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RING-CHAIN TAUTOMERISM AS A FACTOR IN THE REACTION BETWEEN GRIGNARD REAGENTS AND SUBSTITUTED PHTHALIDES

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Abstract—With phthalide two equivalents of Grignard reagent react rapidly in a reaction which could not be controlled to give stepwise addition. In contrast, 3,3- and 4,7-disubstituted phthalides react with only one equivalent of organometallic reagent. The primary addition product formed from one equivalent each of phthalide and Grignard reagent exists in a ring-chain tautomerism whose position is controlled by the interaction between the substituents present in the phthalide and the alkyl group introduced by the Grignard reagent. With substituted phthalides, ring opening of the primary addition product is prevented by these interactions and thus a second equivalent of Grignard reagent does not react. In the absence of substituents, ring opening and the reaction of a second equivalent occurs.

Somewhat related effects appear to exist in the reaction between Grignard reagents and phthalic anhydride and in the dehydration of substituted phthalyl alcohols to their corresponding phthalans.

Substituents have a pronounced effect[1] upon the rate and equilibrium position of ring-closure reactions. The present study was designed to examine this effect as it applied to the reaction between phthalides and Grignard reagents. This reaction became of interest to us as a route to functionally substituted stilbenes **3** needed for our investigation[2] of the reductive metalation of unsaturated compounds.

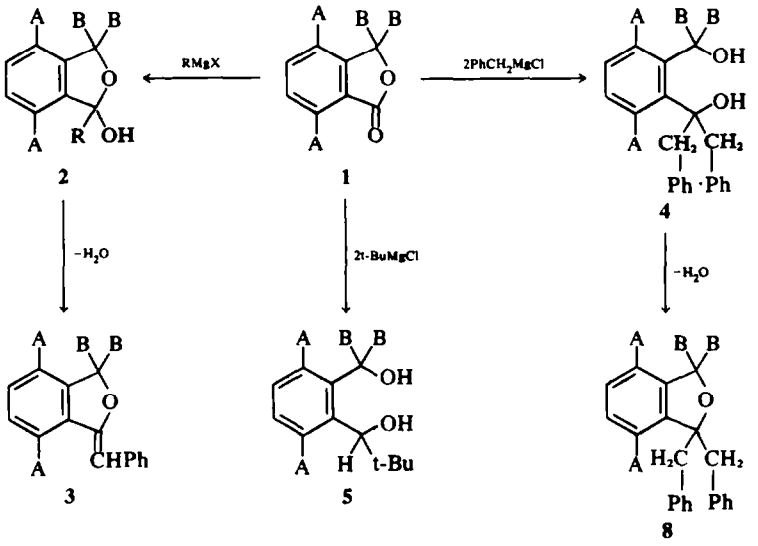
Several examples of the addition of Grignard reagents to phthalides have been reported[3] and the addition of both one[4] (*cf* **2** Scheme 1) and two[4c,5] moles (*cf*. **4**) of the organometallic reagent observed. However, consideration of the mole ratio of the two reagents did not account for all the reported results. Consequently, four substituted phthalides were selected and their behavior towards benzylmagnesium chloride and, to a lesser extent, t-butylmagnesium chloride was examined. The former Grignard reagent was selected because of our original interest in the reaction (i.e. stilbene-like products); the latter, because the steric requirements of the reagent might afford interesting results.

In the case of phthalide itself (**1**, A = B = H), facile addition of two moles of benzylmagnesium chloride occurred to give **4** (A = B = H).[5] Since **3** (*via* **2**) was the desired compound, numerous attempts were made to duplicate the results of Natelson and Pearl[4b] in which only one mole of Grignard reagent reacted. Thus the mole ratio of the two reagents, the solvent and the reaction temperature were varied and inverse addition was employed. In all cases (Table 1) unreacted phthalide and **4** (A = B = H) were the major components of the reaction mixture and **3** (A = B = H) never constituted more than a small portion of the reaction products.

An authentic sample of **3** (A = B = H) was obtained by the reduction[6] of benzalphthalan **6** with lithium aluminium hydride (LAH). The actual product of this reaction appeared to be the hydroxyphthalan **7** but **7** could not be obtained pure because of its exceptionally facile dehydration. Solutions of **7** underwent dehydration to **3** in a few hours at room temperature and the most convenient preparation of **3** involved the addition of **7** to a weakly acidic methanolic solution whereupon **3** crystallized out in a few minutes.

This extreme sensitivity towards acids, which has been noted before[4c] in related compounds, renders the original report[4b] of the preparation of **3** and **7** suspect. The hydrolysis conditions used in this earlier preparation (10% H_2SO_4) would have produced benzalphthalan **3** (A = B = H) rather than the reported hydroxybenzylphthalan, **7**. Indeed, the melting point claimed for this product (137°) suggests that it may have been **4** (A = B = H), m.p. 137°. Certainly from the data reported here, the addition of the second mole of benzylmagnesium chloride proceeded at a rate at least equivalent to that for the first mole and the reaction cannot be controlled to provide chiefly mono-addition.

In an effort to slow the addition of the second mole of Grignard, the behavior of a sterically cumbersome reagent, t-butylmagnesium chloride was examined. Under a variety of reaction conditions (Table 1), only two products were obtained. One was the unreacted phthalide while the second **5** (A = B = H) represented the consumption of two



SCHEME 1. Reaction of Grignard reagents with substituted phthalides.

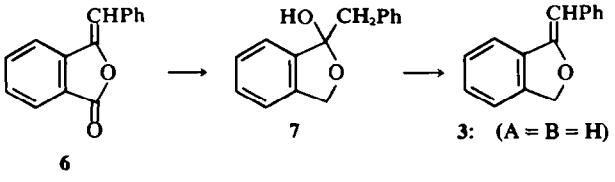
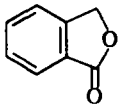
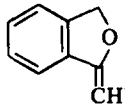
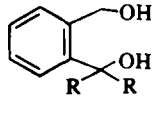
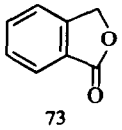
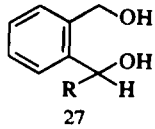


Table 1. Products from the reaction of RMgCl with phthalide

Solvent	Reaction Temp. °C	Mole ratio RMgCl/ phthalide	Product composition,[a] %		
R = $PhCH_2$					
DEE	0	1(I)[b]	40	20	40
DEE	0	1(I)	41	21	38
DEE	−60	1(I)	47	9	44
THF	0	1(I)	52	—	48
THF		1	50	—	50
THF	0	2(I)	—	—	100
R = t-Bu					
DEE	0	1(I)	73		27
DEE	0	2(I)	70		30
DEE	0	3(I)	60		40
DEE	35	3(I)	42		58
DEE/THF	0	3(I)	40		60
DEE/C_6H_6	0	3(I)	26		74
DEE/C_6H_6	reflux	3(I)	12		88
DEE/C_6H_6	reflux	2(I)	22		78

[a] Determined shortly after quenching. Oxidation of 3 to phthalide occurs readily.
[b] I = inverse addition.

equivalents of Grignard reagent with the second mole reacting by hydride transfer.

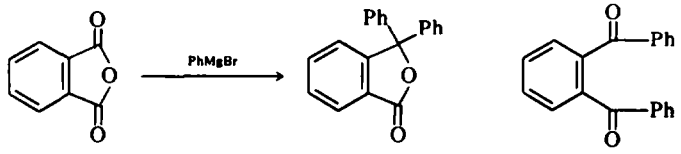
Since the steric size of the Grignard reagent had little effect on the moles of reagent consumed, the study was pursued by varying the substituents on the phthalide itself (i.e. A and B). Two 3,3-disubstituted phthalides, **1**, A = H, B = Me and A = H, B = Ph, were selected and prepared by treating phthalic anhydride with the appropriate Grignard reagent. In the case of 3,3-diphenylphthalide, column chromatography was necessary to remove the co-product, o-dibenzoylbenzene.[7] Several attempts were made to control the formation of this co-product but relatively small variations in the product ratio were obtained under a variety of reaction conditions.

The 3,3-disubstituted phthalides on treatment with one or more equivalents of benzylmagnesium chloride reacted smoothly to give the corresponding hydroxyphthalans **2** (A = H, B = Me or Ph, R = $PhCH_2$) or a mixture of this and its dehydration product **3** (A = H, B = Me or Ph) (Table 2). Again dehydration of the hydroxyphthalan proceeded with ease especially in the case of the 3,3-dimethyl derivative. The 3,3-diphenyl analog was more stable but a catalytic quantity of toluenesulfonic acid and gentle heating effected rapid dehydration.

Shifting the substituent groups to the aromatic ring produced similar results. Thus 4,7-disubstituted phthalides **1** (A = Me or Ph, B = H) reacted with benzylmagnesium chloride to produce the hydroxyphthalan **2** (A = Ph, B = H, R = $PhCH_2$) or a mixture of **2** (A = Me, B = H, R = $PhCH_2$) and its corresponding dehydration product **3** (Table 3). Again dehydration of the hydroxyphthalans proceeded with ease, especially in the case of the 4,7-dimethyl compounds. Interestingly, only one equivalent of t-butylmagnesium chloride reacted with 4,7-dimethylphthalide since no reduction involving a second equivalent was observed.

DISCUSSION

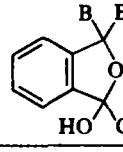
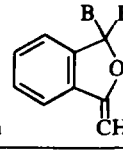
After the addition of the first mole of Grignard reagent to the phthalide **1**, a ring-chain tautomerism



can arise between the primary addition product **6a** and its open-chain isomer **6b**, which then reacts with the second mole of Grignard reagent. The alternative possibly that a displacement reaction occurs between the Grignard reagent and **6a** appears excluded on the basis of the isolated products. In all cases where double addition occurred, the product isolated was the diol[4] corresponding to **7**. Should a displacement reaction occur in the manner suggested by Jones[8] (for organo-cadmium reagents) and Newman,[9] the product would be the phthalan **8**. Furthermore, this displacement reaction has not been convincingly demonstrated with esters and organomagnesium compounds except for the special case reported by Fuson.[10]

It is suggested that in the case of the reaction between phthalides and organomagnesium compounds, the position of the equilibrium between the

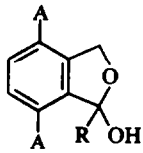
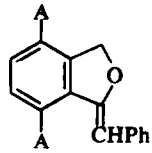
Table 2. Reaction of benzylmagnesium chloride with 3,3-disubstituted phthalides

Solvent[a]	Reaction *temp.* °C	Moles of $PhCH_2MgCl$	Product composition,[b] %	
				
B = CH_3 / DEE	0	1	77	23
DEE(I)	0	1	82	19
DEE(I)	0	2	68	32
THF(I)	0	1	72	28
DEE(I)	reflux	4	91	9
B = Ph / DEE	0	2	100	0

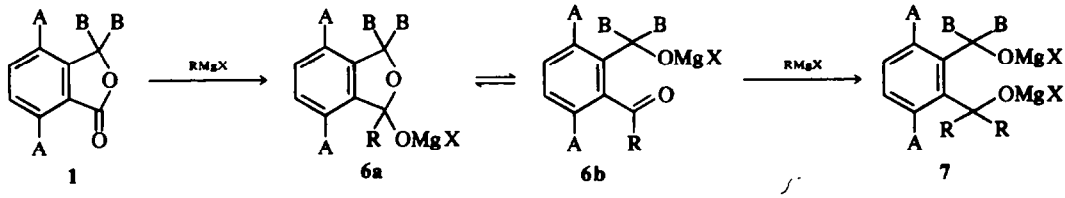
[a](I) indicates inverse addition.

[b]Slow spontaneous dehydration of the hydroxybenzylphthalan (B=CH_3) occurs such that in 72 h dehydration was complete.

Table 3. Reaction of RMgCl with 4,7-disubstituted phthalides

Solvent	Reaction temp. °C	Mole ratio RMgX/ phthalide	Product composition, % 	
A = Me, R = $PhCH_2$				
DEE	0	2	80[b]	20
DEE(I)	20	2	64[b]	36
A = Me, R = t-Bu				
DEE(I)	0	3	64[a]	
DEE(I)	35	3	62[a]	
C_6H_6/DEE	reflux	3	64[a]	
C_6H_6/DEE	reflux	6	67[a]	
A = Ph, R = $PhCH_2$				
DEE	0	2	100	0
DEE	0	2	>90	

[a] Remainder was unreacted phthalide.
[b] Slow dehydration occurs on storage of the product.



1 6a 6b 7

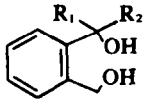
cyclic form **6a** and the open-chain form **6b** is the factor determining whether one or two moles of Grignard reagent appears in the final product. Any factor which prevents the ring opening will restrict the reaction to one equivalent of organomettallic reagent.

It has been known for many years that substituents increase the thermodynamic stability of ring forms over acyclic forms.[1a,11] In the case of the conversion of hydroxy-acids to lactones, Cohen suggests that the substituents narrow the conformational populations and thus enhance the rate of cyclization. Such an effect is designated stereopopulation control. Applying these concepts to the equilibrium between **6a** and **6b** it is necessary to consider the conformation of the substituent groups in **6b**. As the hydroxyphthalan ring opens, rotation about the bonds of the ring allows separation of the two atoms between which bond rupture has occurred.[12] If the 3-position is occupied by substituents groups (i.e. B = CH_3 or Ph), the conformation in which the oxygen of the —CB_2OMgX is furthest removed from the carbonyl carbon is no longer favorable because of the steric interaction between the B-groups and the R—C(=O) group. In effect, the probability of the conformational isomer in which the reacting groups have rotated away from each other is decreased.[13] Ring opening and subsequent reaction with a second equivalent of Grignard is rendered difficult.

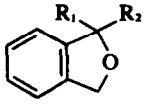
When substituents are present at the 4,7 positions (i.e. A = CH_3 or Ph) and B = H, the steric interactions just described are reduced. However, this decrease is compensated by increased steric interactions between A and B. Again, the net effect is to favor the ring closed member[6a] of the tautomeric pair **6a, b.**

While the steric interactions described here have a pronounced effect on the addition of Grignard reagents to phthalides, they appear to be less than that reported for 3,3,4,7-tetramethylphalide (**1**, A = B = Me), with its so-called "trimethyl lock".[16] While reduction of this last phthalide with LAH provided only the hydroxyphthalan, reduction of the phthalides[14] examined in the present study produced the ring-opened reduction product, the corresponding substituted phthalyl alcohols. Thus while the trimethyl lock freezes the reduced product in the ring-closed tautomer (the hydroxyphthalan), the substituents used in this study permit ring opening and further reduction to the phthalyl alcohol.

The availability of a variety of substituted phthalyl alcohols, **9**, prompted a consideration of their ring closure to phthalans, **10**. With two



9



10

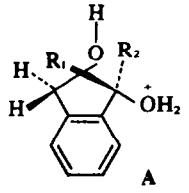
substituent groups, **9** ($R_1 = R_2 = PhCH_2$) underwent intramolecular dehydration even under mild reaction conditions. Under strongly reducing conditions (Zn/HCl) cyclization could not be diverted[15] to reduction and only the phthalan was produced. Facile cyclizations of similar α,α-disubstituted phthalyl alcohols have been reported.[5]

Removal of one benzyl substituent e.g. **9** ($R_1 = H$, $R_2 = PhCH_2$) sharply decreased the ease of cyclization. In our hands, mild conditions were without effect and reducing conditions (Zn/HCl) generated the reduction product, *o*-methylbibenzyl. Strongly acidic conditions have been reported[16] to effect dehydration to the substituted stilbene or cyclization of this to an indene derivative. Thus phthalan formation is sufficiently slow that reduction or alternative dehydrations occur.

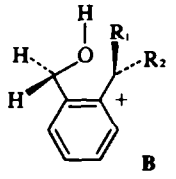
That cyclization can occur, albeit slowly, with monosubstituted phthalyl alcohols, is shown by the fact that the compound **9** ($R_1 = H$, $R_2 = t\text{-Bu}$) slowly cyclized to the corresponding phthalan. Similarly *o*-hydroxymethylbenzhydryl alcohols form the phthalan[17] on heating with 50% phosphoric acid. Here, dehydration to an alkene is no longer possible.

Removal of both substituents gives phthalyl alcohol which cyclizes to phthalan at high temperatures in the presence of acids.[18] In this case, no side reactions can occur and cyclization can be forced. In our comparison, 3,6-diphenylphthalyl alcohol, no cyclization was observed under mild conditions. Under strongly reducing conditions, reduction of the carbinol groups to Me was observed.

These observations can be rationalized by considering the two extreme transition states involved when one OH group (the nucleophile) displaces the other (the protonated OH). Thus **A** is a SN-2 type



A

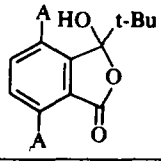
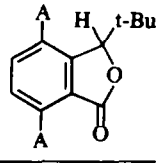


B

nucleophilic substitution while **B** is a SN-1 type. The non-bonded interactions in **B** are clearly less than in **A**. Any structural factor promoting early departure of the leaving group will favour cyclization. Thus two alkyl substituents or a single aryl substituent favor charge separation such as **B** while removal of substituents forces the reaction to proceed *via* transition states such as **A**. Conformationally, such states as **A** are not favored and side reactions can take precedence if such reactions are available.

Some indication that similar steric effects may operate in the reaction between Grignard reagents and phthalic anhydride or its ring-substituted derivatives was obtained. Thus phthalic anhydride and t-butylmagnesium chloride reacted with consumption of one or two equivalents of Grignard reagent (Table 4). However, 3,6-dimethylphthalic anhydride reacted with only one equivalent of Grignard reagent presumably because the interac-

Table 4. The reaction between t-butylmagnesium chloride and phthalic anhydrides

Solvent[a]	Reaction *temp.* °C	Mole ratio t-BuMgCl/ *phthalan*	Reaction products, % 	
A = H				
DEE(I)	0	2	75	25
DEE(I)	0	1	>90	<10
DEE	0	3	10	90
DEE(I)	0	6	—	100
C_6H_6/DEE(I)	reflux	6	—	100
A = Me				
DEE(I)	0	3	100	—
C_6H_6/DEE(I)	reflux	6	100	—

[a] I indicates inverse addition.

tion of the Me and t-Bu groups inhibits ring opening of the initial addition product and further reaction with a second equivalent.

EXPERIMENTAL

M.ps are uncorrected and were determined in open capillaries with a Mel-Temp apparatus. IR spectra were recorded on a Beckmann IR-10 spectrophotometer and NMR spectra on a Varian T-60 spectrometer. Chemical shifts are in ppm downfield from internal TMS (δ scale). Silica gel (0·05–0·2 mm) from E. Merck AG was used for column chromatography and Eastman Chromagram 6060 (silica gel) sheets were used for thin layer chromatography (TLC). Analyses were determined by M-H-W Laboratories, Garden City, Michigan.

In the experimental description following, the solvent diethyl ether is abbreviated to DEE and tetrahydrofuran to THF. Pet. ether refers to petroleum ether of boiling range 35–60°.

Phthalide and benzalphthalide were commercial reagents. The 3,3-dimethylphthalide,[19] 3,6-dimethylphthalic anhydride[9] and 3,6-diphenylphthalic anhydride[20] were preapred by published procedures.

3,3-Diphenylphthalide was prepared[7] from phthalic anhydride and PhMgBr (2 equiv) in ether at 0°. Attempts to purify the product by recrystallisation gave material with a wide melting range. Chromatography on silica gel with benzene as eluent gave 3,3-diphenylphthalide (67–71%, m.p. 117–118° after recrystallisation from EtOH) as the first product to elute and 1,2-dibenzoylbenzene m.p. 147·5–148·5° after recrystallisation from EtOH) as the second.

Increasing the reaction temp or replacing the solvent with benzene or THF led to a small decrease in the yield of the phthalide (48–57%) and a corresponding increase in the yield of diketone (36–45%).

4,7-Dimethylphthalide was prepared by the LAH reduction of 3,6-dimethylphthalic anhydride by a published procedure.[21] Analysis of the crude product by NMR indicated to presence of 10% of 3,6-dimethylphthalyl alcohol. Two recrystallisations of the crude product from pet. ether gave 83% of 4,7-dimethylphthalide m.p. 87–87·5°; NMR ($CDCl_3$) 2·30 (s, 3, CH_3), 2·65 (s, 3, CH_3), 5·21 (s, 2, CH_2), 7·20 and 7·58 (double d, J = 8 Hz, 2, aromatics).

When 2·65 g (0·015 m) of 4,7-dimethylphthalide was refluxed 2 h with 1·05 g (0·31 m) of LAH in 150 ml of ether, the product was entirely 3,6-dimethylphthalyl alcohol, m.p. 69–70°.

4,7-Diphenylphthalide was prepared by a similar[21] reduction of 3,6-diphenylphthalic anhydride. Again the crude product contained the corresponding phthalyl alcohol. Recrystallisation from 1 : 1 benzene; pet. ether gave 72% yield of 4,7-diphenylphthalide m.p. 170–171°; NMR ($CDCl_3$), 5·38 (s, 2, CH_2), 7·3–7·9 (m, 12, aromatics).

The filtrate was evaporated and the residue treated with pet. ether. The crude 3,6-diphenylphthalyl alcohol (**4**, A = Ph, B = H) which precipitated (m.p. 155–158·5°) was recrystallized from isopropyl alcohol, 15% yield, m.p. 161–2°; IR (KBr) 3480 and 3400 (OH), 1460, 1400, 1330, 980 (broad), 8·30, 760, 690 cm^{-1}; NMR ($CDCl_3$) 3·02 (s, 2, OH), 4·73 (s, 4, CH_2), 7·3–7·76 (m, 12, aromatics). (Found: C, 82·53; H, 6·37 Calcd. for $C_{20}H_{18}O_2$: C, 82·73; H, 6·25).

This alcohol (**4**, A = Ph, B = H) was also prepared in 83% yield by LAH reduction of 4,7-diphenylphthalide.

α,α-Diphenylphthalyl alcohol (**4**, A = H, B = Ph)

A mixture of 2·86 g (0·01 m) 3,3-diphenylphthalide, (0·012 m) LAH and 100 ml ether was refluxed for 2 h, hydrolyzed with water and the product isolated by evaporation of ether layer. Recrystallization from isopropyl from isopropyl alcohol–water gave 2·76 g (95% yield) of **4** (A = H, B = Ph), m.p. 162·5–164°.

Grignard reagents were prepared using DEE dried and stored over LAH and freshly distilled from it. The reported[22] yields for t-BuMgCl could not be obtained with Mg from the British Drug House; that from Fisher Chemical Co. proved satisfactory provided iodine initiation was *not* employed.

For inverse additions, the Grignard reagent was prepared in a flask with a stop-cock horizontally arranged in its side. On completion of the preparation, rotation of the flask converted it into an addition funnel.

All reaction mixtures were hydrolyzed by the addition of NH_4Cl aq. The ether layer was separated, washed with water, dried ($MgSO_4$) and evaporated under vacuum at room temp. Isolation of the individual products is described below.

Reaction between phthalide and benzylmagnesium chloride

Preparation of α,α-dibenzylphthalyl alcohol. The product from phthalide (13 g, 0·1 m) and benzyl magnesium chloride (0·2 m) was recrystallized from EtOH to give a 63% yield of α,α-dibenzylphthalyl alcohol m.p. 135–137°; IR ($CHCl_3$) 3560, 3400 (free and H-bonded OH), 1450, 1390, 1080, 690 cm^{-1}; NMR ($CDCl_3$) 2·85 (broad s, 2, OH, exchangeable), 3·33 (q, 4, J = 15 Hz, both CH_2Ph), 4·22 (s, 2, CH_2O), 7·0–7·8 (m, 14, aromatics).

If less benzylmagnesium chloride was used, the crude product contained phthalide (C=O at 1780 cm^{-1} and CH_2 singlet at 5·35 in the NMR spectrum) and benzalphthalan (see below). Analysis was accomplished by NMR and the results are summarized in Table 1.

Preparation of benzalphthalan (**3**, (A = B = H). Benzalphthalide (8·0 g, 0·036 m) was reduced with an equimolar amount of LAH in 400 ml DEE.[6] The mixture was decomposed by the addition of a limited quantity of water, the mixture filtered and the filtrate concentrated under vacuum. The residual yellow oil was 1-hydroxyl-1-benzylphthalan, **7**; IR (neat) 3380 (OH), 1600, 1500, 1110, 1020, 760, 720 and 690 cm^{-1}; NMR ($CDCl_3$) 3·23 (s, 2, CH_2Ph), 4·43 and 4·90 (double d, 2, CH_2O), 4·5 (broad, OH), 6·8–7·5 (m, aromatics). The NMR spectrum also showed the presence of small quantities of benzalphthalan. The product was not purified since it dehydrated on heating or on storage. Conversion to **3** (A = B = H) was effected by adding it to hto EtOH and immediately cooling, giving 50–60% yield of **3** (A = B = H), m.p. 97–102° (becoming yellow); IR (KBr) 1020, 800, 750, 680 cm^{-1}; NMR ($CDCl_3$) 5·45 (s, 2, CH_2), 5·92 (s, 1, =CH), 7·0–7·9 (m, 9, (aromatics). (Found: 86·33; H, 5·69. Calcd. for $C_{13}H_{12}O$: C, 86·51; H, 5·81).

Samples oxidized on exposure to air; storage in sealed tubes under argon has been successfully used to preserve the compound for extended periods.

Reaction between phthalide and t-butylmagnesium chloride

Preparation of α-t-butylphthalyl alcohol **5** (A = B = H). A benzene soln (50 ml) of phthalide (1·34 g, 0·01 m) was treated with 0·03 moles of t-BuMgCl in ether (50 ml) and the mixture refluxed for 24 h. The crude product

(2·01 g) was recrystallized by dissolving in a minimum of warm benzene and adding an equal volume of pet. ether, to give 1·59 g, 82% yield of **5** (A = B = H) m.p. 91·5–93°; IR(KBr) 3260, 2940, 1030, 990, 740 cm^{-1}; NMR ($CDCl_3$) 0·90 (s, 9, $(CH_3)_3C$), 3·02 (s, 2, OHs), 4·42 and 4·70 (doubled d, J = 12 Hz, CH_2) and 4·66 (s, t-BuCH) (total 3), 7·1–7·6 (m, 4, aromatics). (Found: C, 74·11; H, 9·26. Calcd. for $C_{12}H_{18}O_2$: C, 74·19; H, 9·34).

The several variations of this reaction are summarized in Table 1. Analyses are based on the NMR spectra of the crude products. Unreacted phthalide was the only other component detected.

Reaction between 3,3-*dimethylphthalide and benzylmagnesium chloride*

Preparation of 1 - *benzyl* - 1 - *hydroxy* - 3,3 - *dimethylphthalan* (**2**, A = H, B = Me, R = $PhCH_2$) *and* 1-*Benzal* - 3,3 - *dimethylphthalan* (**3**, A = H, B = Me). The product from 3,3-dimethylphthalide (3·1 g, 0·019 m) and benzylmagnesium chloride (0·04 m), **2** (A = H, B = Me, R = $PhCH_2$) (5 g) was dissolved in 25 ml warm benzene, 25 ml pet. ether added and the soln cooled to − 10°. Two repetitions provided an analytical sample, m.p. 94–5°; IR (KBr) 3380, 1230, 1100, 1040, 950, 890, 760, 770 cm^{-1}; NMR ($CDCl_3$) 1·15 (s, 3, CH_3), 1·52 (s, 3, CH_3), 3·07 (s, 1, OH), 3·31 (s, 2, CH_2), 6·8–7·4 (m, 9, aromatics. (Found: C, 80·07; H, 7·11. Calcd. for $C_{17}H_{18}O_2$: C, 80·28; H, 7·13%).

If the crude product in the above experiment is simply stored for 48 h, dehydration occurs spontaneously. Recrystallization from pet. ether gives 1·85 g (41%) of **3**, (A = H, B = Me), m.p. 50–1°; IR (KBr) 2940, 1630, 1580, 1470, 1280, 1080, 1020, 890, 800, 740, 730, 680 cm^{-1}; NMR ($CDCl_3$) 1·64 (s, 6, CH_3), 5·92 (s, 1, vinyl H), 7·1–8·0 (m, 9, aromatics). (Found: C, 86·15; H, 6·80. Calcd. for $C_{17}H_{16}O$: C, 86·40; H, 6·83%).

The results of several experiments using different reaction conditions are summarized in Table 2. Analysis by NMR was performed immediately after isolation. Spontaneous dehydration of the hydroxyphthalan occurred slowly in solution.

Reaction between 3,3-*diphenylphthalide and benzylmagnesium chloride*

Preparation of 1 - *benzyl* - 1 - *hydroxy* - 3,3 - *diphenylphthalan* (**2**, A = H, B = Ph, R = $PhCH_2$) *and* 1 - *benzal* - 3,3 - *diphenylphthalan* (**3**, A = H, B = Ph). The crude product from 1·72 g (0·006 m) of 3,3-diphenylphthalide and 0·012 m of benzylmagnesium chloride was recrystallized from benzene–pet. ether to give 1·38 g (61%) of **2** (A = H, B = Ph, R = $PhCH_2$), m.p. 140° (dec); IR (KBr) 3400 (OH), 1440, 1210, 1080, 1030, 850, 830, 750, 740, 730, 680 cm^{-1}; NMR ($CDCl_3$) 2·85 (s, 1, OH), 3·25 (s, 2, CH_2), 7·0–7·6 (m, 19, aromatics). (Found: C, 85·78; H, 5·63. Calcd. for $C_{27}H_{22}O_2$: C, 85·67; H, 5·86%).

Dehydration was accomplished by warming 0·5 g of **2** (A = H, B = Ph, R = $PhCH_2$) in 20 ml of chloroform containing 0·001 g of toluenesulfonic acid at 40° for 15 min. The soln was washed with dil $NaHCO_3$ aq and water, dried and evaporated. Recrystallization of the residue from pet. ether gave 0·29 g (60%) of **3** (A = H, B = Ph) m 144·5° (decomp.); IR (KBr) 1660, 1550, 1450, 1060, 970, 750, 690 cm^{-1}; NMR ($CDCl_3$), 6·05 (s, 1, vinyl H), 7·2–8·0 (m, 19, aromatics). (Found: C, 90·15; H, 5·46. Calcd. for $C_{27}H_{20}O$: C, 89·97; H, 5·59%).

Reaction between 4,7-*dimethylphthalide and benzylmagnesium chloride*

Preparation of 1 - *benzyl* - 1 - *hydroxy* - 4,7 - *dimethylphthalan* (**2**, A = Me, B = H, R = $PhCH_2$) *and* 1 - *benzal* - 4,7 - *dimethylphthalan* (**3**, A = Me, B = H). The crude product consisted of a mixture of **2** (A = Me, B = H, R = $PhCH_2$) and **3** (A = Me, B = H); the composition from several experiments as determined by NMR is summarized in Table 3.

The crude product (2·4 g) from 1·62 g (0·01 m) of 4,7-dimethylphthalide and benzylmagnesium chloride 0·02 m) was dissolved in a minimum of warm benzene. On adding pet. ether 1·9 g (75%) of **2** (A = Me, B = H, R = $PhCH_2$) m.p. 87–92° (dec); IR (KBr) 3360 (OH), 1530, 1480, 1130, 1050, 870, 840, 820, 700 cm^{-1}; NMR ($CDCl_3$) 1·98 (s, 3, CH_3), 2·49 (s, 3, CH_3), 3·30 (s, 1, OH), 3·32 (s, 2, $PhCH_2$), 4·38 and 4·86 (double d, J = 13 Hz, 2, OCH_2), 6·97 (s, 2) and 7·12 (s, 5) (aromatics). (Found: C, 80·31; H, 7·23. Calcd. for $C_{17}H_{18}O_2$: C, 80·28; H, 7·13).

The **2** (A = Me, B = H, R = $PhCH_2$) (0·30 g, 0·0012 m) was dissolved in 10 ml chloroform, 0·001 g *p*-toluenesulfonic acid added and the soln stirred for 10 min during which time the soln became yellow. After washing with $NaHCO_3$ aq and drying, the soln was evaporated and the crude **3** (A = Me, B = H) twice recrystallized from pet. ether, 0·24 g (83%) m.p. 104° (dec); IR (KBr) 1640, 1500, 1450, 1030, 800, 750, 690 cm^{-1}; NMR ($CDCl_3$) 2·23 (s, 3, CH_3), 2·56 (s, 3, CH_3), (s, 2, CH_2), 5·99 (s, 1, vinyl H), 7·0–8·0 (m, 7, aromatics). (Found: C, 86·60; H, 6·60. Calcd. for $C_{17}H_{16}O$: C, 86·40; H, 6·83%).

Reaction of 4,7-*dimethylphthalide with t-butylmagnesium chloride*

Preparation of 1 - *t* - *butyl* - 1 - *hydroxy* - 4,7 - *dimethylphthalan* (**2**, A = Me, B = H, R = t-Bu). The product from t-BuMgCl (0·03 m) and 1·62 g (0·01 m) of 4,7-dimethylphthalide was a mixture of the unreacted phthalide and the title hydroxyphthalan (NMR analysis). Separation was effected by column chromatography on silica gel using benzene containing 2% EtOAc as the eluting solvent. Unreacted 4,7-dimethylphthalide eluted first (0·57 g, 35%) and was recrystallized from pet. ether, m.p. and mixture m.p. 87–88°. The **2** (A = Me, B = H, R = t-Bu) formed the second fraction (1·12 g, 50%) and was twice recrystallised from pet. ether to give an analytical sample, m.p. 92–93°; IR (KBr) 3410 (OH), 1500–1450 (multiple bands), 1110 (broad), 1030, 1010, 910, 810 cm^{-1}; NMR ($CDCl_3$) 1·00 (s, 9, t-Bu), 2·08 (s, 3, CH_3), 2·45 (S, 3, CH_3), 3·33 (s, 1, OH), 4·64 and 4·91 (double d, J = 13 Hz, 2, CH_2), 7·00 (s, 2, aromatics). (Found: C, 76·51; H, 8·94. Calcd. for $C_{14}H_{20}O_2$: C, 76·32; H, 9·15%).

The results of several experiments are summarized in Table 3.

Reaction of 4,7-*diphenylphthalide with benzylmagnesium chloride*

Preparation of 1 - *benzyl* - 1 - *hydroxy* - 4,7 - *diphenylphthalan* (**2**, A = Ph, B = H, R = $PhCH_2$) *and* 1 - *benzal* - 4,7 - *diphenylphthalan* (**3**, A = Ph, B = H). The crude product (2·4 g) from 1·72 g (0·006 m) of 4,7-diphenylphthalide and 0·012 m benzylmagnesium chloride was recrystallized twice by dissolving in a minimum amount of warm benzene and adding pet. ether to give **2** (A = Ph, B = H, R = $PhCH_2$), 1·19 g (53%) m.p. 80° (dec); IR (KBr) 3350 (OH), 1470, 1140, 1070, 1010, 820, 740,

690 cm^{-1}; NMR ($CDCl_3$) 2·94 (s, 2, $PhCH_2$), 3·05 (s, 1, OH), 4·82 and 5·34 (double d, J = 13 Hz, 2, CH_2O), 7·0–8·0 (m, 17, aromatics). (Found: C, 85·81; H, 5·96. Calcd. for $C_{27}H_{22}O_2$: C, 85·68; H, 5·86%). These results are summarized in Table 3.

The hydroxyphthalan (0·5 g, 0·0013 m) **2** (A=Ph, B=H, R=$PhCH_2$) in 20 ml chloroform was treated with 1 mgm toluenesulfonic acid. After 20 min at room temp, the soln was washed with $NaHCO_3$ aq, dried and evaporated. Recrystallisation of the residue from pet. ether gave 0·41 g (86%) of **3** (A = Ph, B = H) m.p. 130–134° (dec); IR (KBr) 1630, 1460, 1030, 750, 690 cm^{-1}; NMR ($CDCl_3$) 5·30 (s, 1, vinyl H), 5·60 (s, 2, CH_2), 7·0–7·7 (m, 17, aromatics). (Found: C, 89·90; H, 5·59. Calcd. for $C_{27}H_{20}O$: C, 89·97; H, 5·59%).

Preparation of 1,1-*dibenzylphthalan* **8** (A = B = H). α,α-Dibenzylphthalyl alcohol (**4**, A = B = H) (1·06 g, 0·0033 ml) in 30 ml benzene was treated with 0·1 g *p*-toluene-sulfonic acid and the soln refluxed for 10 h. After washing the soln with dil $NaHCO_3$ aq, the soln was evaporated and the residue recrystallized from MeOH to give 0·74 g (74%) of **8** (A = B = H), m.p. 88–90°; NMR ($CDCl_3$) 3·17 (s, 4, $PhCH_2$), 4·53 (s, 2, CH_2O), 6·8–7·3 (m, 14, aromatics).

This procedure failed when applied to α-benzylphthalyl alcohol and 3,6-diphenylphthalyl alcohol.

Preparation of 1-*t-butylphthalan.* The above procedure when applied to α-t-butylphthalyl alcohol (0·30 g, 0·0015 m) required 14 h of reflux to complete the reaction. The crude product was distilled, b.p. 47–53° at 0·2 mm; NMR ($CDCl_3$) 0·97 (s, 9, t-Bu), 4·9–5·2 (m, 3, CH_2 and CH), 7·30 (s, 4, aromatics); IR (neat) 2960, 2860, 1360, 1050, 740 cm^{-1}. (Found: C, 82·00; H, 8·94. Calcd. for $C_{12}H_{16}O$: C, 81·77; H, 9·15%).

Attempted dehydration of α-*benzylphthalyl alcohol.* The α-benzylphthalyl alcohol[16] (0·54 g, 0·0022 m) in 15 ml of benzene was treated with 0·8 g of Zn dust, refluxed and 1 ml conc HCl added dropwise. After 6 h of reflux, the mixture was cooled, filtered, washed with water, dried and evaporated. The residue, 0·34 g (73%) had an NMR and IR spectra identical with that of authentic 2-methyldibenzyl.

Attempted dehydration of 3,6-*diphenylphthalyl alcohol.* The above procedure was repeated with 3,6-diphenylphthalyl alcohol (0·30 g, 0·001 m) giving 0·27 g of crude product. Two recrystallizations from benzene–pet. ether gave 0·07 g (26%) of 2 - methyl - 3,6 - diphenylbenzyl alcohol, m.p. 113–114°; IR (KBr) 3420 (OH), 1600, 1470, 1000 (broad), 820, 760, 700 cm^{-1}; NMR ($CDCl_3$) 1·52 (s, 1, OH), 2·43 (s, 3, CH_3), 4·69 (s, 2, CH_2OH), 7·2–7·6 (m, 12, aromatics). Evaporation of the filtrate and two recrystallizations of the residue from EtOH gave 0·15 g (56%) of 2,3-dimethyl-1,4-diphenylbenzene, m.p. 92·5–93·5°; IR (KBr) 1480, 1400, 1010, 820, 760, 700 cm^{-1}; NMR ($CDCl_3$) 2·25 (s, 6, CH_3), 7·28 (s, 2) and 7·45 (s, 10) (aromatics). (Found: C, 92·84; H, 7·03. Calcd. for $C_{20}H_{18}$: C, 92·98; H, 7·02%).

In a second attempt, the phthalyl alcohol (0·20 g) and 20 ml of 2N H_2SO_4 were refluxed for 12 h. The NMR of the crude product was identical with the starting material and recrystallization provided 50% recovery of the starting 3,6-diphenylphthalyl alcohol.

Reaction between phthalic anhydride and t-butylmagnesium chloride

Preparation of 3-*t-butylphthalide.* Table 4 summarizes the results of several experiments involving phthalic anhydride and t-BuMgCl. Isolation of the reaction products is described below.

The product (2·0 g) from 1·48 g. (0·01 m) of phthalic anhydride and 0·03 m of t-BuMgCl was distilled to give 1·24 g (65%) of b.p. 94–96° at 0·2 mm of 3-t-butylphthalide; IR (neat) 2960, 1480, 1460, 1360, 1050, 740 cm^{-1}; NMR ($CDCl_3$) 0·93 (s, 9, t-Bu), 5·13 (s, 1, CH), 7·5–8·1 (m, 4, aromatics). (Found: C, 75·94; H, 7·31. Calcd. for $C_{12}H_{14}O_2$: C, 75–76; H, 7·42%).

Preparation of 3-*t-butyl*-3-*hydroxyphthalide.* The product from 4·44 g. (0·03 m) of phthalic anhydride and 0·03 m of t-BuMgCl was recrystallized from DEE-hexane to give 2·96 g (48%) of 3 - t - butyl - 3 - hydroxyphthalide m.p. 114–116°. An analytical sample was obtained by chromatographing on silica gel. and eluting with benzene-10% MeOH, m.p. 115·5–116·5°; IR (KBr) 3300 (OH), 1740 (C=O), 1460, 1270, 1120, 900, 750, 690 cm^{-1}; NMR ($CDCl_3$) 1·08 (s, 9, t-Bu), 4·17 (broad s, 1, OH), 7·5–8·0 (m, 4, aromatics). (Found: C, 69·81; H, 6·87. Calcd. for $C_{12}H_{14}O_2$: C, 69·88; H, 6·84%).

Reaction between 3,6-*dimethylphthalic anhydride and t-butylmagnesium chloride*

Preparation of 1 - *t* - *butyl* - 1 - *hydroxy* - 4,7 - *dimethylphthalan* (**2**, A = Me, B = H, R = t-Bu). The product from 1·76 g (0·01 m) of 3,6-dimethylphthalic anhydride and 0·06 m of t-BuMgCl was recrystallized from pet. ether to give 1·21 g (52%) of **2** (A = Me, B = H, R = t-Bu), B=H, R=t-Bu), m.p. 139–140°; IR (KBr) 3400 (OH), 1770 (C=O), 1300 (broad), 1220, 1070 (broad); NMR ($CDCl_3$) 1·03 (s, 9, t-Bu), 2·52 (s, 6, CH_3), 4·00 (s, 1, OH), 7·1–7·5 (m, 2, aromatics). (Found: C, 72·05; H, 7·84. Calcd. for $C_{14}H_{18}O_2$: C, 71·77; H, 7·74%).

Attempts to force the reaction further with excess Grignard reagent failed (see Table 4).

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