Diaryl Ether Formation via Nitro Displacement with 4-Methylphenol and Potassium Carbonate on 4-Nitro-*N*-methylphthalimide

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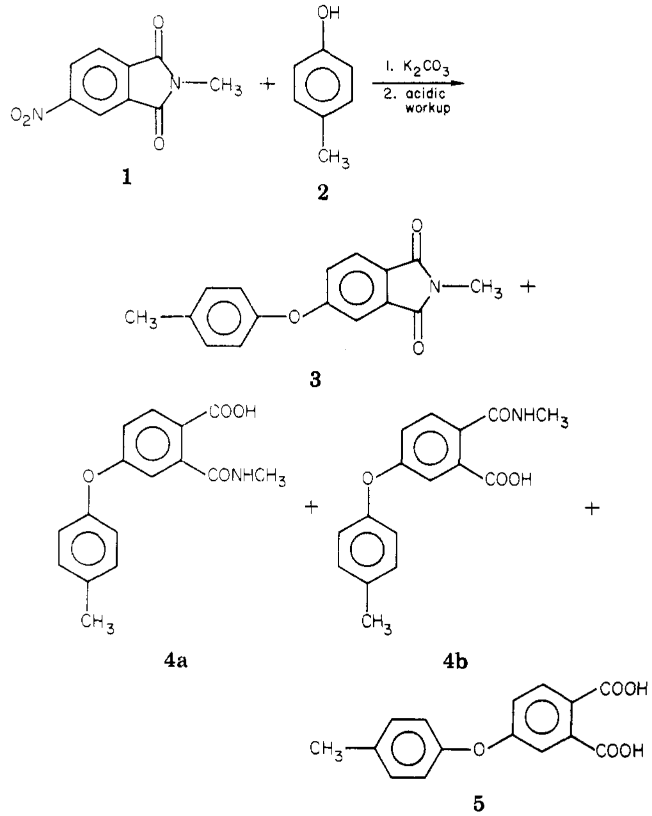
Conditions for the equilibration between a nitro-substituted imide and its ring-opened amide–acid salt were established. Evidence was found that nitro displacement by an aryl oxide nucleophile occurred only in the imide form. Extensive ^{13}C NMR data are presented as structural evidence and for distinguishing amide acid isomers.

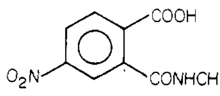
When 4-nitro-*N*-methylphthalimide (**1**) was allowed to react with 1 equiv of 4-methylphenol (**2**) and excess K_2CO_3 in Me_2SO at 142 °C, a mixture of nitro displacement products[1] was obtained and a significant amount of gas evolution was observed. By ^{13}C NMR, it was determined that the reaction mixture contained **3**, the potassium salts of **4a** and **4b**, and the dipotassium salt of **5** in the ratio of 49:38:13. The isolated mixture consisted of the imide **3**, the isomeric amide acids **4a** and **4b**, and the diacid **5** in the ratio of 58:39:3 (some workup losses of **4a**, **4b**, and **5**). Structural identity of the isolated products was confirmed by ^{13}C NMR and ^1H NMR spectroscopy and by the hydrolytic conversion of the entire mixture to **5**.



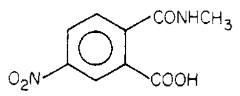
The observed percent yield of **3** increased to a maximum before 30 min and then slowly decreased over the course of the reaction (and well past the time that nitro displacement had been completed, i.e., **2** completely consumed), resulting in a constant increase in the percent of the salts of **4a**, **4b**, and **5**. Thus, these salts were simply arising from secondary hydrolytic reactions of **3**. What was striking was that the nitro compound **1** was consumed considerably faster than the 4-methylphenol (**2**); the mole ratio of **1** to **2** consumed during the first 15 min of reaction, for example, was 1.33:1, respectively. Furthermore, after 15 min, the amount of **1** present was always considerably less than that of **2**; yet, eventually, all of **2** was converted exclusively into the nitro displacement products.

This reaction was repeated with the addition of a large amount of 4-Å molecular sieves. In this case, the amount of **3** observed was much greater throughout since the hydrolytic reactions were significantly suppressed. It was isolated in 86% yield. Once again, however, **1** was consumed faster than **2**; for example, the mole ratio lost was 1.18:1 during the first 30 min.

It was of interest to understand the loss of **1** *other than that due to nitro displacement* as well as the continued consumption of **2** under conditions where the amount of **1** remaining was less than that of **2**. Toward these ends, **1** alone was allowed to react with excess K_2CO_3 in Me_2SO solution at 142 °C. Surprisingly, a substantial amount of gas was evolved which, on mass spectral analysis, proved to be exclusively CO_2.[2] The amount of CO_2 produced was the same whether **2** was present or not and approached *one-half* of the number of moles of **1**. In addition, when the K_2CO_3 + **1** reaction was repeated and the concentration monitored by VPC, it was found that **1** was consumed at very nearly the same rate as in the presence of **2**. After the gas evolution had ceased (ca. 75 min) the resulting suspension was filtered to remove excess K_2CO_3. Analysis of the filtrate by ^{13}C NMR spectroscopy indicated that it contained only the potassium salts of **6a** and **6b**. Neutralization gave a solution containing the corresponding amide acids.



6a



6b

A possible interpretation of these results is shown in Scheme I. Imide ring opening by carbonate[3] followed by protonation and loss of CO_2 would result in the observed products. Moreover, the generation of a hydroxyl ion for every neutralization of the initially formed ring-opened product **7** followed by its expected (see Experimental Section) rapid conversion of **1** to **8** would explain why the number of moles of CO_2 approached only half that of **1**.

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[1] (a) H. M. Relles, D. S. Johnson, and J. S. Manello, *J. Am. Chem. Soc.*, **99**, 6677 (1977); (b) F. J. Williams, H. M. Relles, J. S. Manello, and P. E. Donahue, *J. Org. Chem.*, **42**, 3419 (1977); (c) F. J. Williams, H. M. Relles, P. E. Donahue, and J. S. Manello, *J. Org. Chem.*, **42**, 3425 (1977); (d) F. J. Williams and P. E. Donahue, *J. Org. Chem.*, **42**, 3414 (1977).

[2] It had been assumed up to this time that the gas evolution observed during the reaction between **1**, **2**, and K_2CO_3 had been due to an unexceptional acid (4-methylphenol) and carbonate reaction A subsequent control experiment negated this assumption.

[3] Carbonate functioning as a nucleophile in a different system has recently been suggested: K. Soga, S. Hosoda, and S. Ikeda, *J. Polym. Sci.*, 17, 517 (1979).

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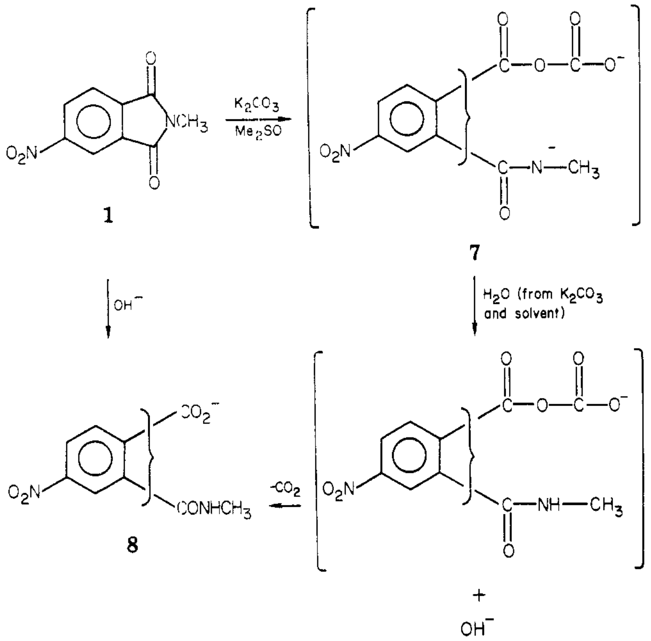
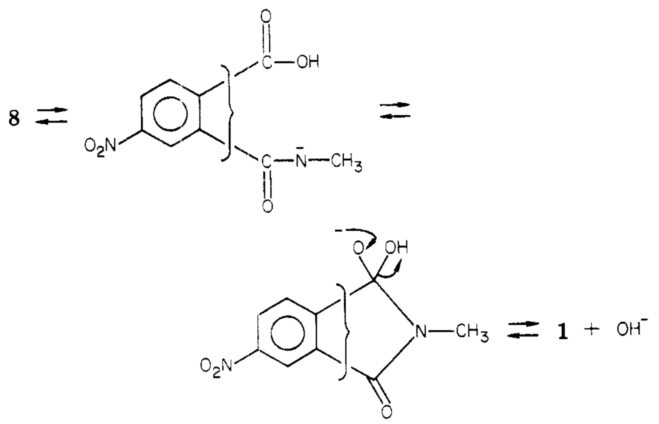
Scheme I

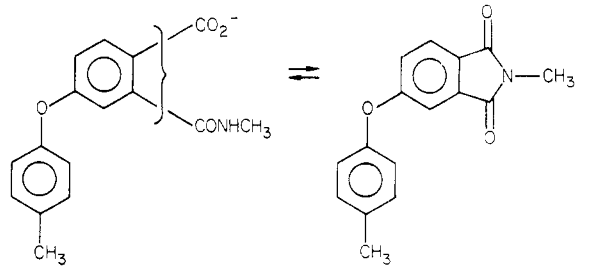


Scheme II



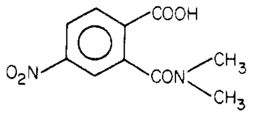
It was anticipated[1] that nitro displacement on **8** by **2** (in the presence of K_2CO_3) would not proceed at any appreciable rate. However, when a sequential reaction was conducted in which first K_2CO_3 and **1** were allowed to react completely to give **8** and then **2** was added, the overall nitro displacement then proceeded at essentially the same rapid rate and the yield and product distribution (**3** + **4a** + **4b** + **5**) vs. time were very nearly the same as when all of the reagents had been present initially. In addition, when **8** was prepared in Me_2SO from authentic **6** and then treated with **2** and K_2CO_3, the ^{13}C NMR spectrum of the resulting solution showed the expected displacement and/or hydrolysis products: **3**, **4a**, and **4b**.

Since displacement should only be facile with **1**, a reasonable explanation of these results is that a relatively rapid equilibration existed under these conditions between **8** and **1**. This may be depicted mechanistically as in Scheme II. At ambient temperatures, this equilibrium must lie very far to the left since, within the limits of ^1H NMR, ^{13}C NMR, and VPC detection, **1** is completely converted to **8** in the presence of hydroxide ion. The credibility of this equilibration is supported by the fact that under the same $K_2CO_3/Me_2SO/142$ °C condition, the salt of **4** underwent a substantial amount of conversion to **3**. After 2 h, 17% of **3** had been generated; after 17 h with KNO_2 added the value had reached 43–45% with 6% of **5** being present also. (Of course, controls also indicated that the reverse reaction proceeded very well under the reaction conditions.)

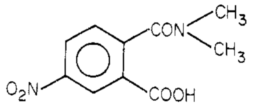


4 **3**

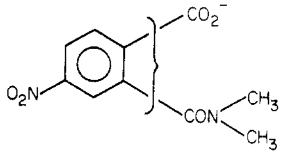
In order to test the equilibration to explain the observed displacement behavior, the mixture of amide acids **9a** and **9b** was prepared. The mixture of salts **10** from these would not be capable of undergoing ring closure to an imide and, therefore, should not be capable of undergoing nitro displacement. Indeed, when this mixture was subjected to the identical set of reaction conditions used for **1** or for **8**, the reaction mixture, by ^{13}C NMR spectroscopy, contained only **10** and **2**; no nitro displacement products could be detected. This result clearly supports the need for the conversion of **8** to **1** prior to displacement.



9a



9b



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An additional consequence of the mechanism depicted in Scheme II is that it should be possible to observe nitro displacement products by simply treating **8** with 4-methylphenol (**2**) at 142 °C in Me_2SO *in the absence of added* K_2CO_3. Since the conversion of **8** to **1** would be accompanied by the liberation of a hydroxide ion, this could neutralize the 4-methylphenol and give the corresponding aryl oxide nucleophile which should undergo nitro displacement. Indeed, when the sodium salt of **8** was treated with **2** under these conditions, an 86% yield of **3** was obtained; ^{13}C NMR and high-pressure liquid chromatography analyses indicated that the reaction mixture contained primarily[4] **1**, **2**, **3**, and **8** in a mole ratio of 2.1:14.1:85.8:7.2. This result strongly supports the hypothesis in Scheme II as well as the overall mechanism for the reaction depicted in Scheme III.

Experimental Section

Dimethyl sulfoxide (Me_2SO) used in this work was Burdick and Jackson reagent grade containing ca. 100 ppm of water. Tetrahydrofuran (THF) was dried and purified by distillation from sodium benzophenone ketyl. All reactions, unless otherwise indicated, were conducted under dry nitrogen in these solvents. Potassium carbonate (K_2CO_3) used was Mallinckrodt anhydrous, granular reagent. Titration with acid indicated that this was 98.6 ± 0.2% K_2CO_3. A new method was developed (see below) to analyze for water in the K_2CO_3; it was found to be 1.3%.

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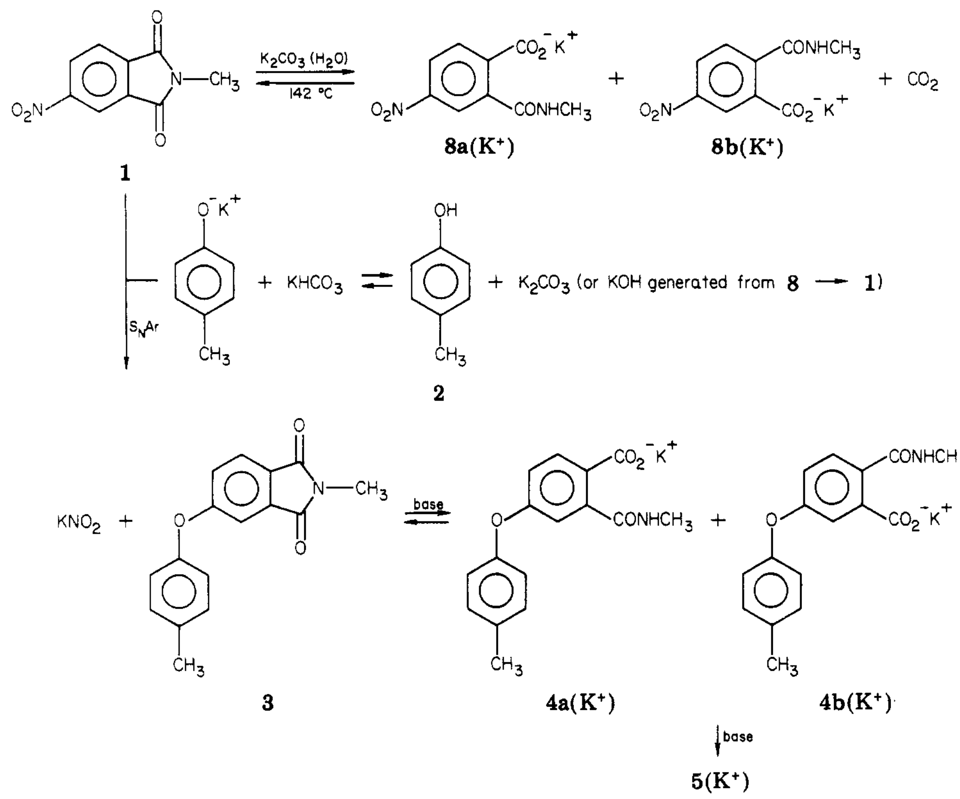
[4] A minor amount (0.7 mol %) of 4,4′-oxybis[*N*-methylphthalimide] was also present in this reaction; see R. L. Markezich and O. S. Zamek, *J. Org. Chem.*, 42, 3431 (1977).

Scheme III

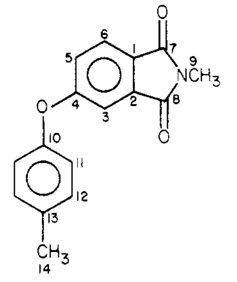


Carbon-13 NMR spectra were obtained on a Varian Associates XL-100 or CFT-20 spectrometer and proton NMR spectra on a Varian Associates T-60 spectrometer. All chemical shifts are given in parts per million downfield from tetramethylsilane (Me_4Si) whether determined from internal Me_4Si or from known shifts of the specific solvents being used. The ^{13}C NMR chemical shift for Me_2SO-d_6 was 39.65 ppm and for Me_2SO-h_6, 40.48 ppm.

High-pressure liquid chromatography was carried out on a Waters Associates liquid chromatograph, equipped with a dual wavelength detector and dual recorders, using a μBondapak-C-18 column and solvent programming: program 6 (linear) for 5 min, then hold; initial solvent 50% (90:10 acetonitrile–methanol), 50% water; final solvent 80% (90:10 acetonitrile–methanol), 20% water; flow rate 1.5 mL/min; simultaneous detection at 254 and 280 mμ; integration of peak areas done at 280 mμ. Predetermined molar response factors at 280 nm were used to convert relative areas to relative moles. Both the retention times and the ratio of ε values at the two wavelengths were used for identification. Sample preparation for high-pressure LC analysis involved adding a ~0.5-mL sample of a reaction mixture to 10 mL of tetrahydrofuran containing ~0.25 mL of acetic acid, stirring vigorously, and filtering through a Millipore filter.

Preparation of *N*-Methyl-4-(4-methylphenoxy)phthalimide (3) Using Preformed Anhydrous Sodium 4-Methylphenoxide. A solution of 0.583 mol of anhydrous sodium 4-methylphenoxide in 600 mL of Me_2SO was prepared from 4-methylphenol and sodium hydroxide by azeotropic removal of water from a toluene/Me_2SO solution (using first a Dean–Stark trap and then a trap adapted to allow the refluxing toluene to be circulated through a bed of calcium hydride before returning to the reaction mixtures); toluene was then removed by distillation.

To this solution, at ca. 70 °C, was added 120.0 g (0.583 mol) of *N*-methyl-4-nitrophthalimide (1) and an additional 50 mL of anhydrous Me_2SO. The resulting mixture, which immediately turned very dark, was heated at 65–70 °C for 2 h and then allowed to cool to 25 °C. The product was isolated by (a) adding the entire reaction mixture to 3800 mL of 1 N HCl and stirring, (b) decanting the aqueous phase, (c) dissolving the semisolid in 1500 mL of benzene, (d) extracting thoroughly with water, (e) drying over $MgSO_4$, (f) evaporating the solvent, and (g) recrystallizing from ethanol. In this way, there was obtained 143.3 g (92%) of 3 as an off-white solid: mp 100.2–101.2 °C; ^1H NMR ($CDCl_3$) δ 2.37 (s, 3, aromatic methyl), 3.10 (s, 3, *N*-methyl), 6.87–7.90 (m, 7, aryl protons). The ^{13}C NMR spectrum in Me_2SO-d_6 was also in complete accord with the proposed structure [carbon atom from 3, observed shift in ppm (calculated[5] shift) given]: 1, 125.3 (124.7); 2 and 13, 134.4 and 134.7 (134.1 and 134.3); 3, 110.6 (110.4); 4, 163.0 (161.7); 5, 121.8 (121.7); 6, 125.1 (125.0); 7 and 8, 167.1 and 167.3 (167.6); 9, 23.7 (23.3); 10, 152.3 (152.2); 11, 120.2 (119.7); 12, 130.9 (130.5); 14, 20.4 (19.9).



3

Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.9; H, 4.9; N, 5.2. Found: C, 72.3; H, 5.1; N, 5.3.

Preparation of the Mixture of *N*-Methyl-4- and -5-(4-methylphenoxy)phthalamic Acids (4a and 4b). To a solution of 2.0 g (0.0075 mol) of 3 in 25 mL of DMF was added 3.5 g of 50% aqueous NaOH. The system was stirred at ~25 °C for 2 h and then poured into 500 mL of 1 N HCl. The resulting white solid precipitate, after 15 min of stirring, was filtered, washed thoroughly with water, and dried with suction. The yield was 1.80 g (83%) of the mixture of **4a** and **4b**: ^1H NMR (Me_2SO-d_6) δ 2.32 (s, 3, aromatic methyl), 2.68 (d,[6] *J* = 4.6 Hz, $NHCH_3$ of minor isomer), 2.73 (d,[6] *J* = 4.6 Hz, $NHCH_3$ of major isomer, total

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[5] Calculated values were obtained for carbons 1–6 by imposing the ^{13}C NMR aromatic substituent effects of a phenoxy group (C-X: +27.9, ortho: −12.1, meta: +2.5, para: −6.9 ppm) on the known shifts of *N*-methylphthalimide (in Me_2SO-d_6); for carbons 7–9, the known values of corresponding carbons of *N*-methylphthalimide were applied; for carbons 10–14, known values of corresponding carbons of *N*-phenyl-4-(4-methylphenoxy)phthalimide[1d] were used.

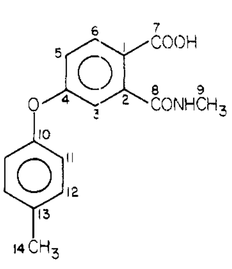
[6] In this strongly hydrogen-bonding medium [see M. T. Tribble and J. G. Traynham, *J. Am. Chem. Soc.*, 91, 379 (1969)], NH exchange was slowed sufficiently to allow coupling with the $-NH-CH_3$ methyl protons to be observed.

Table I. Product Distribution vs. Time in the Reaction of 1 and 2 with K_2CO_3 in Me_2SO at 142 °C

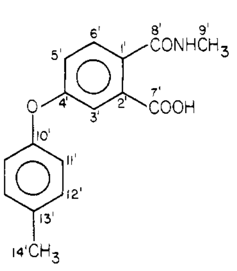
reaction time, h	yield, g	mol % (^{1}H NMR)			actual yield,[a] mol			extent of nitro displacement, %
		3	4	5	3	4	5	
0.25	1.14	73	27	0	0.0034	0.0024	0[b]	58[c]
0.50	1.41	64	36	0	0.0036	0.0032	0[b]	68[c]
1.0	1.73	62	38	0	0.0043	0.0036	0[b]	79[c]
2.0	1.96	67	33	0	0.0052	0.0036	0[b]	88[c]
3.5	2.01	68	32	0	0.0054	0.0036	0[b]	90[c]
7.0	2.14	58	39	3	0.0049	0.0043	0.0014	106[d]
24.0	2.00	33	58	9	0.0028	0.0055	0.0018	101[d]

[a] Obtained by converting mol % to weight %, to isolated weight, to actual weight (taking workup losses into account), to actual moles of each component. Losses observed in identical workups of 30-mL Me_2SO solutions of 0.0100 mol of each material were as follows: imide 3, 0.10 g; amide acids (4a + 4b), 0.37 g and 0.35 g (two separate runs, average 0.36 g); diacid 5, 0.32 g. [b] These actual values were left the same as the isolated values. Without any isolated amount, it is not possible to tell how much might have been lost on workup. [c] These are minimum values since some diacid 5 could have been present and lost during workup. [d] Complete reaction, within experimental error.

NCH_3 integral = 3), 6.80–7.95 (m, 7, aryl protons), 8.15 (br, 1, NH of both isomers). The ^{13}C NMR spectrum (Me_2SO-d_6) was in complete agreement with the mixture (26:74[7,8] mole ratio) of **4a** and **4b** [carbon atom in **4a** and **4b**, observed shift in ppm (calculated[9] shift) given]: 1, 124.0 (120.7); 2, 141.4 (142.3); 3, 115.8 (115.5); 4, 160.0 (163.1); 5, 117.0 (116.3); 6, 132.0 (131.3); 7, 166.9; 8, 168.6; 9 and 9′, 26.1 (26.1); 10, 152.6 (152.5); 11 and 11′, 119.7 (120.0); 12 and 12′, 130.7 (130.7); 13, 134.1 (134.2); 14 and 14′, 20.3 (20.3); 1′ and 2′, 132.5 and 133.3 (130.1 and 132.9); 3′, 117.4 (116.7); 4′, 158.0 (156.3); 5′, 120.0 (123.1); 6′, 129.6 (130.1); 7′, 167.6; 8′, 168.3; 10′, 153.1 (152.5); 13′, 133.7 (134.2).



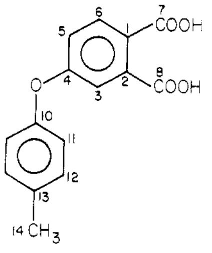
4a



4b

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.4; H, 5.3; N, 4.9. Found: C, 67.8; H, 5.2; N, 4.7.

Preparation of 4-(4-Methylphenoxy)phthalic Acid (5). A 5.00-g sample (0.0186 mol) of **3** was stirred and heated with 50 mL of ethylene glycol and 10 mL of 25% aqueous NaOH. By the time the solution temperature had reached 85 °C, the system was homogeneous. It was heated at reflux (134 °C in the solution) for 18 h. A sample of the product was obtained by adding some of the resulting slurry to 1 N HCl at ~25 °C, filtering it, and drying it in vacuo at 60 °C. The product **5** was homogeneous by vapor-phase chromatography (SE-30 column), giving a peak having the same retention time as the corresponding anhydride,[1c,13] and its ^{13}C NMR (Me_2SO-d_6) spectrum was identical with that of an authentic sample of **5**[1c] (carbon atom from **5** and observed shift in ppm given): 1, 125.5; 2, 136.5; 3, 116.0; 4, 159.9; 5, 118.3; 6, 131.3; 7 and 8, 167.5 and 168.6; 10, 152.6; 11, 120.0; 12, 130.7; 13, 134.2; 14, 20.3.



5

Concurrent Reaction of N-Methyl-4-nitrophthalimide (1) with 4-Methylphenol (2) and Potassium Carbonate in Me_2SO Solution. To a solution of 2.06 g (0.01 mol) of **1** and 1.08 g (0.01 mol) of **2** in 30 mL of Me_2SO at ca. 25 °C under nitrogen was added 6.90 g (0.05 mol) of K_2CO_3. The resulting suspension was stirred and heated in an oil bath for 7 h and 5 min; the internal reaction temperature was 142 °C *after* the initial 5 min of heat-up time. Gas evolution was noted especially during the early part of the heating period.

After this heating period, the reaction mixture was allowed to cool to 25 °C and was then added during ca. 5 min to 300 mL of 3 N HCl, stirred for 15 min at 25 °C, and filtered. The collected solid was washed with three 200-mL portions of 1 N HCl and air-dried overnight with suction on the filter.

The isolated product weighed 2.14 g. The ^{1}H NMR (Me_2SO-d_6) spectral analysis of the methyl-proton region was in agreement with a mixture of 58 mol % **3** (δ 2.99, s, NCH_3), 39 mol % **4a** + **4b** (2.68, d,[6] $NHCH_3$ of one isomer; 2.73, d,[6] $NHCH_3$ of the other isomer), and 3 mol % **5** (determined by the difference between the total integral for the NCH_3 of **3**, **4a**, and **4b** and the aromatic CH_3 peak at δ 2.30 common to all of the molecules, **3**, **4a**, **4b**, and **5**).

Similarly, analysis by ^{13}C NMR (Me_2SO-d_6) indicated that the mixture contained 62 mol % **3**, 35 mol % **4a** + **4b**, and 3 mol % **5**. These values were determined from the relative heights[8] of distinct peaks of protonated carbons in the phthalic rings of these compounds as follows (compound, ring position, chemical shift, and peak height given): **3**, C-3, 110.7 ppm, 56.0 mm; **4a**, C-3, 115.9 ppm, 13.0 mm, and C-5, 117.0 ppm, 13.5 mm (average: 13.3 mm); **4b**, C-3, 117.5 ppm, 18.0 mm; **5**, C-3, 116.4 ppm, 1.5 mm, and C-5, 118.4 ppm, 4.0 mm (average: 2.8 mm). In addition to these peaks, those for all of the other carbons of **3**, **4a**, and **4b** were clearly discernible in the ^{13}C NMR spectrum; three others for carbons

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(7) The isomer ratio was determined from the ^{13}C NMR spectrum by comparing the average of the observed peak heights (23, 24, and 23 mm) for the three protonated carbons of the phthalic ring of the minor isomer **4a** with those of the same carbons of the major isomer **4b** (66, 76, and 61 mm). As in this case, peak intensity patterns are often very helpful in assigning ^{13}C NMR peaks to specific structures in solutions containing mixtures.

(8) The ratio is probably accurate to ±10% since (a) relative peak heights are semiquantitatively related to peak areas and (b) the T_1's of all of the carbons involved are probably very short relative to the 2.0-s pulse delay used in obtaining the spectrum.

(9) Calculated values either were known values for the corresponding carbons of structurally related molecules or were calculated using substituent parameters:[10] for carbons 7, 7′, 8, and 8′ (structures **4a** and **4b**), carbons of the corresponding N-phenylamide acids[11] were used; for carbons 10–14 and 10′–14′ (Figure 7, Supplementary Material), carbons of 4-(4-methylphenoxy)phthalic acid[1c] were used; for 9 and 9′, the N-methyl carbon of N-methylphthalimic acid[11] was used; for the determination of the substituent parameters for the 4-methylphenoxy group and the methods used to obtain calculated values for carbons 1–6 and 1′–6′, see the section on shift calculations.[12]

(10) G. L. Nelson, G. C. Levy, and J. D. Cargioli, *J. Am. Chem. Soc.*, **94**, 3089 (1972).

(11) H. M. Relles, unpublished results.

(12) See paragraph at the end of the paper concerning the availability of supplementary data.

(13) This is identical with the VPC behavior previously found for the same material produced by hydrolysis of the N-phenylimide.[1c]

Table II. Product Distribution Using 15% Excess 1 in the Reaction with 2 and K_2CO_3 in Me_2SO at 142 °C

time sample taken, h	moles isolated[a]			moles calculated[b]	
	1[c]	2[d]	3[e]	(4a + 4b + 5)	(6a + 6b)[f]
0	0.0230	0.0200			
0.25	0.0050	0.0065	0.0114	0.0021	0.0045
0.5	0.0009	0.0041	0.0136	0.0023	0.0062
0.75	0.0004	0.0027	0.0133	0.0040	0.0053
1	0.0002	0.0016	0.0129	0.0055	0.0044
2	0.0001	0.0005	0.0122	0.0073	0.0034
3.5	0	0	0.0110	0.0090	0.0030
6.5	0	0	0.0095	0.0105	0.0030
20	0	0	0.0070	0.0130	0.0030

[a] By comparison to methyl integral of 2,2-diphenylpropane at δ 1.56. With this isolation procedure, the workup losses of 1, 2, and 3 were very minor and were ignored. [b] (4a + 4b + 5) = 0.0200 - 2 - 3; (6a + 6b) = 0.0230 - 1 - 3 - (4a + 4b + 5). [c] Determined using the integral for the NCH_3 peak at δ 3.13. [d] Determined using the integral for the aryl-CH_3 peak at δ 2.15. [e] Duplicate determinations by using the integral for the aryl-CH_3 peak at δ 2.28 and for the NCH_3 peak at δ 3.01. [f] Might also include a small amount of potassium nitrophthalate.

of the diacid **5** (136.4, 159.8, and 168.5 ppm) were also clearly observed.

This reaction was repeated several times in exactly the same manner with exactly the same isolation technique except that the total time of heating at 142 °C (after the 5 min of heat-up time in each case) ranged between 0.25 and 24 h for the different runs. Each product mixture was analyzed as above by ^1H NMR spectroscopy. The yields obtained and the results of the NMR analyses are given in Table I. The actual yields were calculated by taking the losses incurred in the workup procedure into account. These were determined independently in control experiments (vide infra).

Further Structure Proof. A 5.0-g mixture of **3**, **4a**, **4b**, and **5** was hydrolyzed with excess aqueous NaOH and then worked up with aqueous HCl. The isolated product (4.0 g) was shown by ^{13}C NMR (Me_2SO-d_6) spectroscopy to be pure **5**. The chemical shifts (compare to values reported above) were as follows: 125.4, 136.5, 116.0, 159.8, 118.3, 131.3, 167.5, 168.6, 152.5, 120.0, 130.7, 134.2, and 20.3 ppm.

Reaction of *N*-Methyl-4-nitrophthalimide (1) with 4-Methylphenol (2) and 1.2 Equiv of K_2CO_3 in Me_2SO Solution. A. 15% Excess 1. To a solution of exactly 2.16 g (0.02 mol) of **2**, 4.74 g (0.023 mol) of **1**, and 1.96 g (0.01 mol) of 2,2-diphenylpropane (internal ^1H NMR standard) in 30 mL of Me_2SO under N_2 was added 3.32 g (0.024 mol) of K_2CO_3. This suspension was heated at 142 °C (5 min allowed for warm-up before timing began). At various times, 2-mL samples of the slurry were removed and each was diluted with 6-mL portions of CH_2Cl_2. Each was extracted twice with 6 mL of 5% $NaHCO_3$ (to remove all amide acids, nitrite, and some Me_2SO) and twice with 6 mL of 1 N HCl (to remove the rest of the Me_2SO), then dried with $MgSO_4$, filtered, and concentrated to ca. 2 mL under a nitrogen stream. These solutions were then analyzed by ^1H NMR spectroscopy. The molar amounts of **1**, **2**, and **3** were determined directly by comparing the integrals of the appropriate methyl groups to that of the internal standard. Furthermore, since the total moles of bicarbonate extractables **4a** + **4b** + **5** was equivalent to the moles of 4-methylphenoxy groups not accounted for and the number of moles of **1** and **3** was known, the molar amounts of **6a** + **6b** could also be calculated. The results are listed in Table II. .

B. Molecular Sieves and 15% Excess 1. This experiment was conducted exactly the same as in A except that 10.0 g of 4-Å molecular sieves (dried in vacuo at 150 °C) were added to the reaction mixture just before the K_2CO_3. The ^1H NMR results are listed in Table III.

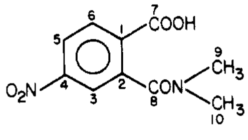
Preparation of the Mixture of *N*,*N*-Dimethyl-4- and -5-nitrophthalamic Acids 9a and 9b. A solution of 24.9 g (0.129 mol) of distilled 4-nitrophthalic anhydride in 200 mL of dry THF was added dropwise during 45 min to a solution of 5.8 g (0.129 mol) of dimethylamine in 100 mL of THF in a 500-mL round-bottomed flask. A slight exotherm (to ca. 45 °C) was observed.

Table III. Product Distribution Using Molecular Sieves and 15% Excess 1 in the Reaction with 2 and K_2CO_3 in Me_2SO at 142 °C

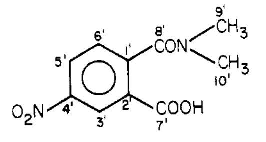
time sample taken, h	moles isolated[a]			moles calculated[b]	
	1[c]	2[d]	3[e]	(4a + 4b + 5)	(6a + 6b)[f]
0	0.0230	0.0200			
0.5	0.0011	0.0014	0.0173	0.0013	0.0033
1	0.0005	0.0003	0.0182	0.0015	0.0028
3	0.0002	0	0.0173	0.0027	0.0028
6	0	0	0.0171	0.0029	0.0030
9	0	0	0.0163	0.0037	0.0030
25	0	0	0.0155	0.0045	0.0030

[a-f] See corresponding footnotes in Table II.

After stirring at 25 °C for an additional 30 min, the solvent was removed in vacuo on a rotary evaporator until the residue weighed 37 g (~6 g of the THF left). Then 150 mL of benzene was added and the system was heated at boiling until 15 mL of solvent had distilled off. Turbidity increased during this distillation (presumably most of the THF had now been removed). The system was then cooled to 25 °C with stirring. After 2 h, the crude crystalline product was filtered, washed with benzene, and dried in vacuo at 50 °C. The isolated material (21.8 g) contained an impurity (possibly hydrogen-bonded dimethylamine) by ^1H NMR. It was triturated with 300 mL of CH_2Cl_2, filtered, and dried in vacuo. This removed the impurity and gave 17.2 g of the mixture of **9a** and **9b**: ^1H NMR (Me_2SO-d_6) δ 2.70 and 2.98, nonequivalent methyls of $(CH_3)_2N$ for major isomer, 2.73 and 2.98, nonequivalent methyls of $(CH_3)_2N$ for minor isomer, total integral = 6.0; 7.40–8.90, aryl multiplet + carboxylic acid protons of both isomers, total integral = 4.9 (includes some HDO in this Me_2SO-d_6 solution). The ^{13}C NMR spectrum (Me_2SO-d_6) was in complete agreement with a 33:67 mixture of **9a** and **9b** [carbon atom from **9a** and **9b**, chemical shift (observed shifts for corresponding carbons of **6a** and **6b** for carbons 1–7 and 1′–7′; known[11] shifts for corresponding carbons of *N*,*N*-dimethylbenzamide for carbons 8–10 and 8′–10′) given]: 1, 134.4 (137.8); 2, 140.3 (139.0); 3, 121.9 (122.8); 4, 149.6 (148.5); 5, 123.7 (124.6); 6, 132.0 (130.9); 7, 165.9 (167); 8, 168.1 (170.1); 9 and 10, 34.5 and 38.2 (34.5 and 38.6); 1′, 144.9 (144.4); 2′, 130.1 (132.2); 3′, 125.1 (124.2); 4′, 147.3 (147.7); 5′, 127.4 (126.4); 6′, 128.9 (129.8); 7′, 165.4 (167); 8′, 168.5 (170.1); 9′ and 10′, 34.4 and 38.0 (34.5 and 38.6). IR (KBr) 1715 cm^{-1}, acid carbonyl; 1608, amide carbonyl; 1528 and 1352, nitro group. Anal. Calcd for $C_{10}H_{10}N_2O_5$: C, 50.4; H, 4.2; N, 11.8. Found: C, 50.5; H, 4.2; N, 11.8.

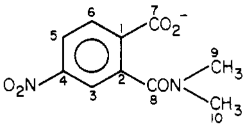


9a

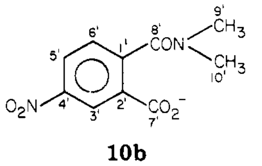


9b

Preparation and ^{13}C NMR Spectra of the Mixture of Potassium Salts of 9a and 9b. A solution of 1.19 g (0.005 mol) of the mixture of **9a** and **9b** (prepared above) in 15 mL of Me_2SO was stirred with 3.45 g (0.025 mol) of K_2CO_3 at 25 °C for 1 h until well after CO_2 evolution subsided. The supernatant was then analyzed by ^{13}C NMR spectroscopy which was in complete accord with the expected mixture of **10a** and **10b**; the observed mole ratio in this case was 24:76, respectively [carbon atom of structures **10a** and **10b**, observed chemical shift (predicted shift based on **8a**,



10a



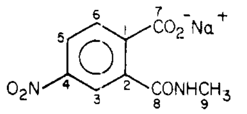
10b

8b, or *N,N*-dimethylbenzamide) given]: 1, 145.4 (145.7); 2, 138.5 (133.0); 3, 122.4 (124.2); 4, 146.9 (148.8); 5, 120.8 (123.9); 6, 130.8 (130.0); 7, 170.5 (170.4); 8, 166.7 (166.5); 9 and 10, 34.2 and 37.9 (34.5 and 38.6); 1′, 143.9 (143.3); 2′, 140.6 (139.6); 3′, 123.2 (121.6); 4′, 146.7 (147.5); 5′, 124.4 (123.6); 6′, 127.3 (129.6); 7′, 171.1 (169); 8′, 165.9 (168); 9′ and 10′, 34.2 and 37.9 (34.5 and 38.6).

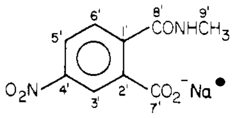
(Assignments for C-3 and C-5 might be switched; also those of C-3′ and C-5′ might be switched.)

Attempted Reaction of the Mixture of 10a and 10b with 2 and K_2CO_3 in Me_2SO. Exactly 1.19 g (0.005 mol) of the mixture of **9a** and **9b** (isolated above) and 0.54 g (0.005 mol) of **2** in 15 mL of Me_2SO were stirred with 3.45 g (0.025 mol) of K_2CO_3 at 25 °C for 10 min (CO_2 gas evolution) and then at 142 °C for 3.5 h under N_2. Analysis of the resulting supernatant solution indicated that only **10a**, **10b**, and **2** were present. No detectable nitro displacement had occurred. For **2**, the ^{13}C chemical shifts were 20.16, 115.2, 126.8, 129.6, and 155.5, all identical with those for authentic **2**;[11] for **10a**: 145.3, 138.6, 122.5, 147.1, 120.9, 130.8, 170.4, 166.1, 34.2, 37.9; for **10b**: 144.0, 140.2, 123.4, 146.8, 124.4, 127.4, 171.0, 166.1, 34.2, 37.9. The mole ratio determined for **10a**:**10b** in this spectrum was 26:74.

Preparation of the Mixture of Sodium Salts of 6a and 6b. A mixture of 20.62 g (0.100 mol) of **1**, 12 mL of H_2O, and 7.90 g of 50.62% NaOH (0.100 mol of NaOH) was stirred and heated at 45–50 °C for 40 min. (The system had become homogeneous after ca. 10 min.) Complete water removal (as determined by ^1H NMR) in vacuo at ca. 80 °C gave 24.3 g (99%) of **8a**(Na^+) + **8b**(Na^+) as a yellow powder. Structural confirmation was obtained by ^{13}C NMR (Me_2SO-d_6) spectroscopy [carbon atom (**8a** and **8b**), chemical shift given]: 1, 146.3; 2, 135.1; 3, 124.2; 4, 147.5; 5, 123.3; 6, 130.2; 7, 171.4; 8, 168.1; 9 and 9′, 26.5; 1′, 141.9; 2′, 141.2; 3′, 122.8; 4′, 147.1; 5′, 124.2; 6′, 129.4; 7′, 169.9; 8′, 169.8; mole ratio of **8a**(Na^+):**8b**(Na^+) 61:39.



8a



8b

Reaction of 8a(Na^+) + 8b(Na^+) with 2 in Me_2SO. A mixture of 2.46 g (0.0100 mol) of **8a**(Na^+) + **8b**(Na^+) from above and 1.08 g (0.0100 mol) of **2** in 30 mL of Me_2SO (*no K_2CO_3*) was heated at 142 °C under N_2 for 3.5 h. **2** and **3** in the mole ratio of 20:80 were readily observed by ^{13}C NMR spectroscopy of the reaction mixture, as was a small amount of **8**. High-pressure LC analysis of a sample of the reaction mixture indicated that **1**, **2**, **3**, and **8** were present in the ratio of 2.1:14.1:85.8:7.2, respectively. A minor impurity (ratio 0.7) of 4,4′-oxybis(*N*-methylphthalimide] was also detected. The high-pressure LC parameters (retention time in seconds, $\epsilon^{254}/\epsilon^{280}$, and the area to moles conversion factors) were as follows: **1**: 266, 5.78, 2.50; **2**: 232, 0.12, 4.41; **3**: 534, 5.26, 2.27; **8**: 82, 1.0, 0.88; the bisimide impurity: 391, 6.32, 1.52.

Registry No. **1**, 41663-84-7; **2**, 106-44-5; **3**, 72709-41-2; **4a**, 72709-42-3; **4a**, potassium salt, 72709-43-4; **4b**, 72709-44-5; **4b**, potassium salt, 72709-45-6; **5**, 63196-15-6; **5**, dipotassium salt, 72709-46-7; **6a**, 72709-47-8; **6a**, sodium salt, 72709-48-9; **6b**, 72709-49-0; **6b**, sodium salt, 72709-50-3; **8a**, 72709-51-4; **8b**, 72709-52-5; **9a**, 72709-53-6; **9a**, potassium salt, 72709-54-7; **9b**, 72709-55-8; **9b**, potassium salt, 72709-56-9; **11**, 63196-09-8; **12**, 63196-28-1; **13**, 72709-57-0; 2-methyl-1*H*-isoindole-1,3(2*H*)-dione, 550-44-7; 1,2-benzenedicarboxylic acid, 88-99-3; 1,3-isobenzofurandione, 85-44-9; 2-phenyl-1*H*-isoindole-1,3(2*H*)-dione, 520-03-6; sodium 4-methylphenoxide, 106-44-5; 4-nitrophthalic anhydride, 5466-84-2; dimethylamine, 124-40-3.

Supplementary Material Available: A substantial amount of the Experimental Section, methods used for calculating chemical shifts, the method used to calculate the ^{13}C NMR substituent effects of a 4-methylphenoxy group, and accompanying tables of data (25 pages). Ordering information is given on any current masthead page.

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(15) The low yield and low relative proportion of **6b** suggest that this isomer was preferentially lost in the workup procedure used.

Use of Liquid-Crystal-Induced Circular Dichroism for Determination of Absolute Configuration of Alcohols and Oxaziridines

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Addition of small amounts of chiral dopants to the achiral nematic liquid crystal, *N*-*p*-methoxybenzylidene-*p*′-*n*-butylaniline (MBBA), gives rise to liquid-crystal-induced circular dichroism (LCICD). For a variety of secondary alcohol dopants, it is shown that the sign of the LCICD band can be correlated with the absolute configuration of the dopant. The reasons underlying this phenomenon are discussed and the technique is extended to assign absolute configurations to two optically active oxaziridines.

Introduction

Recent studies of liquid crystals have provided the basis for an interesting and potentially useful technique for assigning absolute configuration.[1-5] This technique, liquid-crystal-induced circular dichroism (LCICD),[1] is extremely sensitive and can be considered as a method of chirality amplification.

Achiral molecules exhibit chiroptic behavior during association with a chiral medium.[1] Conversely, an achiral medium can assume chiroptic properties upon addition of a chiral substance.[2,4,5] For example, addition of a small amount of a chiral dopant to an achiral nematic liquid crystal such as *N*-*p*-methoxybenzylidene-*p*′-*n*-butylaniline (MBBA) causes the latter to become cholesteric and to show strong CD activity for the MBBA chromophore. The sign of the CD band depends upon the helical sense of the mesophase and is independent of the presence or absence of chromophores in the chiral dopant. This technique has been proposed as a basis for determining the absolute configuration of the chiral dopant[4] and is especially at-

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