 281 (11 600), 209 (6100); LRMS, m/z 296 (M^+, 1.91), 254 (5.0), 227 (15.5), 212 (18.3), 185 (100), 158 (23.6).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.45. Found: C, 64.72; H, 3.93; N, 9.34.

Other isomers were obtained from the pyrolysis.[26] 13(*Z,E*): ^{1}H NMR 2.21 (3 H, s, AcO of the *E* moiety), 2.32 (3 H, s), 6.91 (1 H, s, =CH— of the *E* moiety), 7.08 (1 H, s), 7.45–7.55 (1 H, m), 7.75–7.87 (1 H, m); 13(*Z,Z*): ^{1}H NMR 2.27 (6 H, s), 7.07 (2 H, s), 7.57 (4 H, m).

1,4-Bis(2-acetoxy-2-cyanoethenyl)benzene (17). The preparative procedure which was similar to that described for 13 gave 17 in 34% yield. 17(*E,E*): mp 140–142 °C; ^{1}H NMR 2.35 (6 H, s), 6.73 (2 H, s), 7.55 (4 H, s); ^{13}C NMR 20.544 (CH_3), 114.25 (CN), 121.06 (=CH), 130.42 (aromatic =CH), 130.81 (aromatic =C), 132.86 (=C), 166.49 (CO); IR (KBr) 2220, 1770, 1640, 1210, 1150 cm^{-1}; UV λ_{max} (EtOH) 315 (26 900), 327 (21 300), 226 (9300).

Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.45. Found: C, 64.96; H, 4.04; N, 9.24.

Irradiation of the *E,E* isomer for 6 h afforded two other isomers. 17(*Z,E*): ^{1}H NMR 2.23 (3 H, s), 2.27 (3 H, s), 6.72 (1 H, s), 6.97 (1 H, s), 7.70 (4 H, m). 17(*Z,Z*): ^{1}H NMR 2.27 (6 H, s), 6.97 (2 H, s), 7.78 (4 H, s).

General Procedure for the Photoisomerization of Dienes. Under an N_2 atmosphere, a $CDCl_3$ solution (0.4 mL) of a diene (11 mg) was placed in an NMR sample tube (Pyrex) which was then irradiated with a medium pressure Hg lamp. Time-dependent changes of the components in the solution were examined by NMR and the results for 3, 8, 13, and 17 are summarized in Table I.

Photocyclization of 13. A $CDCl_3$ solution of 13(*E,E*) was irradiated without sensitizers through a Pyrex filter for 18 h. Cyclization products *endo,exo*- and *exo,exo*-5,6-diacetoxy-5,6-dicyano-2,3-benzobicyclo[2.1.1]hex-2-enes (*endo,exo*-22 and *exo,exo*-22) appeared in the reaction mixture in addition to *Z,E* and *Z,Z* isomers of 13. After 42 h, isomers of 13 disappeared and only two isomers of 22 remained in the solution. ***endo,exo*-22** (65%): mp 120 °C; ^{1}H NMR 1.71 (3 H, s, *endo*-AcO), 2.31 (3 H, s), 4.51 (2 H, s), 7.32 (2 H, m), 7.38 (2 H, m); ^{13}C NMR 19.65 and 20.75 (CH_3), 61.22 (CH), 84.52 and 85.18 (AcOCCN), 113.77 and 115.48 (CN), 123.33, 128.21, and 128.89 (three sets of aromatic C), 168.07 and 168.75 (CO); IR (KBr) 2230, 1770 cm^{-1}; LRMS, m/z 296 (M^+), 254, 212, 194, 167. Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; 9.45. Found: C, 64.38; H, 3.93; N, 9.44. ***exo,exo*-22** (18%): mp 133–135 °C; ^{1}H NMR 2.20 (6 H, s), 4.45 (2 H, s), 7.45 (2 H, m), 7.52 (2 H, m); ^{13}C NMR 20.40 (CH_3), 59.58 (CH), 88.87 (AcOCCN), 114.40 (CN), 123.27 and 129.61 (two sets of aromatic =CH), 138.77 (aromatic =C), 168.17 (C=O); IR (KBr) 2230, 1770 cm^{-1}; LRMS, m/z 296 (M^+), 254, 227, 212, 194, 167; CI-MS m/z 297 (MH^+). Anal. Found: C, 64.72; H, 4.05; N, 9.40.

Independent irradiation of a $CDCl_3$ solution of 13(*Z,E*) or 13(*Z,Z*) for 30 min gave a mixture of three isomers of 13 containing a small amount of 22, whereas that of *E,E* formed only a mixture of three isomers of 13. After 1 h, the formation of 22 from *Z,E* was first observed. After 3 h, a mixture of two isomers of 22 containing no diene isomers was formed from both *Z,E* and *Z,Z*, whereas in the irradiated product mixture starting from *E,E* the diene isomers remained to some extent and later disappeared after 6 h.

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Registry No. 1, 543-20-4; 2, 63979-84-0; (*E,E*)-3, 139131-43-4; (*Z,E*)-3, 139131-44-5; 6, 111-50-2; 7, 80317-75-5; (*Z,Z*)-8, 139131-45-6; (*Z,E*)-8, 139131-46-7; (*E,E*)-8, 139131-47-8; 10, 7500-53-0; 11, 41640-86-2; 12, 139131-48-9; (*E,E*)-13, 139131-49-0; (*Z,E*)-13, 139131-50-3; (*Z,Z*)-13, 139131-51-4; 14, 7325-46-4; 15, 21062-19-1; 16, 139131-52-5; (*E,E*)-17, 139131-53-6; (*Z,E*)-17, 139131-54-7; (*Z,Z*)-17, 139131-55-8; *endo,exo*-22, 139166-26-0; *exo,exo*-22, 139240-39-4; Me_3SiCN, 7677-24-9.

Supplementary Material Available: Spectral data for dienes 3, 8, 13, and 17 and cycloadducts 22 and explanations for structure determination (22 pages). Ordering information is given on any current masthead page.

(26) Under an N_2 atmosphere in sealed tubes without solvent, 3(*E,E*), a mixture of 8 (*Z,Z*/*Z,E*/*E,E* = 88/11/1), 13(*E,E*), or 17(*E,E*) was heated at 150 °C for 8 h except 3(*Z,Z*) which was heated at 170 °C for 1 h. Isomer ratios were analyzed by ^{1}H NMR.

The Ortho–Para Ratio and the Intermediate in the Persulfate Oxidation of Aromatic Amines (the Boyland–Sims Oxidation)

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The previous belief that the persulfate oxidation of aromatic amines gives the *o*-sulfate exclusively is untrue; substantial quantities of the para isomer are produced. Kinetic studies on 2,4- and 2,6-disubstituted aromatic amines show that the rate of reaction with persulfate is nearly the same for both isomers. The probable intermediate in this reaction is the arylhydroxylamine-*O*-sulfonate. This was demonstrated by showing that the reaction between *N,N*-dimethylaniline *N*-oxide and the sulfur trioxide–pyridine complex gives material which rearranges to a mixture of *N,N*-dimethylaniline *o*- and *p*-sulfates in the same ratio as is given by the persulfate oxidation of *N,N*-dimethylaniline. The ortho–para ratio is unaffected by dilution. This leads to the conclusion that the degree of intramolecularity of the rearrangement is the same for the formation of both the ortho and para isomers.

Persulfate ions have been reported to react with aromatic amines in neutral or basic aqueous solutions to form *o*-amino aryl sulfates exclusively with the exception that small amounts of the para isomers were reported for the

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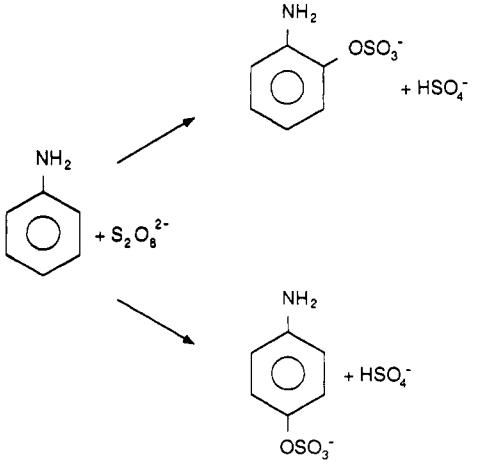
Table I. The Ortho–Para Ratio in the Reaction of Aromatic Amines with Persulfate Ions

amine	M, amine	M, persulfate	M, NaOH	o/p[d]	total yield, % (o + p)
aniline[a]	0.1	0.1	0.5	1.9 ± 0.4[f]	22 ± 4[f]
	0.09	0.09	0.45	1.9 ± 0.3[e]	n.d.
				2.2 ± 0.2[f]	
	0.01	0.01	0.5	1.6 ± 0.1[f]	22 ± 2[f]
	0.009	0.009	0.045	1.7 ± 0.3[e]	n.d.
				2.2 ± 0.2[f]	
	0.01	0.01	0.05	1.5 ± 0.3[f]	40 ± 4[f]
	0.1	0.01	0.5	1.5 ± 0.3[f]	32 ± 1[f]
	0.001	0.001	0.005	2.0 ± 0.3[e]	n.d.
2-methylaniline[b]	0.1	0.1	0.5	1.0 ± 0.1[f]	16 ± 2[f]
	0.09	0.009	0.45	0.85 ± 0.1[f]	n.d.
	0.01	0.01	0.05	0.9[f]	24[f]
	0.009	0.009	0.045	0.80 ± 0.1[f]	n.d.
2-aminobenzoic acid[a]	0.09	0.09	0.45	1.7 ± 0.1[g]	n.d.
	0.009	0.009	0.045	1.8 ± 0.1[g]	n.d.
N,N-dimethylaniline[c]	0.1	0.1	0.5	4.6[f]	34[f]
	0.09	0.09	0.45	5.1 ± 0.3[f]	n.d.
	0.01	0.01	0.05	4.0[f]	42[f]
	0.009	0.009	0.045	4.2 ± 0.3[f]	n.d.
	0.1	0.01	0.05	2.5[f]	36[f]

[a] Solvent, water. [b] Solvent, 25% ethanol. [c] Solvent, 50% ethanol. [d] Per ortho position. [e] Analysis by HPLC of the sulfate esters. [f] Analysis by NMR. [g] Analysis by HPLC of the free aminophenols.

reactions with anthranilic acid, *o*-aminoacetophenone, kynurenine, and 2-aminobiphenyl.[1,2] Except for these cases, the para isomer was reported only when both ortho positions were occupied by non-hydrogen substituents.[3] This situation contrasts sharply with the Elbs oxidation of phenols in which the *p*-sulfate predominates.[1] In this paper, I show that the formation of the para isomer in the Boyland–Sims oxidation is general.

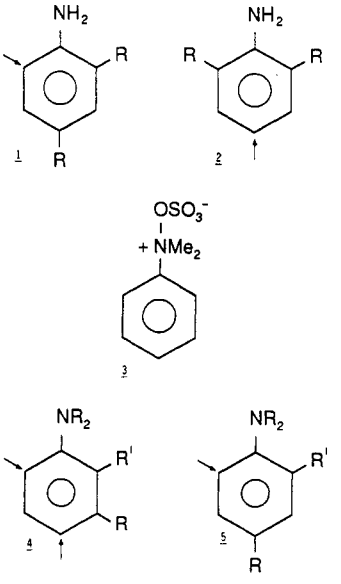


The question of the intermediate in the Boyland–Sims oxidation has been the subject of some controversy. Evidence is presented to show that arylhydroxylamine-*O*-sulfonates are the probable intermediates.

Results

The Ortho–Para Ratio. I have carried out product analyses on four amines in order to examine the ortho–para ratio quantitatively. The data are reported in Table I. It is clear that ortho substitution is by no means exclusive. This table also reports yield data. As previously noted,[4] the yield depends on both the amine–persulfate ratio and on the pH. The ortho–para ratio is, however, independent of these factors and also independent of amine concentration.

Kinetics of the Reaction for 2,4- and 2,6-Disubstituted Aromatic Amines. The data of Table I show that, except for *o*-toluidine, the ortho product, while not exclusive, nevertheless predominates. This might suggest, in view of previous arguments against direct attack at the ortho carbon,[4,5] that the *o*-sulfate is formed by rearrangement from some intermediate,[4-6] while the *p*-sulfate is formed by direct attack. If this were so, comparison of the rates of reaction of 2,4- and 2,6-disubstituted anilines **1** and **2** should reflect the observed ortho–para ratios. Table II shows that this agreement is not good. In fact, the 2,4–2,6 ratio is close to 1 for all cases.



The Intermediate in the Boyland–Sims Oxidation. Edward and Whiting[7] reported that *N,N*-dimethylaniline *N*-oxide reacted with the pyridine–sulfur trioxide complex to produce *N,N*-dimethylanilino sulfate (**3**) for which they

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Table II. Rates of Reaction of Ortho- and Para-Substituted Aromatic Amines with Persulfate Ions

compd	no. of runs	amine concn range, M	$t_{1/2}$, min	k_2, M^{-1} min^{-1}
Conditions: 30 °C, 0.2 M KOH, water[a]				
2-aminobenzoic acid	4	0.05–0.10	9.4–20	0.71 ± 0.02
2-amino-3-methylbenzoic acid	8	0.025–0.05	9.5–19.5	1.43 ± 0.04
2-amino-5-methylbenzoic acid	5	0.025–0.05	8.1–17	1.69 ± 0.04
Conditions: 40 °C, 0.2 M KOH, water[a]				
2-aminopyridine[b,c]	4	0.5	38.7–39	0.036 ± 0.01
2-amino-3-methylpyridine	5	0.095–0.5	7.9–40	0.18 ± 0.01
2-amino-5-methylpyridine	4	0.25–0.39	14.7–21.8	0.12 ± 0.01
Conditions: 20 °C, 0.2 M KOH, 24% ethanol–76% water, v/v[a]				
2-methylaniline	4	0.05–0.10	8.7–17.2	0.77 ± 0.03
2,4-dimethylaniline	4	0.036–0.082	6.3–13.6	1.36 ± 0.04
2,6-dimethylaniline	8	0.013–0.074	7.6–41.9	1.37 ± 0.20

[a] In all cases, the amine–persulfate concentration ratio was 10 or greater. [b] See also ref 4. [c] o/p ~ 1.8.

reported an IR spectrum and a good elemental analysis. They further found that treatment of this material in hot water resulted in hydrolysis to *N,N*-dimethylaniline *N*-oxide and sulfate. This report has been the basis for excluding the arylhydroxylamine-*O*-sulfonate as an intermediate in the Boyland–Sims oxidation.[5,8] Repetition of the procedure of Edward and Whiting (with some slight modifications, see Experimental Section) has produced a strikingly different result. Treatment of the product formed from *N,N*-dimethylaniline *N*-oxide and sulfur trioxide in dry pyridine with water resulted in the formation of *N,N*-dimethylaniline *o*-hydrogen sulfate in 45% isolated yield. The material was identified by mp, by identity of its IR and proton NMR spectra with those of authentic material, and also, quantitatively, by its extinction coefficient. Treatment of the reaction mixture with 1 M NaOH instead of water yielded the same product but as the sodium salt (identification by NMR and IR). Examination of the crude reaction mixture by NMR showed the presence of the *p*-sulfate as well as other unidentified compounds. The ortho–para ratio for the sulfates was identical to that given in Table I for the products of the reaction between persulfate and *N,N*-dimethylaniline.

Discussion

The data of Tables I and II which show a lack of agreement between the ortho–para ratio of the products and the rates of reaction of 2,4- and 2,6-disubstituted amines **1** and **2** suggest a common intermediate which rearranges at different rates to form the ortho and para products. Two questions arise: (a) what is this common intermediate and (b) what is the mechanism of its rearrangement? First, however, it is necessary to reconsider the previous data[4,5] which were used to argue against formation of the *o*-sulfate by direct attack at the ortho carbon atom in view of the fact that significant quantities of the *p*-sulfate are formed. At the time these arguments were advanced, the formation of the para product was not known. The kinetics for the reaction of persulfate with five pairs of 2,3- and 2,4-disubstituted aromatic amines **4** and **5** had been measured.[4,5] In this way, the relative rates of reaction of the two isomers could be correlated with the meta and para σ constants for the 3- or 4-substituent (**4** and **5**). The observed reactivity pattern, on the assumption of exclusive ortho substitution, for all five pairs was consistent with attack at the nitrogen atom or the ipso-carbon, but not with direct attack at the ortho carbon. The fact that para substitution occurs as well does not seriously affect the argument, however. The 2,3-isomer **4** has both an ortho and a para position available for substitution; the 2,4-isomer **5** has only an ortho position. Thus, the occurrence of para substitution in the 2,3-isomer could only make its reactivity greater. However, this isomer is the more slowly reacting one in four out of the five pairs examined (R = Me, Cl). The data for the fifth pair, R = NO_2, can no longer be used to support the argument.

The Nature of the Intermediate and the Mechanism of Its Formation and Rearrangement. The evidence in this paper that the reaction between *N,N*-dimethylaniline *N*-oxide and sulfur trioxide leads to a good yield of *N,N*-dimethylaniline *o*-hydrogen sulfate constitutes strong evidence that the arylhydroxylamine-*O*-sulfonate **3** is the probable intermediate in Boyland–Sims oxidation as postulated some time ago.[4] The probability is enhanced by the finding that the *p*-sulfate is also found in crude reaction mixtures of the *N*-oxide and sulfur trioxide and in the same ratio with the ortho isomer as is found in the persulfate oxidation of the parent amine. The argument is further strengthened by a number of previous reports[9] that other arylhydroxylamine-*O*-sulfonates rearrange to yield, predominantly, the *o*-amino hydrogen sulfates. The work of Boyland and Nery and of Novak et al. is particularly relevant.[9a,e]

On the assumption that the formation of the arylhydroxylamine-*O*-sulfonate is the slow step in the sequence (this has yet to be established), the available evidence is consistent with nucleophilic attack by the neutral amine on the peroxide oxygen of persulfate. A nitrene mechanism is not consistent with the fact that tertiary anilines behave similarly to primary anilines. A single electron-transfer scheme involving a tight ion pair can be written (tight since radical traps have no effect),[4] but the observed activation parameters[4,8] are typical of an S_N2 process rather than a SET mechanism.[10]

On the assumption of a common intermediate leading to the formation of both the ortho and para products, the question of intra- vs intermolecular rearrangement arises. The "obvious" conclusion that the ortho isomer is formed exclusively by an intramolecular process and the para isomer exclusively by an intermolecular one has been shown to be untrue for the Fries and related rearrangements by the labeling experiments of Hart and his colleagues.[11] These proceed in more complicated ways. We

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have tested the effect of dilution[12] of the amine on the ortho–para ratio. An intermolecular process would be second-order in amine and so dilution would increase the ortho–para ratio. We see no such effect. We think it probable that both the ortho and the para product are formed by an intramolecular rearrangement. However, the strongest statement that can be definitely made is that the evidence shows that the ortho product is formed by a process that is no more intramolecular than the process which forms the para product.

Novak et al.[9e] have given evidence to support a mechanism for rearrangement of at least some arylhydroxylamine-*O*-sulfonates by heterolysis of the N–O bond to form an "intimate" ion pair. We have no direct evidence for the cases discussed here. Labeling studies with ^{18}O would be informative.[11,13]

Experimental Section

Syntheses of the Sulfate Esters. Compounds **6**, **7**, **8**, and **11** have been previously reported in the literature with satisfactory elemental analyses but without spectroscopic data. Compounds **9**, **10**, and **12** have been briefly reported in the toxicological literature but without adequate characterization. All of these compounds showed a strong IR band around 1060 cm^{-1} characteristics of the sulfate esters.

Assignment of the NMR resonances was uncomplicated at 500 MHz for most cases, but **6** required selective decoupling while H-4 and -6 of **8** were distinguished by NOE enhancement of H-4 during irradiation of the methyl group. *J* values are given in Hz.

Characterization of the Para Isomers in Reaction Mixtures. Chromatographic analysis of the products of the persulfate oxidation of anthranilic acid, kynurenine, and *o*-aminoacetophenone had previously given evidence for the presence of the *p*-sulfates in addition to the ortho isomers.[2] Identification was made not only by characteristic R_f values but also by distinctive color reactions and fluorescence.

In this paper, the products from the oxidations of aniline, 2-methylaniline, and *N,N*-dimethylaniline have been identified by their characteristic aromatic proton resonances at 500 MHz.

Reference spectra of the authentic *o*- and *p*-sulfates and of typical reaction mixtures containing both isomers are given in the supplementary material. The NMR spectra of the basic aqueous fraction following ether extraction showed only resonances assignable to the *o*- and *p*-sulfates as major components. In addition, for both aniline and 2-methylaniline, the aminophenols resulting from acid-catalyzed hydrolysis of the sulfate esters were identified by GC–MS. Ether extracts of the *o*-toluidine reaction contained both azo- and hydrazotoluene (GC–MS) (see also Table F, ref 1). For anthranilic acid (2-aminobenzoic acid), we confirmed the findings of ref 2 by showing material of identical mobility to authentic 3- and 5-hydroxyanthranilic acids upon HPLC of acid hydrolysates of reaction mixtures. The UV spectra of the isolated materials also matched those of the genuine samples.

Analysis of the Ortho–Para Ratio. Initial attempts to measure this ratio used GC–MS of the aminophenols formed by acid hydrolysis of the sulfate esters. This method was plagued by differential loss of the para isomers. The ratio in the anthranilic acid system was carried out by HPLC analysis of acid hydrolysates using a C-18 reversed-phase column and a 10-min linear gradient from 0.1% aqueous H_3PO_4 to 50% acetonitrile. Anthranilic acid, 3-hydroxyanthranilic acid, and 5-hydroxyanthranilic acid were well separated with elution times of about 7, 5, and 3 min. Two techniques were used to determine the sulfate esters themselves. These methods have the advantage of avoiding the formation of the easily oxidizable aminophenols. The first of these was an HPLC method which used an RP-18 column (Brownlee Labs, Spheri-5, 5 μm, 220 × 4.6 mm) and a linear gradient from 0.01 M phosphate buffer, pH 6.8, in water to acetonitrile, 30 min, rate = 1 mL/min. The alkaline reaction mixtures were thoroughly extracted with ether to remove excess amine. The aqueous residue was made about 0.01 M in phosphate and then brought to pH 7 with HCl. *o*- and *p*-aminophenyl sulfate were separated in this system with retention times of about 3 min (*p*) and 3.5 min (*o*). Detection was at 282 nm. Areas were measured by triangulation and molar ratios calculated from the extinction coefficients. The products from the persulfate oxidation of *o*-toluidine were also separated by this procedure; however, the sulfate esters formed from *N,N*-dimethylaniline were not well resolved.

The second (and preferred) method for the sulfate esters was based on nonoverlapping proton resonances in their 500-MHz NMR spectra. The *o*- and *p*-sulfate esters formed from *N,N*-dimethylaniline and from *o*-toluidine have methyl resonances separated from each other by 0.1 and 0.04 ppm, respectively. For aniline itself, the proton resonances of the *p*-sulfate ester overlap the resonances of H-4 and 5 of the *o*-sulfate ester, but the resonances of H-3 and 6 of the *o*-sulfate ester are cleanly resolved. For analysis, the same reaction mixtures used for HPLC were thoroughly dried and then taken up to D_2O.

Yield determinations were carried out by adding known quantities of dry tetramethylammonium chloride to aliquots of ether-extracted dried reaction mixtures dissolved in D_2O. Ratios of the integrated intensities, following sufficient pulse delays to allow for differing T_1 values, then gave absolute quantities of the sulfate esters.

Kinetics. Kinetics were measured by following persulfate disappearance as previously described.[4]

2-Aminophenyl potassium sulfate (6) was synthesized by the persulfate oxidation of aniline according to Boyland et al.[14] Tan needles from 90% ethanol, mp 260–265 °C dec. IR (Nujol): 3430, 3340, 1645, 1510, 1290, 1240, 1060, 890, 800, 765 cm^{-1}. UV (water) λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 230, 7890; 281, 2110. ^1H NMR (D_2O): δ H-3 6.879 (ddd, $J_{3,4}$ 8.05, $J_{3,5}$ 1.6, $J_{3,6}$ 0.3), H-4 7.052 (ddd, $J_{3,4}$ 8.05, $J_{4,5}$ 7.5, $J_{4,6}$ 1.4), H-5 6.780 (ddd, $J_{5,6}$ 8.0, $J_{4,5}$ 7.5, $J_{3,5}$ 1.4), H-6 7.190 (dd, $J_{5,6}$ 8.0, $J_{4,6}$ 1.5).

4-Aminophenyl potassium sulfate monohydrate (7) was synthesized by reduction of 4-nitrophenyl sulfate (Sigma) according to Burkhardt and Wood.[15] Tan plates from 80% ethanol, mp 212–217 °C dec. IR (Nujol): 3560, 3400, 3330, 1645, 1520, 1260, 1240, 1055 cm^{-1}. UV (water) λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 234, 7400; 286, 1110. ^1H NMR (D_2O): δ H-2 and -6 7.033 (dd, J_{ortho} 6.6, J_{meta} 2.2), H-3 and -5 6.750 (dd, J_{ortho} 6.6, J_{meta} 2.2).

2-Amino-3-methylphenyl potassium sulfate (8) was synthesized by persulfate oxidation of *o*-toluidine according to Boyland and Sims.[16] Colorless plates from 90% ethanol, mp 237–243 °C dec. IR (Nujol): 3400, 3320, 1640, 1280, 1240, 1060, 950, 780, 750 cm^{-1}. UV (water) λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 230, 7190; 281, 2110. ^1H NMR (D_2O): δ H-4 6.96 (dd, $J_{4,5}$ 8.0, $J_{4,6}$ 0.7), H-5 6.71 (dd, $J_{4,5}$ 7.9, $J_{5,6}$ 7.8), H-6 7.07 (dd, $J_{5,6}$ 7.8, $J_{4,6}$ 0.8), $-CH_3$ 2.11.

3-Methyl-4-nitrophenyl potassium sulfate (9) was synthesized by reaction of 3-methyl-4-nitrophenol (Aldrich) with chlorosulfonic acid according to the general procedure of Feigenbaum and Neuberg.[17] Pale yellow dendritic needles from 95% ethanol, mp 219–225 °C dec. IR (Nujol): 1625, 1600, 1530, 1360, 1290, 1250, 1065, 960, 895, 770, 720, 690 cm^{-1}. UV (water) λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 220 (sh), 5720; 275, 6550. ^1H NMR (D_2O) δ H-2 7.23 (d, $J_{2,6}$ 2.4), H-5 8.00 (d, $J_{5,6}$ 8.9), H-6 7.22 (dd, $J_{5,6}$ 8.8, $J_{2,6}$ 2.4), $-CH_3$ 2.49. Anal. Calcd for $C_7H_6NO_6SK$: C, 30.97; H, 2.21. Found: C, 30.55; H, 2.29.

3-Methyl-4-aminophenyl potassium sulfate (10) was synthesized by reduction of the nitro compound according to the general procedure of Burkhardt and Wood.[15] Tan rhombs from 85% ethanol, mp 232–236 °C, dec. IR (Nujol): 3390, 3330, 1510, 1260, 1240, 1225, 1050, 950, 780 cm^{-1}. UV (water) λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 233.5, 8570; 285, 1710. ^1H NMR (D_2O): δ H-2 6.96 (d, $J_{2,6}$ 2.5), H-5 6.72 (d, $J_{5,6}$ 8.6), H-6 6.90 (dd, $J_{5,6}$ 8.5, $J_{2,6}$ 2.5), $-CH_3$ 2.07. Anal. Calcd for $C_7H_8NO_4SK$: C, 34.8; H, 3.34. Found: C, 34.3; H, 3.56.

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2-(*N,N*-Dimethylamino)phenyl potassium sulfate (11) was synthesized by persulfate oxidation of *N,N*-dimethylaniline according to Boyland et al.[14] Tan needles from 95% ethanol, mp 226–228 °C dec. IR (Nujol): 1605, 1500, 1275, 1255, 1050, 945, 870, 745 cm^{-1}. UV (water): λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 240, 5725; 278.5 (sh), 1390. ^1H NMR (D_2O): δ H-3 and -4 7.1 (m), H-5 7.03 (ddd, $J_{4,5}$ 5.9, $J_{5,6}$ 7.5, $J_{3,5}$ 3.2), H-6 7.44 (dd, $J_{5,6}$ 8.2, $J_{4,6}$ 1.1), $-NMe_2$ 2.66.

4-(*N,N*-Dimethylamino)phenyl Sodium Sulfate Monohydrate (12). (*N,N*-dimethylamino)-4-anisidine (Dixon Fine Chemicals) was converted to 4-(*N,N*-dimethylamino)phenol by the procedure of Slotta and Behnisch.[18] The phenol was converted to the sulfate by the general procedure of Feigenbaum and Neuberg,[17] but isolated as the sodium salt according to Eyer and Gaber.[19] Colorless plates from acetone-ether, mp 210–215 °C dec. IR (Nujol): 3640, 3410, 1645, 1525, 1475, 1390, 1270, 1250, 1075, 1065, 955, 875, 830, 775 cm^{-1}. UV (water) λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 246, 10, 160; 290 (sh), 1470. ^1H-NMR (D_2O): δ H-2 and -6 7.14 (dd, J_{ortho} 6.8, J_{meta} 2.3), H-3 and -5 6.92 (dd, J_{ortho} 6.8, J_{meta} 2.3), $-NMe_2$ 2.75. Anal. Calcd for $C_8H_{10}NO_4SNa \cdot H_2O$: C, 37.3; H, 4.70. Found: C, 37.4; H, 4.54.

***N,N*-Dimethylaniline *N*-oxide** was prepared by treatment of *N,N*-dimethylaniline with 30% H_2O_2 according to Oae et al.[13] After 5 days at rt, the clear solution was evaporated to about one-third of its initial volume on a rotary evaporator at 55 °C. The solution was then extracted three times with ether to remove excess dimethylaniline. Excess H_2O_2 was decomposed by treatment with 3A molecular sieves (caution: exothermic) according to Edward and Whiting.[7] The product was extracted with $CHCl_3$ (not benzene). Evaporation of the solvent gave an oil which crystallized. The crystals were slurried with CCl_4, filtered rapidly, and dried over P_2O_5 to give slightly yellow, very hygroscopic crystals of *N,N*-dimethylaniline *N*-oxide, mp 144–145 °C, raised to 152–3 °C by recrystallization from benzene (lit.[20] mp 154 °C). IR: (neat, slightly wet): 1580, 1475, 1440 (s), 1380, 1310, 1240, 1190, 1170, 1110, 1050, 1010, 950 (s), 930, 860, 740 (s), 690 (s). ^1H NMR (DMSO-d_6, TMS): δ H-2 and -6 8.095 (ddd, $J_{2,3}$ 8, $J_{2,4}$, $J_{2,6}$ 1.5), H-3 and -5 7.461 (ddd, $J_{2,3}$ 8, $J_{3,4}$ 5.5, $J_{3,5}$ 2), H-4 7.388 (tt, J_{ortho} 5.5, J_{meta} 1.5), $-NMe_2$ 3.397 (s).

A 1:1 H_2O_2 adduct of *N,N*-dimethylaniline *N*-oxide was isolated from a reaction mixture in which the excess H_2O_2 had not been destroyed. The proton NMR of this adduct in D_2O was identical to that of authentic *N,N*-dimethylaniline *N*-oxide. The IR spectra taken as a mull in Nujol or in KBr were similar to those of the parent compound but the N–O stretch was less intense and was shifted to 975 cm^{-1}. There was also a new broad multiplet centered at 850 cm^{-1} attributable to the O–O stretch. H_2O_2 was measured quantitatively by reaction with Ti(IV).[21] A useful characteristic of this compound is that, in contrast to its parent, it is not hygroscopic. Colorless plates and needles from $CHCl_3$, mp 112–113 °C. Anal. Calcd for $C_8H_{13}NO_3$: C, 56.1; H, 7.65; N, 8.18. Found: C, 55.8; H, 7.48; N, 8.16.

Reaction between *N,N*-Dimethylaniline *N*-Oxide and Sulfur Trioxide.[22] *N,N*-Dimethylaniline *N*-oxide (1.37 g, 0.01 mol) was partially dissolved in 20 mL of dry pyridine (CaH_2) at rt. Sulfur trioxide–pyridine complex (Aldrich, 1.9 g, 0.012 mol) was added. A homogeneous brown solution formed rapidly with some warming. After 15 min, 75 mL of hexane was added to precipitate the products and to extract the pyridine. The hexane-soluble fraction was decanted and the oily residue washed with 5 × 50 mL of hexane. Residual pyridine was removed with an oil pump. The IR spectrum of the crude products lacked the bands reported by Edward and Whiting[7] for *N,N*-dimethylanilino sulfate at 1340 and 615 cm^{-1}. Water (10 mL) was added to the products at rt whereupon a granular solid formed. The pH of the mixture was about 5. The solid was filtered and washed with cold water, 95% ethanol, and ether to yield 0.8 g of crude product. The mother liquors, after the addition of a little HCl and cooling gave a second crop (0.12 g) for a total yield of 0.92 g (42%) of 2-(*N,N*-dimethylamino)phenyl hydrogen sulfate. Recrystallization from water with a little Norite gave nearly colorless needles, mp 212–214 °C dec (lit.[14] mp 217–219 °C). IR (KBr): 1605, 1490, 1475, 1460, 1400, 1370, 1280 (s), 1240 (s), 1235 (s), 1185, 1040 (s), 845, 775, 685. ^1H NMR (DMSO-d_6, internal TMS): δ H_6 7.749 (dd, $J_{5,6}$ 8, $J_{4,6}$ 1.1), H_3 7.634 (dd, $J_{3,4}$ 8, $J_{3,5}$ 1.5), H_4 7.462 (ddd, $J_{3,4}$ 8, $J_{4,5}$ 8, $J_{4,6}$ 1.4), H_5 7.298 (ddd, $J_{4,5}$ 8, $J_{5,6}$ 8, $J_{3,5}$ 1.3), $-NMe_2$ 3.187 (s). UV (water, pH 7) λ_{max} (nm), ϵ (M^{-1} cm^{-1}): 240, 5860; 278 (sh), 1250. The sodium salt of this material gave IR and NMR spectra identical to those of the potassium salt 11 (see above).

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Supplementary Material Available: ^1H NMR spectra of reaction mixtures (3 pages). Ordering information is given on any current masthead page.

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Stereoselective Synthesis of the Pyrrolizidine Alkaloids (-)-Integerrimine and (+)-Usaramine

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Two routes to the pyrrolizidine alkaloid (-)-integerrimine (1) are described. The first, starting from methyl (*R*)-(-)-3-hydroxy-2-methylpropionate, proceeded in 19 steps to integerrinecic acid lactone (5) which was transformed to the necic acid derivative 30. The latter was coupled to protected retronecine 31, and the synthesis of 1 was completed by lactonization employing Vedejs' protocol. A second, shorter synthesis of (-)-1 was accomplished via 5, starting from (*R*)-(+)-β-citronellol (36). This pathway invoked Katsuki–Sharpless epoxidation of 42 for stereoselective construction of the tertiary alcohol of integerrinecic acid. A parallel sequence proceeding via the stereoisomeric epoxide 44 led to the necic acid segment 75 of the alkaloid (+)-usaramine (2). This acid was coupled to the retronecine borane 82 and then lactonized to 2.

Alkaloids of the pyrrolizine family are widespread in nature, occurring in over 150 plant species and nearly 70 genera.[1] Extensive pharmacological investigation of the pyrrolizidine alkaloids[2] has shown that many are acute

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