Reductive Metalation of 1,3-Diphenylisobenzofuran. Stereoselective Formation of Cis Products

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1,3-Diphenylisobenzofuran was reduced in tetrahydrofuran by alkali metals to a dianion. This dianion on protonation, methylation, or carboxylation gave products which were predominantly cis. It is suggested that the dianion or the intermediate monoreacted monoanion adopts a preferred conformation in which steric interaction between the phenyl substituents is minimized and orbital overlap between the carbanion and the benzene ring is maximized. By use of this stereoselectivity of the dianion, a series of 1,3-polymethylene-bridged 1,3-diphenylphthalans was prepared. The possibility of single electron transfer during the alkylation of the dianion was examined by alkylating the dianion with *tert*-butyl halides. Complex reaction mixtures were formed but extensive alkylation occurred and mono- and dialkylation products were characterized.

While numerous heterocyclic compounds have been subjected to reductive metalation,[1] isobenzofuran and its derivatives appear to have been neglected. Since isobenzofuran has a small energy gap between its highest occupied and lowest unoccupied molecular orbital,[2] it was of interest to examine the behavior of this nonalternate conjugated system toward alkali metals. The obvious choice of a specific compound was 1,3-diphenylisobenzofuran, **1**.

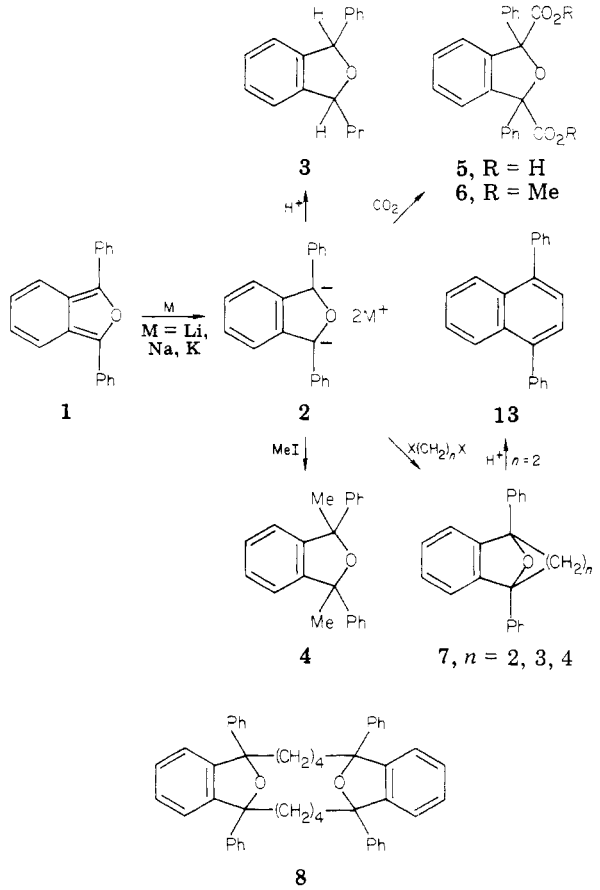
Experimentally, it was found that in tetrahydrofuran (THF) **1** reacted rapidly with lithium, sodium, or potassium to form a deep blue solution of dianion **2** (Scheme I). This solution was stable at least for 24-h periods since deuteration of the solution eliminated any evidence of benzhydrylic protons in the NMR of the reaction products.[3]

Protonation of **2** produced a product containing both isomers of 1,3-diphenylphthalan (**3**), since, in the NMR spectrum, benzhydrylic protons were observed at δ 6.45 and 6.23 in a ratio of 1:9, respectively. The major isomer isolated from this mixture was assigned the cis configuration because base-catalyzed isomerization of the reaction mixture increased the minor component at the expense of the major (from this reaction product the minor isomer was obtained). From steric considerations, the trans isomer would be expected to be the more thermodynamically stable isomer and thus the minor isomer was the trans isomer and the major isomer was the cis. Supporting this assignment was the observation that *cis*-**3** was the only isomer produced on hydrogenation of **1** (1,3-diphenyl-4,5,6,7-tetrahydroisobenzofuran was the other product).

This stereoselective perference for cis products was observed both in the methylation and the carboxylation of **2**. The reaction product from the methylation showed two methyl resonances in the NMR spectrum at δ 1.95 and 1.82 in the ratio of 4 to 1. The minor component was considered to be *trans*-**4** since in this isomer each methyl group would be expected to be shielded by the phenyl substituent opposing it across the tetrahydrofuran ring.

Isolation of the two isomers permitted comparison of their infrared spectra. The only appreciable difference in the infrared spectra of *cis*- and *trans*-**4** was the absorption bands centered at 1320 and 940 cm^{-1}; the major isomer had a single band at these positions while the minor isomer had two bands centered at each of these positions. These bands can be attributed to a C–H deformation mode of the methyl protons and a $C-CH_3$ stretching mode, respectively. The two conformations of *trans*-**4** are enantiomeric and thus equally populated. The methyl groups are in different environments and each would have characteristic absorption frequencies. Thus two absorption bands would be expected for *trans*-**4**. *cis*-**4** can also exist in two conformations, one with the methyl groups pseudoaxial and one with the methyl groups pseudoequatorial. In each conformation, the methyl groups are enantiotopic and should show absorption at the same frequency. However, the conformation with the phenyl groups pseudoequatorial would have considerably less steric interactions than the other conformation and would be heavily populated. In

Scheme I. Reactions of the 1,3-Diphenylisobenzofuran Dianion



(1) V. Kalyanaraman and M. V. George, *J. Organomet. Chem.*, **47**, 225 (1973).

(2) M. Palmer and S. Kennedy, *J. Chem. Soc., Perkin Trans. 2*, 81 (1976).

(3) In diethyl ether some reaction with the solvent occurred. This was evident from the varied color changes observed and from the evidence of ethyl groups in the NMR spectrum of the hydrolysis products. Consequently, THF was the only reaction solvent used.

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Table I. Effect of Solvation of the Cation of 2 on the Stereoselectivity of Protonation

	cis-3/*trans*-3 using as solvent THF plus			
2, M^+ =	THF	HMPA[a] (2:1)[b]	HMPA[a] (4:1)[b]	other
Li	2.4	tr[c]	tr[c]	2.0 (TMEDA[d] (1:1)[a])
Na	9.0	5.7	3.8	
K	6.7	5.7	4.6	2.4 (18-crown-6 (1:1)[a])

[a] Moles of cosolvent per mole of counter ion. [b] HMPA = hexamethylphosphoric triamide. [c] Only a trace of 3 was detected in the reaction products. [d] TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

practice, a single absorption at each characteristic frequency for the methyl group would be expected.[4]

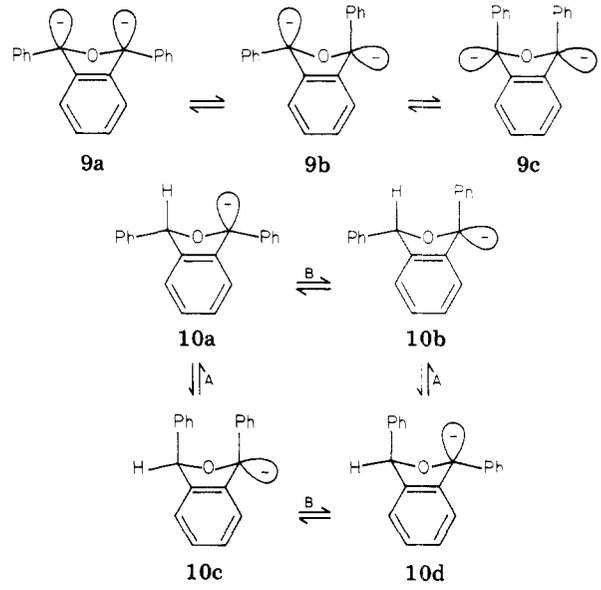
The dicarboxylic acids **5**, formed on treating **2** with carbon dioxide, showed an 11:1 ratio of the two isomers as determined from the NMR spectrum after converting the mixture of acids to their methyl esters **6**. The major isomer was isolated both as the carboxylic acid, *cis*-**5**, and as the methyl ester, *cis*-**6**, while the minor isomer was isolated only as the methyl ester, *trans*-**6**.

trans-**6** would be expected to show a more shielded methyl group in the NMR spectrum because of the opposing phenyl group than would *cis*-**6**. The minor isomer (methyl signal at δ 3.64) was therefore assigned trans stereochemistry while the major isomer (methyl signal at δ 3.82) was considered to have cis stereochemistry. This assignment was supported by the infrared spectrum in which *cis*-**6** showed a single carbonyl frequency while *trans*-**6** showed two. Finally, the stereochemical assignments were confirmed by an X-ray crystallographic structure determination on the major acid, *cis*-**5**.[5]

The high stereoselectivity of these reactions prompted a more detailed study of the effect of the cation and the degree of solvation of the cation on the stereochemical outcome of the protonation. Various cosolvents capable of more strongly solvating the cation of **2** were added to the THF solution and the cis/trans ratio was determined by the NMR of the protonation products. As can be seen by the results summarized in Table I, variations in the stereochemical ratio do occur and the stereoselectivity decreases as the solvation of the cation of **2** increases.[6]

Given the rapid rates of protonation of dianions[7] such as **2**, it is possible that the observed stereochemical results reflect the conformation of the dianion itself rather than that of the intermediate monoprotonated monoanion **10** (Scheme II). However, whether conformations of either **2** or **10** are considered, comparison with the well-known 9-alkyl-10-lithio-9,10-dihydroanthracenes[8] is instructive.

Scheme II.[a] Anionic Conformations



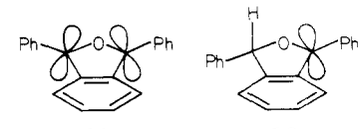
[a] A = Ring inversion, B = pyramidal inversion.

In the latter case, the favored conformation is the one which minimizes steric interactions of the substituent groups at the 9 and 10 positions with one another and with the peri hydrogens of the benzene rings and which maximizes orbital overlap between the anionic center and the benzene rings. In the case of **2** (or **10**) where only one benzene ring is present, peri interactions are less important than the other two factors. Indeed **10** is more closely analogous to the dihydronaphthalene monoanions recently described.[9]

On the basis of the above considerations, **9a** would be the most stable conformation for **2**. The slight puckering of the dihydrofuran ring places the phenyl substituents in pseudoequatorial positions and reduces their steric interaction while the pseudoaxial anionic orbitals overlap effectively with the benzene ring.

Again, if one assumes that isomerization of the monoprotonated monoanion can compete with its protonation, then the conformations **10a–d** can be considered. Again the factors of minimum steric interaction and maximum overlap clearly favor **10a** (phenyls pseudoequatorial, anionic orbital pseudoaxial). Thus considering the preferred conformations of either the dianion **2** or the monoprotonated monoanion **10** rationalizes the preponderance of cis products on protonation.

This argument requires that the anionic center maintain sp^3 character. However, it is known that the degree of sp^2 character increases with increased solvation of the cation,[10] leading to the formation of solvents-separated ion pairs. This would lead to a flattening of the anion (i.e., **11** or **12**)



and a decrease in the stereoselectivity of its reactions. This decrease can be observed in the data of Table I. Cosolvents which are known to solvate the cations more strongly than

(4) A similar argument is employed by H. Zieger, D. Schaeffer, and R. Padronaggio, *Tetrahedron Lett.*, 5027 (1969).

(5) G. Ferguson and M. A. Khan, *Acta Crystallogr., Sect. B*, **35**, 1720 (1979).

(6) Attempts at increasing the hexamethylphosphoric triamide concentration above those shown resulted in complex reaction mixtures which contained little or no **3**.

(7) M. Szwarc, "Ions and Ion Pairs in Organic Reactions", Vol. 2, Wiley, New York, 1974, pp 221–240.

(8) (a) M. Malissard, M. P. Mazaleyrat, and Z. Welvart, *J. Am. Chem. Soc.*, **99**, 6933 (1977); (b) M. Daney, R. Lapouyade, and H. Bouas-Laurent, *Tetrahedron Lett.*, 783 (1978); (c) S. Bank, J. Bank, M. Daney, B. Labrande, and H. Bouas-Laurent, *J. Org. Chem.*, **42**, 4058 (1977); (d) M. Daney, R. Lapouyade, M. Mary, and H. Bouas-Laurent, *J. Organomet. Chem.*, **92**, 267 (1975); (e) C. Fabre, M. Salem, J. P. Mazaleyrat, A. Tchapio, and Z. Welvart, *ibid.*, **87**, 9 (1975); (f) P. P. Fu, R. G. Harvey, J. W. Paschal, and P. W. Rabideau, *J. Am. Chem. Soc.*, **97**, 1145 (1975); (g) E. J. Panek, and T. J. Rodgers, *ibid.*, **96**, 6921 (1974); (h) M. E. Zieger and L. T. Gelbaum, *J. Org. Chem.*, **37**, 1012 (1972).

(9) P. W. Rabideau and E. G. Burkholder, *J. Org. Chem.*, **44**, 2354 (1979).

(10) (a) R. Waak, M. Doran, E. Baker, and G. Olah, *J. Am. Chem. Soc.*, **88**, 1272 (1966); (b) F. Kronzer and V. Sandel, *ibid.*, **94**, 5750 (1972).

Table II. Formation of Bridged Phthalans from 2 and Polymethylene Halides

X(C-H_2)$_n$X				anal				
				calcd		found		
X	n	% yield	mp, °C	C	H	C	H	NMR,[c] δ
Cl	2	82	152-153	88.56	6.08	88.67	6.15	2.0-2.25 (m, 2 H), 2.32-2.57 (m, 2 H), 6.9-7.8 (m, 14 H)
Br	2[a]	9						
Cl	3[b]	76	119-120	88.43	6.45	88.64	6.49	1.0-1.3 (m, 1 H), 1.7-1.9 (m, 1 H), 2.0-2.3 (m, 4 H), 6.7-7.8 (m, 14 H)
Br	3	40						
Cl	4	65	175-176	88.31	6.79	88.44	6.82	1.2-1.4 (m, 2 H), 1.7-1.9 (m, 2 H), 2.3-2.6 (m, 4 H), 6.7-7.7 (m, 14 H)
Br	4	10						

[a] 80% of 1 was recovered. [b] Isolated by recrystallization from ethanol. [c] 220-MHz spectra.

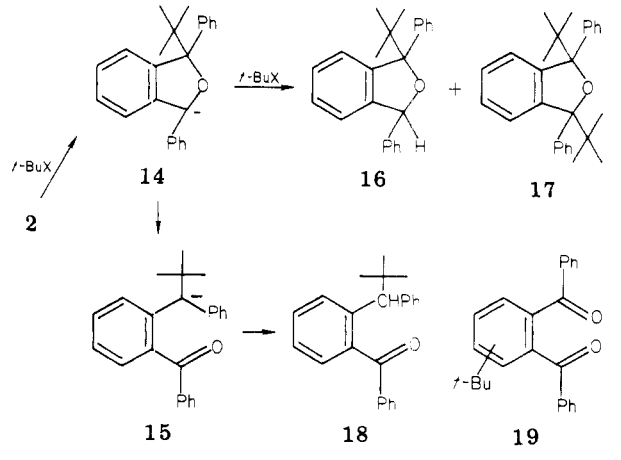
THF, thus increasing the concentration of solvent-separated ion pairs, decrease the stereoselectivity observed in the protonation. The change of cation from potassium or sodium to lithium has the same result since the lithium cation is inherently more solvated and lithium carbanion salts have a tendency to exist as solvent-separated ion pairs.[11]

Advantage was taken of the tendency for **2** to yield cis products by alkylating **2** with polymethylene dihalides to produce a series of 1,3-bridged-1,3-diphenylphthalans **7** (n = 2, 3, 4). The structures of **7** were clearly supported by their NMR spectra and, in addition, **7** (n = 2) was readily dehydrated to 1,4-diphenylnaphthalene, **13**.

The experimental results of these dialkylations are summarized in Table II (see Experimental Section). It will be noted that these reactions proceeded well with the dichlorides, but product yields were less favorable with the dibromides. In the latter cases, products other than **7** were isolated such as recovered starting material (**1**), dimeric products such as **8**, and glassy solids (presumably polymeric) which gave broad unresolved NMR spectra.

This leaving-group effect suggested that a change in reaction mechanism from nucleophilic substitution to single electron transfer (SET) was occurring as the leaving group is changed from chloride to bromide. Evidence for such a mechanistic change has been presented elsewhere both for radical anions[12] and vicinal dianions.[13] Additional evidence that SET can occur in the case of **2** was the observation that extensive alkylation occurs (50–80%) when **2** is treated with *tert*-butyl halides.[14] Unlike the earlier reported case[14] of extensive alkylation with *tert*-butyl halides, reaction mixtures were quite complex due to heterocyclic ring opening of the intermediate monoalkylated monoanion (i.e., **14** → **15**). The products isolated and characterized are shown in Scheme III and these, together with recovered **1** and *o*-dibenzoylbenzene, accounted for 85 ± 5% of the reaction products.

Scheme III



Experimental Section

Melting points were determined in open capillaries and are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian T-60 or Perkin-Elmer R12B spectrometer, using deuteriochloroform as solvent, and are reported in parts per million downfield from internal tetramethylsilane (Me_4Si) as reference (δ units). Infrared (IR) spectra were recorded on a Beckman IR-10 spectrophotometer and mass spectra on a Varian MAT CH7 spectrometer. High-resolution mass spectra were measured on a VG 7070 mass spectrometer. Chemical analyses were performed by MHW Laboratories, Phoenix, AZ. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were dried over lithium aluminum hydride and distilled from it immediately before use. Hexamethylphosphoric triamide (HMPA) was dried over sodium and distilled from it when needed. *N,N,N′,N′*-Tetramethylethylenediamine (TMEDA) was dried by distilling from calcium hydride. The crown ether, 18-crown-6, was prepared as described[15] and purified via its acetonitrile complex. Final drying was effected by vacuum distillation. Column chromatography was performed with silica gel 60 (E. Merck AG) and thin-layer chromatography was performed on Eastman Chromatogram 6060 silica gel sheets. Vapor-phase chromatography (VPC) was conducted on a Varian 1520 instrument equipped with flame-ionization detectors. Either a 5 ft × $^1/_8$ in. stainless steel column packed with 3% SE-52 on 100/120 mesh Varaport 30 (column A) or a 6 ft × $^1/_8$ in. stainless steel column packed with 4% OV-101 and 6% OV-210 on 80/100 mesh HP Chromosorb W (column B) was used. 1,3-Diphenylisobenzofuran, mp 129.5–131 °C, was prepared in 71% overall yield from *o*-benzoylbenzoic acid.[16]

General Procedure. The nitrogen used to protect the dianion **2** during formation and subsequent reaction was purified-grade nitrogen further purified by passing through a refluxing xylene solution of sodium benzophenone ketyl. Reductive metalations on a preparative scale were performed as previously described in modified Schlenk tubes,[17] using 100 ± 10 mL of THF per 0.01 mol of **1**. Removal of weighed aliquots of the solution during reaction between **1** and sodium (or lithium, potassium), quenching these aliquots in 1:1 water–ethanol, and titrating with standardized hydrochloric acid demonstrated that formation of the deep blue

(11) (a) E. Buncel and B. Menon, *J. Org. Chem.*, **44**, 317 (1979); (b) D. H. O'Brien, C. R. Russell, and A. J. Hart, *J. Am. Chem. Soc.*, **101**, 633 (1979).

(12) (a) M. Malissard, J.-P. Mazaleyrat, and Z. Welvart, *J. Am. Chem. Soc.*, **99**, 6933 (1977); (b) E. Hebert, J.-P. Mazaleyrat, and Z. Welvart, *J. Chem. Soc., Chem. Commun.*, 877 (1977).

(13) J. G. Smith and D. C. Irwin, *J. Am. Chem. Soc.*, **102**, 2757 (1980).

(14) J. G. Smith and D. J. Mitchell, *J. Am. Chem. Soc.*, **99**, 5045 (1977).

(15) G. Gokel and D. J. Cram, *J. Org. Chem.*, **39**, 2445 (1974).

(16) (a) A. LeBerre and R. Ratsembazafy, *Bull. Soc. Chim. Fr.*, 229 (1963); (b) A. Guyot and J. Catel, *ibid.*, **35**, 1124 (1906); (c) A. Étienne, *Ann. Chim. (Paris)*, **1**, 57 (1946).

(17) J. W. B. Reesor, J. G. Smith, and G. F. Wright, *J. Org. Chem.*, **19**, 940 (1954).

anion **2** was rapid, that the reaction equilibrated at 2 mol of alkali metal per mole of **1** (a dianion), and that this point was reached in 6 h. Reaction times of 8 h were used to ensure complete reduction. The THF solution of **2** was drained under nitrogen into a nitrogen-filled flask equipped with a magnetic stirrer and a septum. After the solution was cooled to −70 °C, the second reagent (excess H_2O, D_2O, 0.02 mol equiv of methyl iodide, *tert*-butyl chloride, or *tert*-butyl bromide, or 0.01 mol equiv of a dihaloalkane (vide infra)) was injected through the septum. In the case of the reaction with carbon dioxide, the nitrogen atmosphere was replaced with CO_2. Reaction with allowed to continue for 2 h at −70 °C and 12 h at 20 °C. Methanol (1 mL) was then added and the reaction products were isolated by ether extraction after adding 50 mL of water. Specific quantities and isolation of the products are described in the following sections.

Protonation Studies for Table I. These reactions were performed with 0.22 g (0.8 mmol) of **1** and 30 mL of THF, using a special apparatus. This apparatus consisted of a 100-mL Erlenmeyer flask capped with a 100-mL round-bottom flask, the latter equipped with a side arm plus stopcock. Both flasks had magnetic stirring bars and the neck (juncture) of the flasks was partially blocked by an insert cut from a 2-mm-thick sheet of Teflon. The dual flask assemblage was evacuated and filled with nitrogen through the stopcock. The flasks were transferred to a drybox where (after disassembling) the Erlenmeyer flask was charged with **1**, THF, and excess alkali metal. After the apparatus was reassembled, the side arm was capped with a septum, and the apparatus was removed from the drybox, the reductive metalation was effected. Inversion of the assembly allowed the solution of **2** to drain from the excess alkali metal that was retained by the Teflon insert. Cosolvent (if used) was then injected, and the solution was stirred for 6–8 h, cooled to −70 °C, and treated with methanol. The reaction products (isolated as described) were concentrated, dried in vacuo, and analyzed by NMR. Results are summarized in Table I.

1,3-Diphenylphthalan (3). The reaction product from the protonation of **2** (M = Na) derived from 0.68 g (2.5 m mol) of **1** was chromatographed on silica gel, using benzene–hexane (40:60) as the eluting solvent, to give 0.54 g (80%) of an isomeric mixture of 1,3-diphenylphthalans. Repeated recrystallization from ethanol provided a sample of *cis*-1,3-diphenylphthalan: mp 86–87 °C; NMR 6.23 (s, 2 H), 6.9–7.7 (m, 14 H); IR (KBr) 1495, 1450, 1350, 1285, 1155, 1070, 1005, 960, 905, 745, 695, 625 cm^{-1}. Anal. Calcd for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.08; H, 5.86.

A mixture (0.53 g, 2 mmol) of *cis*- and *trans*-**3** (3:1) was treated with an excess of potassium *tert*-butoxide in 25 mL of *tert*-butyl alcohol and refluxed under nitrogen for 17 h. The solution was diluted with water and neutralized and the product (0.50 g) isolated by ether extraction. The isomer ratio was now 55:45 cis/trans. Chromatography (as before) gave, in order of elution, 0.03 g (6%) of 1,3-diphenylisobenzofuran, 0.44 g (83%) of *cis*- and *trans*-**3** (collected in two fractions, the second being predominantly *trans*-**3**), and finally 0.03 g (5%) of *o*-dibenzoylbenzene. The fraction rich in *trans*-**3** was recrystallized twice from ethanol–water to afford pure *trans*-1,3-diphenylphthalan:[18] mp 99.5–100.5 °C; NMR 6.45 (s, 2 H), 6.95–7.6 (m, 14, H); IR ($CHCl_3$) 1495, 1455, 1010, 690 cm^{-1}. Anal. Calcd for $C_{20}H_{16}O$: C, 88.20; H, 5.92. Found: C, 88.34; H, 5.91.

Hydrogenation of 1,3-Diphenylisobenzofuran (1). Hydrogenation of **1** (0.68 g, 2.5 mmol) was effected in 50 mL of ethyl acetate, using 0.1 g of 5% Pd on charcoal and 50 psi of hydrogen pressure at 20 °C for 12 h. After filtration, the solvent was removed and the residue dissolved in ethanol. On standing, 0.27 g (39%) of 1,3-diphenyl-4,5,6,7-tetrahydroisobenzofuran separated: mp 89–90 °C; NMR 1.4–2.1 (m, 4 H), 2.5–3.1 (m, 4 H), 7.0–7.9 (m, 10 H). Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.54; H, 6.60.

The ethanolic filtrate was concentrated and chromatographed on silica gel, using benzene–hexane (40:60) for elution. The first fraction was a mixture of *cis*-**3** and the tetrahydro derivative while the second fraction was *cis*-**3** (0.24 g, 35%), mp 85–87 °C.

(18) While the stereochemistry of the product was not established, earlier reports of *trans*-**3** have appeared (lit.[14b] mp 95 °C): G. Pifferi, A. Vigevani, and P. Consonni, *Ann. Chim. (Rome)*, **58**, 1294 (1968), mp 97.5–98 °C.

1,3-Dimethyl-1,3-diphenylphthalan (4). The crude reaction mixture from 1.85 mmol of **2** (M = Na) and 0.79 g (5.5 mmol) of methyl iodide (0.50 g, orange oil) showed two resonances in the NMR spectrum at δ 1.82 and 1.95 in a 1:4 ratio, respectively. Chromatography on silica gel using benzene–petroleum ether (bp 30–60 °C; 40:60) as eluent gave, in order of elution: 0.04 g (8%) of **1**; 0.06 g (11%) of *trans*-**4** [mp (from methanol) 89–90 °C; NMR 1.82 (s, 6 H), 7.2–7.8 (m, 14 H); IR ($CHCl_3$) 1602, 1500, 1445, 1370, 1320, 1310, 1290, 1245, 1045, 945, 935, 690 cm^{-1}. Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 88.13; H, 6.68]; 0.22 g (40%) of *cis*-**4** [mp (from petroleum ether (bp 30–60 °C)) 34.5–35.5 °C; NMR 1.95 (s, 6 H), 7.0–7.5 (m, 14 H); IR ($CHCl_3$) 1600, 1595, 1445, 1370, 1320, 1280, 1245, 1045, 940, 690 cm^{-1}. Anal. Calcd for $C_{22}H_{20}O$: C, 87.96; H, 6.71. Found: C, 87.95; H, 6.63]; and 0.08 g (15%) of *o*-dibenzoylbenzene.

1,3-Diphenyl-1,3-phthalandicarboxylic Acid (5). The dianion **2** (M = Na) prepared from 0.50 g (1.85 mmol) of **1** was treated at −70 °C with gaseous carbon dioxide until the blue color of the dianion disappeared. The solution was treated with 100 mL of water and 50 mL of ether. Separation of the ether layer and evaporation gave 0.11 g (22%) of **1**. The aqueous layer was acidified (aqueous HCl) and extracted with ether. After the ether extract was dried and evaporated, the residue (0.53 g) was crystallized from chloroform to give 0.48 g (72%) of *cis*-1,3-diphenylphthalan-1,3-dicarboxylic acid. Two recrystallizations from chloroform provided the analytical sample: mp 223–224 °C; NMR 7.0–7.9 (m, 14 H), 14.7 (s, 2 H); IR (KBr) 3060 (br), 1715, 1500, 1450, 1350, 1190, 1025, 780, 765, 720, 680 cm^{-1}. Anal. Calcd for $C_{22}H_{16}O_5$: C, 73.33; H, 4.48. Found: C, 73.51; H, 4.38.

In a second experiment, the base-soluble products of the carboxylation were dissolved in ether and esterified with diazomethane. Removal of the solvent gave 0.54 g of crude dimethyl ester whose NMR spectrum showed two singlets at δ 3.64 and 3.82 in the ratio of 8:92, respectively. Recrystallization of the crude product from Et_2O afforded 0.30 g (42%) of dimethyl *cis*-1,3-diphenylphthalan-1,3-dicarboxylate, *cis*-**6**: mp 157–185 °C; NMR 3.82 (s, 6 H), 7.2–7.7 (m, 14 H); IR (KBr) 1725, 1600, 1495, 1445, 1425, 1230, 1105, 1005, 900, 805, 745, 730, 690 cm^{-1}. Anal. Calcd for $C_{24}H_{20}O_5$: C, 74.21; H, 5.19. Found: C, 74.35; H, 5.25.

The material in the filtrate from the recrystallization was chromatographed on silica gel, using benzene/chloroform (90:10) for elution. *trans*-**6** eluted first (0.03 g, 4%) followed by 0.16 g of *cis*-**6** (total yield 64%). The *trans*-**6** was recrystallized from Et_2O: mp 188–188.5 °C; NMR 3.64 (s, 6 H), 7.2–7.8 (m, 14 H); IR ($CHCl_3$) 1755, 1740, 1500, 1460, 1450, 1435, 1240, 1105, 1045, 1010, 900, 800, 690 cm^{-1}. Anal. Calcd for $C_{24}H_{20}O_5$: C, 74.21; H, 5.19. Found: C, 74.06; H, 5.10.

Reaction with Polymethylene Halides. The dianion **2** (M = Na) prepared from 0.50 g (1.85 mmol) of **1** was treated at −70 °C with 1.9 mmol of the selected polymethylene halide. Isolation of the reaction products was accomplished by column chromatography on silica gel, using benzene–hexane (1:1) as eluant. The results for the bridged phthalans are summarized in Table II.

Reaction with 1,4-Dibromobutane. The crude reaction product was chromatographed on silica gel, using petroleum ether (bp 30–60 °C) graded to benzene for elution. Early fractions were glassy solids showing broad unresolved peaks in the NMR spectrum. These were presumed to be polymeric in nature and were not investigated further. Between these fractions and the fraction containing 1,3-diphenyl-1,3-butanophthalan, **7** (n = 4), 0.04 g (3%) of 1,1′:3,3′-dibutanobis(1,3-diphenylphthalan), **8**, was collected. Recrystallization from ethanol gave an analytical sample: mp 228.5–229 °C; NMR 0.93–1.60 (m, 12 H), 1.60–2.50 (m, 4 H), 7.0–7.7 (m, 28 H); IR (KBr) 1600, 1495, 1445, 1355, 1255, 1030, 970, 745, 695 cm^{-1}; mass spectrum, m/e (relative intensity) 652 (M^+, 7), 283 (22), 271 (20), 270 (21), 105 (20), 91 (100). Anal. Calcd for $C_{48}H_{44}O_2$: C, 88.31; H, 6.79. Found: C, 88.40; H, 6.96. Reactions of **2** with dichloro- and diiodomethane were also attempted but the only characterizable products were **1** and *o*-dibenzoylbenzene.

Dehydration of 1,3-Diphenyl-1,3-ethanophthalan (7, n = 2). A sample (0.07 g, 0.21 mmol) of **7** (n = 2) was dehydrated by refluxing a benzene solution containing a catalytic amount of *p*-toluenesulfonic acid for 12 h. After the solution was washed with water and the solvent evaporated, the residue was recrystallized from ethanol to give 0.054 g (96%) of 1,4-diphenyl-

naphthalene (**13**), mp 134.5–135.5 °C (lit.[19] mp 136 °C, 135–136 °C).

Reaction with *tert*-Butyl Halides. Treatment of a solution of **2** (1.85 mmol) with 0.35 g (3.8 mmol) of *tert*-butyl chloride resulted in only limited reaction at −70 °C (little color change). Warming the solution to ambient temperature resulted in a color change from blue to light orange. The crude product (oil, 0.60 g) was analyzed by gas chromatography using column A and an initial column temperature of 180 °C for 10 min, then heating at 3 °C/min to 210 °C, and holding isothermally at the upper limit. The compounds which eluted had the following retention times relative to **17** [normalized percent peak area, identity (if known)]: 0.63 (1, **18**), 0.77 (32, **16**), 0.85 (4), 1.0 (51, **17**), 1.08 (4), 1.19 (3, *o*-dibenzoylbenzene),[20] 1.27 (1, **1**),[20] 1.37 (2), 1.46 (2). The crude product was chromatographed, using petroleum ether (bp 30–60 °C) containing 10% benzene as eluant. The first fraction contained 0.15 g (21%) of 1,3-di-*tert*-butyl-1,3-diphenylphthalan, **17**: mp (from ethanol) 213–214 °C; NMR 0.70 (s, 18 H), 7.0–7.55 (m, 8 H), 7.55–8.0 (m, 6 H); IR ($CHCl_3$) 1480, 1445, 1395, 1360, 1160, 1025, 1005, 995, 900, 695 cm^{-1}; mass spectrum, *m/e* (relative intensity) 369 (1, $M^+ - CH_3$), 328 (14), 327 (49, $M^+ - t$-Bu), 272 (15), 271 (100), 270 (36), 193 (14), 119 (13). Anal. Calcd for $C_{28}H_{32}O$: C, 87.45; H, 8.39. Found: C, 87.31; H, 8.51.

The second fraction was identified as 1-*tert*-butyl-1,3-diphenylphthalan (**16**): 0.10 g (16%); an oil; NMR 1.13 (s, 9 H), 5.79 (s, 1 H), 6.7–8.2 (m, 14 H); mass spectrum, *m/e* (relative intensity) 313 (1, $M^+ - CH_3$), 272 (19), 271 (100, $M^+ - t$-Bu), 194 (11), 193 (24), 165 (42), 105 (18), 77 (24). Rechromatographing **16** and collecting the central fraction provided an analytical sample. Anal. Calcd for $C_{24}H_{24}O$: C, 87.75; H, 7.38. Found: C, 87.44; H, 7.03.

The third fraction contained *o*-(α-phenylneopentyl)benzophenone (**18**): 0.05 g (8%); mp (from methanol) 65–65.5 °C; NMR 0.97 (s, 9 H), 4.07 (s, 1 H), 7.0–8.1 (m, 14 H); IR (KBr) 1660, 1595, 1580, 1475, 1445, 1365, 1275, 1150, 925, 765, 735, 715, 700, 655, 635; mass spectrum, *m/e* (relative intensity) 313 (3, $M^+ - CH_3$), 273 (14), 272 (92), 271 (100, $M^+ - t$-Bu), 270 (17), 253 (17), 194 (39), 193 (47), 165 (44), 105 (19), 91 (20). Anal. Calcd for $C_{24}H_{24}O$: C, 87.76; H, 7.37. Found: C, 88.00; H, 7.48.

Repeating the preceding reaction using 0.51 g (3.72 mmol) of *tert*-butyl bromide resulted in a marked color change at −70 °C. The crude product was analyzed by gas chromatography as before, with the following retention times relative to **14** (normalized percent peak area, identity): 0.31 (4), 0.53 (1), 0.63 (3, **18**), 0.76 (23, **16**), 0.85 (6), 1.0 (25, **17**), 1.11 (4), 1.21 (13, *o*-dibenzoylbenzene),[20] 1.28 (11, **1**),[20] 1.42 (10).

Repeating the preceding experiment using 0.26 g (1.90 mmol) of *tert*-butyl bromide resulted in a color change from blue to red-brown at −70 °C, but decolorization did not occur on warming. Chromatography of the crude product (0.56 g) as before gave, in order of elution, 0.13 g of a fraction containing three *tert*-butylated compounds (attempts to resolve this mixture were not successful), 0.22 g (36%) of **10**, 0.03 g (6%) of *o*-dibenzoylbenzene, and finally 0.10 g (16%) of **19**: mp (from ethanol) 140–141 °C; NMR 1.32 (s, 9 H), 7.1–7.9 (m, 13 H); IR ($CHCl_3$) 1650, 1605, 1450, 1410, 1365, 1315, 1280, 935, 845 cm^{-1}; mass spectrum, *m/e* (relative intensity) 342 (73 M^+), 286 (21), 265 (14), 209 (100), 152 (20), 105 (12). Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.18; H, 6.48. Found: C, 84.40; H, 6.39.

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Registry No. **1**, 5471-63-6; **2** (M = Li), 74563-16-9; **2** (M = Na), 74563-17-0; **2** (M = K), 74563-18-1; *cis*-**3**, 21596-49-6; *trans*-**2**, 74563-19-2; *trans*-**4**, 74563-20-5; *cis*-**4**, 74563-21-6; *cis*-**5**, 71176-48-2; *trans*-**5**, 74563-22-7; *cis*-**6**, 74563-23-8; *trans*-**6**, 74563-24-9; **7** (*n* = 2), 74563-25-0; **7** (*n* = 3), 74563-26-1; **7** (*n* = 4), 74563-27-2; **8**, 74577-81-4; **10**, 74563-28-3; **13**, 796-30-5; **16**, 74563-29-4; **17**, 74563-30-7; **18**, 74563-31-8; **19**, 74577-82-5; *o*-dibenzoylbenzene, 1159-86-0; 1,3-diphenyl-4,5,6,7-tetrahydroisobenzofuran, 74563-32-9; $Cl(CH_2)_2Cl$, 107-06-2; $Br(CH_2)_2Br$, 106-93-4; $Cl(CH_2)_3Cl$, 142-28-9; $Br(CH_2)_3Br$, 109-64-8; $Cl(CH_2)_4Cl$, 110-56-5; $Br(CH_2)_4Br$, 110-52-1.

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Reaction of Ortho Esters with Secondary Amines

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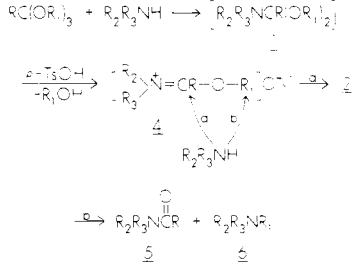
The scope of the reaction of ortho esters with secondary amines has been explored. With *p*-toluenesulfonic acid as catalyst, *N*-alkylanilines and orthoformates gave high yields of *N*-alkylformanilides and *N,N*-dialkylanilines in contrast to previous work with other acid catalysts where ortho amides were produced in low yield. Aliphatic cyclic amines (e.g., morpholine, piperidine) and orthoformates gave the corresponding ortho amides. This constitutes a new convenient synthesis of these useful reagents.

In theory the acid-catalyzed reaction of secondary amines with ortho esters could yield the amide acetals **1**, the ester aminals **2**, or the ortho amides **3**. To date the

$RC(OR_1)_2NR_2R_3$ $RC(OR_1)(NR_2R_3)_2$ $RC(NR_2R_3)_3$
1 **2** **3**

only examples have yielded the ortho amides, and these few examples have been limited to *N*-alkylanilines and orthoformates[1-6] (ortho amides of higher ortho carboxylic acids are unknown[7]). We have attempted to react a variety of secondary amines with ortho esters to explore the

Scheme I



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