Base-Catalyzed Condensations of *o*-Phthalaldehyde with Primary Amides. Synthesis and Characterization of Some Isoindoline and Phthalan Derivatives

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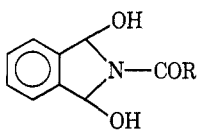
Aliphatic primary amides [$RCONH_2$ (R = H, CH_3, C_2H_5, n-C_3H_7, CH_3OCH_2, or CH_3NH)] react with *o*-phthaladehyde in aqueous sodium hydroxide at room temperature to yield *N*-acyl-1,3-dihydroxyisoindolines (**1a–f**). Under the same reaction conditions, primary amides of structure $ArCONH_2$ (Ar = C_6H_5, p-ClC_6H_4, or p-$CH_3OC_6H_4$) and trimethylacetamide give 1-hydroxy-3-amidylphthalans (**2b–e**). The method employing ethanolic sodium ethoxide previously used for preparation of **1b** was found to be applicable to synthesis of **1c** and **1d**. Its use with benzamide resulted in formation of 1-ethoxy-3-benzamidylphthalan (**2a**). Production of phthalans rather than isoindolines is considered to be primarily the result of steric factors. All products were characterized physically *via* ir and nmr spectra. Chemical characterization included an examination of hydrolytic and oxidative behavior.

In a previous paper[1] we reported the preparation of *N*-acetyl-1,3-dihydroxyisoindoline (**1b**) from *o*-phthalaldehyde and acetamide in the presence of ethanolic sodium ethoxide. Reactions of this type, in which the same atom of an attacking nucleophile reacts with both formyl groups of *o*-phthalaldehyde, are still relatively rare, and further investigation of base-catalyzed condensations of *o*-phthalaldehyde with amides seemed warranted.

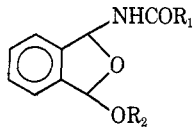


1a, R = H
b, R = CH_3
c, R = C_2H_5
d, R = n-C_3H_7
e, R = CH_3OCH_2
f, R = CH_3NH

The previously reported method was successfully applied to synthesis of *N*-*n*-propionyl- and *N*-*n*-butyryl-1,3-dihydroxyisoindolines (**1c** and **1d**); however, yields were only fair (averaging 50%). More satisfactory results were obtained when aqueous suspensions of appropriate amides and *o*-phthalaldehyde were treated with aqueous sodium hydroxide and stirred for a few hours at room temperature. Slow dissolution of reactants was followed by gradual precipitation of products in nearly pure form and in high yield.

Use of the sodium ethoxide–ethanol system in condensation of benzamide with *o*-phthalaldehyde resulted in formation of 1-ethoxy-3-benzamidylphthalan (**2a**). The yields (averaging 50%) and the difficulty experienced in product isolation led us to abandon this system in favor of aqueous sodium hydroxide. Again reactions proceeded smoothly; the products isolated were the phthalan derivatives, **2b–e**.

Structural assignments for all compounds of structures **1** and **2** were based on spectral evidence as well as chemical reactivity. Solid state infrared spectra of all compounds were consistent with structural assignments (see Experimental Section). The only significant differences in the spectra **1** and **2** were in the NH and OH stretching regions. Since bonded OH absorption bands are often quite broad and the NH bands in **2c–e** appeared as shoulders, the infrared spectra must be considered as supporting evidence only.[2]



2a, $R_1 = C_6H_5$; $R_2 = C_2H_5$
b, $R_1 = C_6H_5$; $R_2 = H$
c, $R_1 = p$-ClC_6H_4; $R_2 = H$
d, $R_1 = p$-$CH_3OC_6H_4$; $R_2 = H$
e, $R_1 = (CH_3)_3C$; $R_2 = H$

Nuclear magnetic resonance spectra (Table I) provided strong support for both the isoindoline and phthalan structures. All compounds showed similar absorption behavior in the **CHOH** region; relative areas of these sets of signals corresponded to four protons in the isoindoline series and to two protons in the phthalan derivatives. In the aromatic region all of the isoindoline derivatives showed a four proton singlet, normal for benzene derivatives bearing identical ortho substituents which do not interact strongly with the ring.[3] More complexity would, of course, be expected for aromatic proton absorption in **2a–d**, but even **2e** shows complex multiplicity in this area.

Chemical shifts and multiplicities of signals for all other protons of general structure, **1**, were normal with one exception. The methylene protons of **1e** absorbed as two broad singlets suggesting that the singlets were really doublets. This apparent anomaly might be explained by postulating intramolecular hydrogen bonding between the ether oxygen and hydrogen of either OH group resulting in rigidity of the methylene group and consequent magnetic nonequivalence of the two protons.

In compounds of the general structure **2**, signals for **NH** and **CHN** were quite distinct, and coupling constants could be measured in most cases. It is of interest to note that the **CHN** signal for **2a** is split not only by the neighboring **NH** but also by the proton on C-1.

Chemically, all the isoindolines behaved in a manner analogous to that previously reported for **1b**.[1] Base-

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(1) R. D. Reynolds and R. J. Conboy, *J. Org. Chem.*, **30**, 2251 (1965).

(2) Definite assignments for the amide II bonds of **2** could not be made because of the complexity of the spectra.

(3) J. Martin and B. P. Daily, *J. Chem. Phys.*, **37**, 2594 (1962).

TABLE I

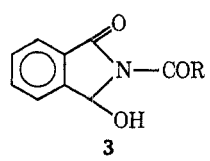
NMR SPECTRA OF N-ACYL-1,3-DIHYDROXYISOINDOLINES AND 1-HYDROXY- (OR -ETHOXY-) 3-AMIDYLPHTHALANS[a]

Compd	ArH	CHOH[b]	CHN	NH	Other
1a	2.54, s	3.63, q			CHO, 1.35, s
1b	2.47, s	3.72, m			CH_3, 7.78, s
1c	2.57, s	3.74, m			CH_3, 8.93, t (7) CH_2, 2.5, q[c]
1d	2.58, s	3.80, m			$CH_3CH_2CH_2$, 0.8–3.0, m
1e	2.54, s	3.60, q			CH_3, 6.62, s CH_2, 5.67, s 6.10, s
1f	2.60, s	3.90, m		~3.9[d]	CH_3, d (7)
2a	2.50, m 2.05, m	3.65, d (2)[e]	2.90, 2 d's (2) (9)	0.72, d (9)	CH_3, 8.84, t (7) CH_2, 6.32, q (7)
2b	2.53, m 2.05, m	3.47, q[f]	2.92, d (9)[f]	0.89, d (9)[f]	
2c	2.53, s[g] 2.47[i] 2.05[i]	3.63, q	3.05, q[h]	2.27, q[h]	
2d	2.98, d (9) 2.05, d (9) 2.52, s	3.65, q	3.11, d (7)[j]	1.13, d (7)	OCH_3, 6.17, s
2e	2.60, m	...[k]	...[k]	2.09, d (9)[l] 1.82, d (9)	CH_3, 8.88, s

[a] Chemical shifts are given in τ from TMS in DMSO-d_6; relative areas all were as expected; when possible, J values (hertz) are given in parentheses. [b] Because the quartets expected were badly deformed in some cases and showed further multiplicity in others, specific assignments for CH and OH were not made. [c] Superimposed on residual DMSO absorption. [d] Superimposed on CHOH absorption. [e] CHOC; coupling is with CHN as noted. [f] Multiplicity nearly collapses upon heating to 80°. [g] Relative area of highest field peak = 4; sum of relative areas of lower field peaks = 4. [h] Probably two doublets with J = 9 Hz. [i] Signals for protons of para-substituted ring; consisted of 4 sets of 2 pairs, J = 9 and 2 Hz. The highest field pair is superimposed on the signal for the protons of the ortho-substituted ring. [j] Superimposed on upfield aromatic proton signal. [k] Splitting pattern was too complex to allow assignments. [l] Two doublets are possibly due to rotamers. Overall area = 1 proton.

catalyzed hydrolysis led to formation of α-hydroxy-o-toluic acid as expected. Acid-catalyzed hydrolysis was not particularly useful in structural assignments. Apparently, complex decomposition and recombination occur; this problem will be discussed in a later paper.

Oxidation to the corresponding N-acyl-3-hydroxyphthalimidines (3) and N-acylphthalimides (4) was possible in some cases. It was found that such oxidations



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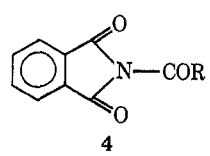

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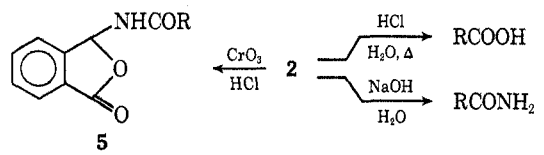
take place more cleanly and effectively with a chromic anhydride–hydrochloric or sulfuric acid system than with the previously used acid dichromate reagents.[1] It was possible, by the former method, to obtain from compounds **1b–d** and **1f** the corresponding oxidation products, **3b–d** and **3f** as well as **4b**, **4c**, and **4f**. All except **3b** and **4b** were previously unknown compounds and were identified from their typical infrared spectra, elemental analyses, and, in some cases, nmr spectra (see Experimental Section) Oxidation of **1a** and **1e** resulted in formation of phthalimide only under all conditions used.

Base-catalyzed hydrolysis of **2b–e** led to formation of the starting amides, $RCONH_2$; with **2a** no identified products were isolated. After acid-catalyzed hydrolysis at reflux, the corresponding carboxylic acids, RCOOH, were isolated. Oxidation with the chromic anhydride–hydrochloric acid system led to the corresponding phthalides (**5**) (Scheme I). These phthalides, previously unknown, were identified from their infrared

SCHEME I



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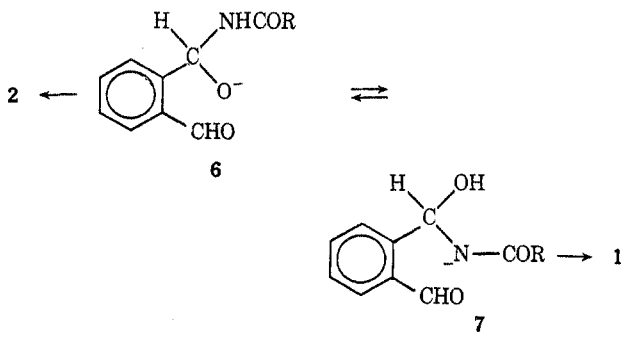
and nuclear magnetic resonance spectra and elemental analyses (See Experimental Section).

Conversion of **2b** to **2a** was easily effected. When an ethanolic solution of **2b** was acidified and allowed to stand overnight at room temperature, the product was **2a** in high yield.

It seems clear, then, that under the conditions used, condensations of o-phthalaldehyde with primary amides proceeded to yield two different product types. A reasonable first step in both reactions would involve attack by the anion of the amide on a carbonyl group of o-phthalaldehyde to yield the intermediate, **6**, which could well exist in equilibrium with **7** (Scheme II).

SCHEME II



6

7

Ring closures would result in the observed products. Normally one would expect the more stable intermediate, **7**, to predominate; hence, **2** should form only if formation or ring closure of **7** were difficult.

Attempted explanations of the different courses of reaction based on resonance and/or inductive effects lead to predicted results which are the opposite of those observed. Therefore, it is postulated that product composition is controlled by steric factors. Fisher–Hirschfelder models of the intermediates, **6** and **7**, support this explanation. When R is any group sufficiently small or elongated, there is no steric interference with attack of either oxygen or nitrogen on the formyl group; hence, reaction proceeds through the more stable intermediate, **7**, and isoindolines are the products. However, when R is aromatic or the *tert*-butyl group, there is steric interference to attack by nitrogen. Oxygen attack appears not particularly hindered, and phthalans can then be formed in high yields.

The extreme experimental simplicity of the syntheses reported here renders production of these new compounds a very easy matter and invites further investigation.

Experimental Section[4]

Materials.—Amides and *o*-phthalaldehyde were purchased from Aldrich Chemical Co., Milwaukee, Wis., and purified by standard methods.

***N*-Acyl-1,3-dihydroxyisoindolines (1).**—*o*-Phthalaldehyde (3.0 g, 0.0224 mol) and the appropriate amide (0.0224 mol) were suspended in distilled water in an erlenmeyer flask. Maximal yields were obtained with various amides by varying the amounts of distilled water as follows: for syntheses of **1e**, 30 ml; **1a** and **1d**, 50 ml; **1b**, **1c**, and **1f**, 200 ml. Aqueous NaOH (5 ml, 2.5% by weight) was added dropwise over a period of 15 min to the magnetically stirred suspension. Dissolution of reactants took place during this period and was followed shortly by gradual precipitation of products. Total reaction times were varied from 1.25–30 hr with little effect on yields. Products were suction filtered and, except for **1a**, recrystallized from acetonitrile; water was used as recrystallizing solvent for **1a**. All compounds were obtained as white crystals.

Yields and melting points were obtained: **1a**, 70%, 164–165°; **1b**, 78%, 157–158°; **1c**, 65%, 176–177°; **1d**, 73%, 150–152°; **1e**, 80%, 114–116; **1f**, 78%, 178.5–180°. Ir (cm^{-1}): bonded OH, **1a** (3230), **1b** (3247), **1c** (3225), **1d** (3250), **1e**, (3300), **1f** (3370); amide I C=O, **1a** (1645), **1b** (1621), **1c** (1610), **1d** (1610), **1e** (1630), **1f** (1640); CH out-of-plane deformation, **1a** (752), **1b** (750), **1c** (750), **1d** (755), **1e** (760), **1f** (758).

Anal.[5] Calcd for $C_9H_9NO_3$ (**1a**): C, 60.28; H, 5.58; N, 7.82. Found: C, 60.28; H, 5.45; N, 7.73. Calcd for $C_{11}H_{13}NO_3$ (**1c**): C, 63.75; H, 6.32; N, 6.76. Found: C, 63.68; H, 6.26; N, 6.76. Calcd for $C_{12}H_{15}NO_3$ (**1d**): C, 65.10; H, 6.84; N, 6.33. Found: C, 64.92; H, 6.86; N, 6.26. Calcd for $C_{11}H_{13}NO_4$ (**1e**): C, 59.19; H, 5.83; N, 6.28. Found: C, 59.21; H, 5.90; N, 6.22. Calcd for $C_{10}H_{12}N_2O_3$ (**1f**): C, 57.64; H, 5.76; N, 13.45. Found: 57.72; H, 5.72; N, 13.39.

1-Hydroxy-3-amidylphthalans (2b–e).—The preparative procedure was identical with that used for preparation of the *N*-acyl-1,3-dihydroxyisoindolines. Best yields were obtained using the following amounts of distilled water: **2b**, **2c**, and **2e**, 200 ml; **2d**, 100 ml. Reactions to produce **2b–d** were allowed to proceed for 1.5 hr; that to produce **2e** was much slower and was carried on for 24 hr. Recrystallization was effected from acetonitrile; all compounds existed as white crystals.

Yields and melting points were obtained: **2b**, 69%, 135–136°; **2c**, 38%, 148–149°; **2d**, 74%, 139–140°; **2e**, 62%, 140–141°. Ir (cm^{-1}): bonded OH, **2b** (3400), **2c** (3300, sh), **2d** (3380, sh), **2e** (3405, sh); NH, **2b** (3245), **2c** (3280), **2d** (3300), **2e** (3375); amide I C=O, **2b** (1620), **2c** (1600), **2d** (1600), **2e** (1610); CH out-of-plane deformation, **2b** (758, 690–720, 3 peaks), **2c** (752, 845, **2d** (752, 840), **2e** (755).

Anal. Calcd for $C_{15}H_{13}NO_3$ (**2b**): C, 70.60; H, 5.13, N, 5.48. Found: C, 70.49; H, 5.12; N, 5.43. Calcd for $C_{16}H_{12}NO_3Cl$ (**2c**): C, 62.07; H, 4.13; N, 4.83; Cl, 12.24. Found: C, 62.27; H, 3.98; N, 4.74; Cl, 12.04. Calcd for $C_{16}H_{15}NO_4$ (**2d**): C, 67.35; H, 5.29; N, 4.90. Found: C, 67.35; H, 5.23; N, 4.94. Calcd for $C_{13}H_{17}NO_3$ (**2e**): C, 66.36; H, 7.28; N, 5.95. Found: 66.45; H, 7.30; N, 5.92.

1-Ethoxy-3-benzamidylphthalan (2a).—This compound was prepared using a modification of the method previously described for preparation of **1b**.[1] Reaction was carried out at reflux, and, after rotary evaporation of the reaction mixture, water was added to effect precipitation. Recrystallization from acetonitrile yielded **2a** in 53% yield: mp 189–190°; ir (cm^{-1}), 3280 (NH), 1620 (amide I C=O), 758, 700, 735 (CH out-of-plane deformation.)

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.08; H, 6.01; N, 4.95. Found: C, 72.12; H, 6.01; N, 4.99.

***N*-Acyl-3-hydroxyphthalimidines (3) and *N*-Acylphthalimides (4). Oxidation of *N*-Acyl-1,3-dihydroxyisoindolines. General Procedure.**—The isoindoline derivative, **1** (0.002 mol), was added to 5 ml of acetone contained in a 50-ml erlenmeyer flask. The oxidizing mixture (1.03 g, 0.01 mol of chromium trioxide, 3 ml of distilled water, and 0.9 mol of concentrated HCl) was added dropwise to the magnetically stirred acetone solution over a period of 1.5 hr. Stirring was allowed to proceed for another 0.5 hr after which 30 ml of distilled water was added. The mixture was filtered following another 0.5-hr stirring period. The residue was washed with distilled water and recrystallized. Yields of oxidized products ranged from 50–60%.

Oxidation of 1a and 1e.—The above procedure, as well as many modifications of that procedure (temperature variation: ice bath, room temperature, reflux; acid variation: HCl, H_2SO_4, HOAc; variation in molar quantities), led only to formation of phthalimide identified by comparison of its infrared spectrum with that of an authentic sample.

Oxidation of 1c.—Use of the general procedure at reflux led to phthalimide formation; at room temperature or under ice bath conditions, the half-oxidized product, **3c**, was formed. It was recrystallized from water: mp 144–145°; ir 3450 (OH), 1724 (imide C=O), 1666 (amide I C=O), 752 (CH out-of-plane deformation).

Anal. Calcd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.38; H, 5.37; N, 6.71.

The fully oxidized product was obtained when **1c** was treated as noted in the general procedure at room temperature except that concentrated H_2SO_4 was used instead of concentrated HCl. Recrystallization from ether yielded white crystals of **4c**: mp 129–132°; ir 1720 (imide C=O), 1650 (amide I C=O), 725 (CH out-of-plane deformation).

Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.30; H, 4.41; N, 6.70.

Oxidation of 1d.—Use of the general procedure under ice bath conditions resulted in formation of **3d**, white crystals from acetonitrile: mp 78–79°; ir 3440 (OH), 1724 (imide C=O), 1660 (amide I C=O), 752 (CH out-of-plane deformation); nmr (DMSO-d_6) τ 9.07 (t, 3, J = 9 Hz, CH_3), 7.1–8.7 (m's, 4, CH_2CH_2), 3.30 (q, 4, J = 7 Hz, CHOH), 2.20 (m, 4, ArH).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.68; H, 5.92; N, 6.38. Found: C, 65.82; H, 5.89; N, 6.43.

At room temperature and at reflux, only phthalimide was formed by oxidation of **1d**.

Oxidation of 1f.—Ice bath conditions and the general procedure followed by recrystallization from acetonitrile resulted in formation of **3f**: mp 182–183°; ir 3400 (OH), 3333 (NH), 1700 (imide C=O), 1670 (amide I C=O), 740–760 (3 strong peaks); nmr τ 7.18 (d, 3, J = 5 Hz, CH_3), 3.35 (q, 4, J = 7 Hz, CHOH), 2.31 (m, 4, ArH), 1.85 (broad absorption, 1, NH).

Anal. Calcd for $C_{10}H_{10}N_2O_3$: C, 58.19; H, 4.84; N, 13.57. Found: C, 58.27; H, 4.85; N, 13.63.

At room temperature, and with concentrated H_2SO_4 instead of concentrated HCl, **4f**, white crystals from acetonitrile, was formed: mp 185–186°; ir 3311 (NH), 1720 (imide C=O), 1666 (amide I C=O), 760 (CH out-of-plane deformation); nmr τ 7.18 (d, 3, J = 5 Hz, CH_3), 2.06 (s, 4, ArH), 1.75 (broad absorption, 1, NH).

(4) Melting points were taken on a Büchi melting point apparatus previously calibrated against standard substances. Infrared spectra were determined on a Beckman IR8 spectrophotometer in KBr pellets (0.5 mg sample/50 mg KBr). A Varian A60A spectrometer was used for nmr spectra. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(5) Analysis for **1b** and its oxidation products are in ref 1.

Anal. Calcd for $C_{10}H_8N_2O_3$: C, 58.76; H, 3.91; N, 13.71. Found: C, 58.84; H, 3.97; N, 13.59.

3-Amidylphthalides (5). Oxidation of 1-Hydroxy-3-amidylphthalans.—All oxidations were carried out using the procedure described above for oxidation of compounds of structure **1**. Ice bath conditions were employed. Products were recrystallized from acetonitrile. Yields ranged from 50–60%.

Oxidation of 2a and 2b.—The product in both cases was **5b**: mp 175–176°; ir (cm^{-1}) 3257 (NH), 1748 (phthalide C=O), 1626 (amide C=O), 755, 688, 745 (CH out-of-plane deformation); nmr (DMSO-d_6) τ 2.68 (d, 1, J = 9 Hz, CHN), 1.90–2.08 (2 m's, 9, ArH), 0.42 (d, 1, J = 9 Hz, NH).

Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.34; N, 5.53. Found: C, 71.02; H, 4.40; N, 5.58.

Oxidation of 2c.—The product, **5c**, had mp 162–163°; ir (cm^{-1}) 3250 (NH), 1755 (phthalide C=O), 1630 (amide I CO), 750, 840 (CH out-of-plane deformation); nmr (DMSO-d_6) τ 7.1–8.1 (m's, 9, ArH, CHN), 0.15 (d, 1, J = 9 Hz, NH).

Anal. Calcd for $C_{15}H_{10}NO_3Cl$: C, 62.50; H, 3.47; N, 4.86. Found: C, 62.25; H, 3.66; N, 4.81.

Oxidation of 2d.—Use of the general procedure with **2d** led to formation of **5d**, mp 180–182° from acetonitrile: ir (cm^{-1}) 3257 (NH), 1757 (phthalide C=O), 1630 (amide I C=O), 747 840, (CH out-of-plane deformation); nmr (DMSO-d_6) τ 6.16 (s, 3, OCH_3), 2.68 (d, 1, J = 10 Hz, CHN), 2.95 and 2.06 (2 d's, 4, J = 9 Hz, ArH on *para*-substituted ring), 2.50–2.00 (m, partially superimposed on down field ArH of para-substituted ring, 4, ArH in ortho-substituted ring), 0.48 (d, 1, J = 10 Hz, NH).

Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.59; N, 4.95. Found: C, 67.84; H, 4.59; N, 4.90.

Oxidation of 2e.—The product of this oxidation was **5e**: mp 179–180°; ir (cm^{-1}) 3256 (NH), 2959 (CH_3), 1754 (phthalide C=O), 1653 (amide I C=O), 745 (CH out-of-plane deformation); nmr (DMSO-d_6) τ 8.85 (s, 9, CH_3), 2.94 (d, 1, J = 9 Hz, CHN), 2.30 (m, 4, ArH), 1.25 (d, 1, J = 9 Hz, NH).

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 67.05; H, 6.40; N, 5.95.

Acid-Catalyzed Hydrolysis of 2.—Acid-catalyzed hydrolysis of the phthalans *via* the method described in ref 1 led to formation of benzoic acid from **2a** and **2b**, *p*-chlorobenzoic acid from **2c**, *p*-methoxybenzoic acid from **2d**, and trimethylacetic acid from **2e**. Products were identified *via* undepressed mixture melting points when applicable and ir spectra which were identical with those of authentic samples.

Base-Catalyzed Hydrolysis of 2.—The procedure used for base-catalyzed hydrolysis of the phthalans was that described in ref 1; however, all reactions except one were carried out at room temperature. Such reactions resulted in formation of benzamide from **2b**, *p*-chlorobenzamide from **2c**, *p*-methoxybenzamide from **2d**, and trimethylacetamide from **2e**. No identified products were isolated from base-catalyzed hydrolysis of **2a**.

All products isolated were identified by undepressed mixture melting points and infrared spectra which were identical with those of authentic samples.

Conversion of 2b to 2a.—Compound **2b** (0.51 g, 0.002 mol) was dissolved in 20 ml of absolute ethanol; 1 ml of 1 *M* HCl was added, and the mixture was allowed to stir overnight. Removal of solvent on the rotary evaporator and recrystallization from acetonitrile yielded 0.46 g (80%) of **2a** identical with that prepared by reaction of *o*-phthalaldehyde with benzamide in ethanolic sodium ethoxide.

Registry No.—**1a**, 26268-85-9; **1b**, 1968-04-3; **1c**, 26268-87-1; **1d**, 26268-88-2; **1e**, 26268-89-3; **1f**, 26268-90-6; **2a**, 26268-91-7; **2b**, 26322-33-8; **2c**, 26268-92-8; **2d**, 26268-93-9; **2e**, 26322-34-9; **3c**, 26268-94-0; **3d**, 26322-35-0; **3f**, 26322-36-1; **4c**, 26268-95-1; **4f**, 26268-96-2; **5b**, 26268-97-3; **5c**, 26322-37-2; **5d**, 26322-38-3; **5e**, 26268-98-4.

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Rate and Equilibrium in Carbanion Formation[1a] by Bis(methylsulfonyl)methane

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Bis(methylsulfonyl)methane has been found to have a pK_a of 12.54 in water at 25°. The rate constant for exchange of its methylene hydrogen atoms in deuterium oxide at 25° is (8 ± 2) × 10^{-4} sec^{-1} per hydrogen atom, and the Arrhenius activation energy is 8 ± 3 kcal/mol. Between one tenth and one half of the ion pairs formed by donation of a proton from the sulfone to water are estimated to recombine with exchange instead of dissociating.

A number of studies of the kinetics and stereochemistry of the formation of carbanions stabilized by α-sulfone substituents have been made.[2] Several of these studies provide evidence that the pyramidal form of the carbanion is not as unstable relative to the planar form as is the case for carbanions stabilized by α-carbonyl, α-aryl, and certain other substituents, and it is not even clear that the most stable form of α-sulfonyl carbanions is necessarily the planar one. According to the principle of least motion,[3,4] if α-sulfonyl carbanions are not preferentially planar or if the difference in stabilities between their planar and pyramidal forms is particularly small, then, other things being equal, they should be formed more rapidly than equally basic carbanions whose planar forms are much more stable than their pyramidal forms.

The data available in 1953 were sufficient to convince Pearson and Dillon that "sulfones are characterized by high rates of ionization for a given acid strength."[5] However, these data included only five observations on sulfones, and there was no sulfone for which both the rate and equilibrium constants for carbanion formation had been determined. We therefore decided to make such a determination, using bis (methylsulfonyl) methane, a sulfone for which both constants seemed likely to be measurable.

The pK_a of this bissulfone was found by potentio-

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