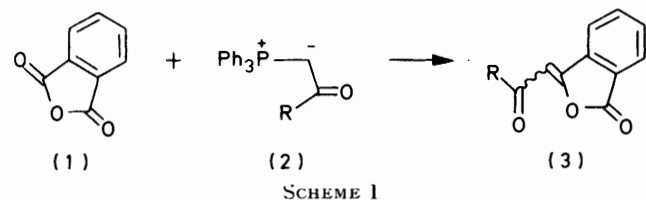


An Investigation of the Wittig Reaction between a Series of Mono-substituted Phthalic Anhydrides and Ethoxycarbonylmethylidetriphenylphosphorane

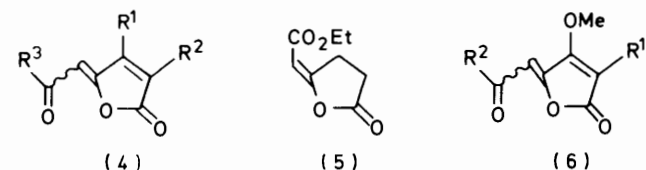
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The title reaction has been investigated using a range of phthalic anhydrides substituted at the 3- or 4-positions with electronically dissimilar functional groups. The structures of the 3-ethoxycarbonylmethylidene-phthalides formed in these reactions have been determined by both chemical and spectroscopic means. The regioselectivity of attack by the phosphorane on an unsymmetrical phthalic anhydride appears to be largely dependent upon the electronic effects of the substituent which render one of the anhydride carbonyls relatively more or less susceptible to nucleophilic attack. In general, (*E*)-ylidene-phthalides are formed predominantly.

THE Wittig reaction between phthalic anhydride (1) and stabilized phosphoranes (2) was first reported in 1965,¹ and shown to be a useful route to the ylidene-phthalides (3) (Scheme 1). Subsequently, it has been found that ylidenebutenolides (4) and the ylidenebutanolide (5) can also be easily obtained by this method using various maleic anhydrides and succinic anhydride respectively.^{2,4}



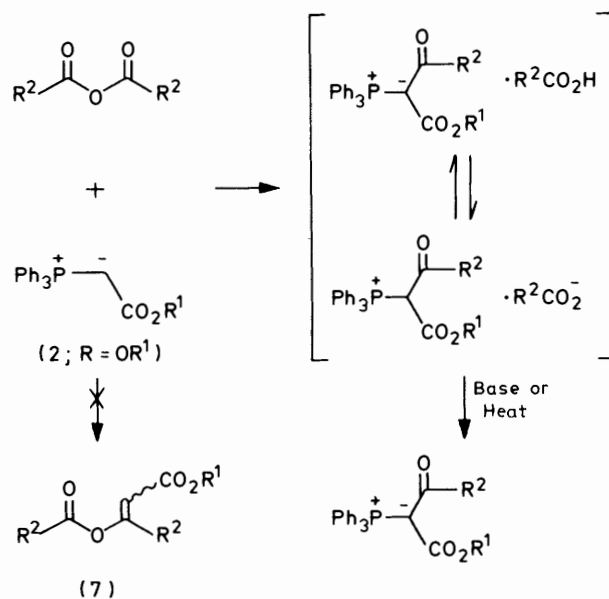
The former reaction has been used to prepare the highly unsaturated sesquiterpene free-lingyne.³ The ylidene-tetronic acid derivatives (6; R¹ = alkyl, aryl) can also be successfully prepared from the corresponding methoxymaleic anhydrides by this method.⁴ A reaction of this type constitutes the key step in a recently



reported⁵ synthesis of methyl multicolanate *O*-methyl ether, (*E*)-(6; R¹ = *n*-pentyl, R² = OMe), the permethylated derivative of a metabolite of *Penicillium multicolor*. Interestingly, reactions between phosphoranes (2; R = OR¹) and acyclic anhydrides result in the formation of acylated phosphoranes rather than the 3-acyloxy-acrylates (7) (Scheme 2), which would be formed if the reaction proceeded in a Wittig manner as in the case of phthalic anhydride *etc.*⁶ Glutaric anhydride also undergoes an acylation rather than a Wittig reaction with phosphoranes (2; R = OR¹),⁶ indicating that the latter mode of reaction only occurs in the case of anhydrides when they are cyclic and five-membered.

Similar Wittig reactions can also be carried out using 5- and 6-membered imides as substrates.⁷

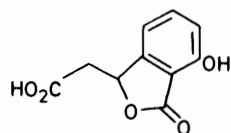
We have recently used the reaction between 3-methoxyphthalic anhydride and phosphorane (2; R = O-CH₂Ph) as the key step in a total synthesis of the fungal



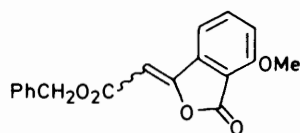
metabolite iso-ochracinic acid (8).⁸ We anticipated both on steric and electronic grounds that the phosphorane would react largely at the 7-carbonyl of the anhydride to provide the ylidene-phthalides (9) required for the synthesis of (8). In the event, the reaction was not regioselective and we obtained the ylidene-phthalides (9; mixture of isomers) and (10) in a ratio of 44 : 56. Since the reasons for this lack of regioselectivity were far from clear, we decided to study the outcome of such reactions with a range of monosubstituted phthalic anhydrides. The results of this work are reported herein.

The Wittig condensations were all carried out by refluxing equivalent amounts of the anhydride and the phosphorane (2; R = OEt), derived from ethyl bromoacetate, in dry chloroform for 18 h. The resulting iso-

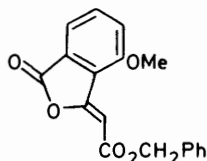
meric ylidene-phthalides, which were formed in 80–85% total yield, were separated by standard chromatographic techniques. We found that the most accurate method for determining the isomeric ratios was by careful ^1H n.m.r. analysis of the crude reaction mixture after removal of the triphenylphosphine oxide by filtration



(8)



(9)

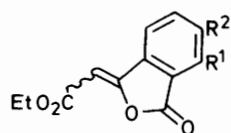


(10)

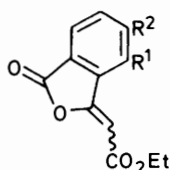
through silica gel eluted with ether. We found the ratios to be reproducible to $\pm 3\%$. The results obtained are presented in the Table. The identity of each isomer was determined by a combination of ^1H n.m.r. data and appropriate hydrogenation experiments as follows. In the 3-substituted phthalic anhydride series, the (*E*)-3-ethoxycarbonylmethylidene-7-substituted phthalides (11a) could be readily identified by the presence, in their ^1H n.m.r. spectra, of a double doublet (J 8 and 2 Hz), shifted downfield by approximately τ 1.0 relative to the other aromatic protons, due to the proximity of the ester carbonyl group. This phenomenon has been used for assignments of structure to compounds of this type on a

TABLE

Products from phthalic anhydrides and phosphorane
(2; R = OEt)



(11)



(12)

a; (*E*)-; $\text{R}^1 = \text{R}; \text{R}^2 = \text{H}$
b; (*Z*)-; $\text{R}^1 = \text{R}; \text{R}^2 = \text{H}$
c; (*E*)-; $\text{R}^1 = \text{H}; \text{R}^2 = \text{R}$
d; (*Z*)-; $\text{R}^1 = \text{H}; \text{R}^2 = \text{R}$

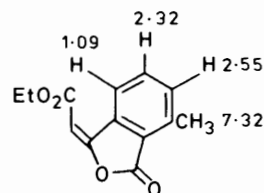
a; (*E*)-; $\text{R}^1 = \text{R}; \text{R}^2 = \text{H}$
b; (*Z*)-; $\text{R}^1 = \text{R}; \text{R}^2 = \text{H}$
c; (*E*)-; $\text{R}^1 = \text{H}; \text{R}^2 = \text{R}$
d; (*Z*)-; $\text{R}^1 = \text{H}; \text{R}^2 = \text{R}$

% Composition

(11a)	(11b)	(12b)	R	(11c)	(11d)	(12c)	(12d)
36	13	51	A; OMe	20	t	61	18
60	40	t?	B; NMe ₂	t	t	65	35
73	23	4	C; CH ₃	29	11*	44	16*
60	—	40	D; CO ₂ Me	58	11	31	—
22	18	60	E; NO ₂	57	5	38	—
43	52	5	F; Cl	34	—	46	20
95	5	—	G; Br	36	5	54	5

t = Trace. * Values only tentative.

number of occasions.^{1,2,9,10} However, we felt that it was essential to establish the correctness of this interpretation and this we have been able to do by using *X*-ray crystallography. The compound chosen for this study was the major product from the reaction between 3-methylphthalic anhydride and phosphorane (2; R = OEt), which was assigned structure (11aC) mainly on the basis of its ^1H n.m.r. spectrum [see data associated with formula (11aC)]. *X*-Ray measurements have confirmed that this compound does indeed possess the (*E*)-con-

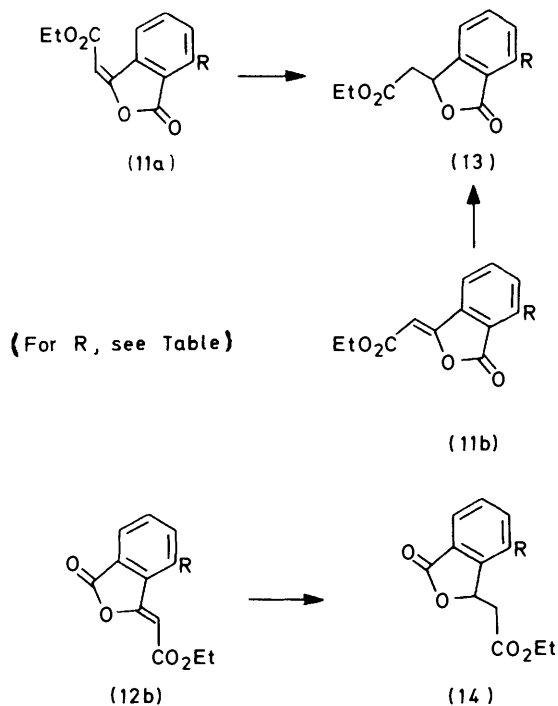


(11aC)

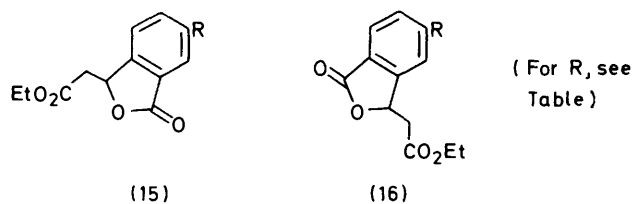
figuration shown.¹¹ There are three other possible products [(11b), (12a), and (12b)] which could be formed from these types of Wittig reaction. We assumed that the other (*E*)-isomer (12a) would not be isolated due to the severe steric interaction between the substituent and the ester group; during this work, no evidence of this type of isomer was found. The two remaining (*Z*)-isomers (11b) and (12b) usually exhibited closely similar spectroscopic and chromatographic characteristics but these could be distinguished by hydrogenation to the corresponding 3-ethoxycarbonylmethylphthalides using 10% Pd on carbon in ethyl acetate. One of these products, (13), was found to be identical with the hydrogenation product arising from the (*E*)-isomer (11a) and was therefore derived from the (*Z*)-3-ethoxycarbonylmethylidene-7-substituted phthalide (11b). Thus the remaining product was (14), derived from the (*Z*)-4-substituted phthalide (12b). In general, the hydrogenation products (13) and (14) were readily distinguished by both spectroscopic and chromatographic methods.

Much the same approach was used in the analysis of the products obtained from the 4-substituted phthalic anhydrides. In these cases, all four possible isomers were often formed, as expected. The two (*E*)-isomers (11c) and (12c) were easily recognised by the occurrence in their ^1H n.m.r. spectra of a low-field doublet with J 8 or 2 Hz respectively. The (*Z*)-isomers (11d) and (12d) were then identified by a combination of the hydrogenation procedure described above, (11c) or (11d) giving the phthalides (15) while (12c) or (12d) gave phthalides (16), together with a comparison of their ^1H n.m.r. spectral data with those of the corresponding (*E*)-isomers (see Experimental section).

The regioselectivity of attack by the phosphorane on the 4-substituted phthalic anhydrides seems to be dependent largely on the electronic effects of the substituent. Electron-donating groups (NMe₂, OMe, Cl, Br, and Me) cause predominant attack at the 2-carbonyl which is *meta* to them. Conversely, the electron-with-



drawing groups (CO_2Me and NO_2) induce attack mainly at the 7-carbonyl. While these results can be explained simply in terms of the relative electron densities of the two carbonyls (*i.e.* their relative electrophilicities) there is good evidence that the Wittig reactions of stabilised phosphoranes [*e.g.* (2)] are reversible¹² and hence it may

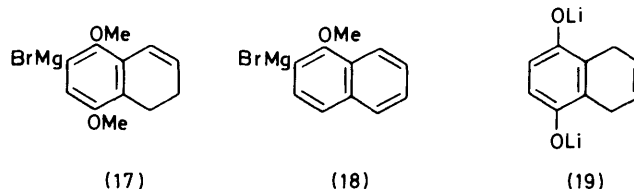


be that the substituents affect the stabilities and rates of decomposition of the intermediate betaines. Further work is needed to establish whether or not the reactions reported herein are reversible or irreversible (*e.g.* by changing the nature of the substituents at phosphorus).

Much the same arguments apply in the 3-substituted series but, in addition, steric factors, quite reasonably, play a significant role, presumably by destabilising the intermediate betaines and interfering with their ability to decompose to the products. When the substituent is NO_2 , or CO_2Me , the electronic factors, however they operate, are sufficiently powerful to overcome the steric constraints.

Complexation between these substituents and the phosphorane phosphorus may help to overcome such steric factors. The total lack of regioselectivity of attack by the phosphorane on 3-methoxyphthalic

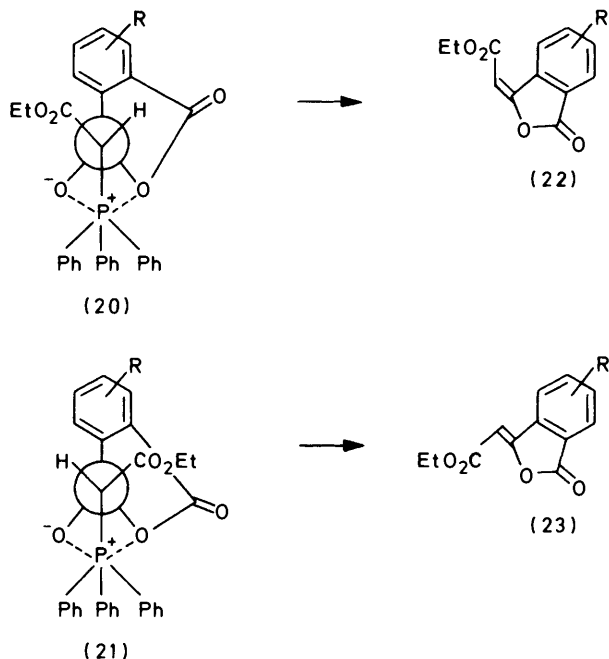
anhydride does not fit into this pattern. By analogy with all of the other results discussed here, predominant attack at the 7-carbonyl would be expected on both electronic and steric grounds, and it seems most likely that, in this case, complexation between the phosphorus and the oxygen of the methoxy-group plays a significant role. The coupling of 3-methoxyphthalic anhydride with a variety of organometallic reagents has been used recently in a number of approaches to anthraquinones and anthracenes.¹³⁻¹⁵ While many of these



reactions are almost totally regioselective, the site of attack seems to be highly dependent on the precise nature of the organometallic species and on the reaction conditions used and it is not yet possible to formulate any rules which could be used to predict the influence of electronic, steric, or complexational effects on such reactions, although it seems highly likely that the latter factor plays a role in some cases. For example, Braun¹³ has reported that the aryl Grignard (17) attacks only the 7-carbonyl of 3-methoxyphthalic anhydride while Swenton's group¹⁴ has found that the closely related reagent (18) adds to this anhydride in a relatively non-regioselective manner (64 : 23 in favour of attack at the 2-carbonyl), and Sih *et al.*¹⁵ have found that the dithiophenolate (19) attacks the 2-carbonyl almost exclusively! A similar combination of factors is needed to explain some earlier work reported by Newman *et al.*, in which 3-methyl-¹⁶ and 3-chlorophthalic anhydride¹⁷ were subjected to both Grignard and Friedel-Crafts reactions. In the former anhydride, steric shielding of the 2-carbonyl seems to be a major factor in these reactions while predictably the electronic effects are much less than in the case of 3-chlorophthalic anhydride which undergoes exclusive attack at the 2-carbonyl in Friedel-Crafts arylations using aluminium trichloride and either benzene or *m*-xylene. Presumably the aluminium trichloride preferentially complexes with the relatively more electron rich 2-carbonyl.

The stereochemical outcome of the reactions reported herein is also of interest. In all cases, with the exception of 3-chlorophthalic anhydride, the (*E*)-isomers are formed predominantly, when they are isolable (*vide supra*). In contrast, the classical Perkin synthesis of ylidene-phthalides (3; $\text{R} = \text{OR}^1$) leads exclusively to the (*Z*)-isomers.¹⁸ This observation together with other work on the preparation of ylidene-phthalides (3; $\text{R} = \text{Ph}$)¹⁰ suggests that the (*Z*)-isomers of these compounds are the more thermodynamically stable. We did not observe any (*E*) \rightarrow (*Z*) isomerisation under the conditions that we have used (*i.e.* reflux in chloroform) to prepare the

ylidenephthalides reported here. The propensity for the formation of (*E*)-isomers in these Wittig reactions has been explained in terms of a complexational effect between the carbonyl of the ester group and the electron-deficient aryl ring of the anhydride.¹ An alternative explanation arises from a consideration of the conformations of the two possible diastereoisomers of the intermediate betaine. If it is assumed that the phosphonium



atom will occupy a position where it is flanked by two oxygen atoms then the two possibilities can be presented as projections (20) and (21) which would lead to the (*E*)- (22) or (*Z*)-ylidenephthalides (23) respectively upon elimination of triphenylphosphine oxide.¹⁹ The diastereoisomer (20) is significantly less sterically congested and would be expected to be formed predominantly if the initial attack by the phosphorane was reversible.¹²

EXPERIMENTAL

General Methods.—Melting points were determined on a Köfeler hot-stage apparatus and are corrected. I.r. spectra were obtained using a Pye-Unicam SP 200G spectrometer and chloroform as solvent. U.v. spectra were measured in methanol using a Pye-Unicam SP 800 spectrometer. ¹H N.m.r. data were obtained using either a Perkin-Elmer R32A (90 MHz) spectrometer or a Jeol MH-100 instrument, with CDCl₃ as solvent and Me₄Si as internal standard. Splittings are in Hz. Mass spectra were determined using an A.E.I. MS 902 spectrometer.

Petroleum refers to light petroleum (b.p. 40–60 °C) and ether to diethyl ether. Dry, ethanol-free chloroform was prepared from reagent grade material by washing the latter with equivalent volumes of water (6×), followed by sequential drying over anhydrous magnesium sulphate and calcium chloride and finally distillation.

High-pressure liquid chromatography was carried out using stainless-steel columns packed with 5μ Partisil, in conjunction with a Waters Associates M-6000 pump and a Cecil CE 272 detector.

Phthalic Anhydrides.—The 3-nitro-, 4-nitro-, and 4-methyl-phthalic anhydrides were commercially available. 4-Chlorophthalic anhydride was obtained from commercially available 4-chlorophthalic acid by crystallisation from hot acetic anhydride. 3-Methoxyphthalic anhydride was prepared by permanganate oxidation of 2,3-dimethylanisole according to the method of Grewe.²⁰ 3-Nitrophthalic anhydride was used as a precursor for the 3-dimethylamino-,²¹ 3-chloro,¹⁷ and 3-bromophthalic anhydrides.²² 3-Methylphthalic anhydride was obtained from the Diels-Alder adduct of 2-methylfuran and maleic anhydride using cold, concentrated sulphuric acid.²³ The 3- and 4-methoxycarbonylphthalic anhydrides were prepared from the corresponding, commercial benzenetricarboxylic acids by recently described procedures.²¹ 4-Methoxyphthalic anhydride was prepared from methyl 3-methoxybenzoate and chloral hydrate.^{24,21} 4-Dimethylaminophthalic anhydride was obtained from 4-nitrophthalimide²⁵ by hydrogenation in the presence of aqueous formaldehyde.²¹ Finally, 4-bromophthalic anhydride was prepared from β-naphthol by sequential bromination and oxidation with potassium permanganate.²²

Reactions between Phthalic Anhydrides and Ethoxycarbonylmethylenetriphenylphosphorane (2; R = OEt); General Procedure.—Equivalent amounts of the phthalic anhydride and ethoxycarbonylmethylenetriphenylphosphorane were dissolved in dry, ethanol-free chloroform (5 ml per 1 mmol of reactant) and the solution gently refluxed for 18 h, and then cooled and evaporated. The residue was filtered through a column of silica gel eluted with ether to remove triphenylphosphine oxide and the resulting pure mixtures of isomeric ylidenephthalides were separated as described below.

As far as possible, isomer ratios were determined by careful ¹H n.m.r. analysis of the product mixture after removal of triphenylphosphine oxide (see Table).

Hydrogenation of 3-Ethoxycarbonylmethylidenephthalides; General Procedure.—A solution of the phthalide (20–50 mg) in ethyl acetate (10–20 ml) containing 10% palladium on carbon catalyst (ca. 5 mg) was shaken under hydrogen (1 atm) until the appropriate volume of hydrogen had been taken up (usually 2–3 h); the mixture was then filtered and the filtrate evaporated.

(*E*)-3-Ethoxycarbonylmethylidenephthalide (11a; R = H).—By the general procedure, reaction between phthalic anhydride (1.48 g) and the phosphorane (3.48 g) gave only one isomer, the (*E*)-phthalide (1.90 g), which crystallised from methanol as colourless needles, m.p. 69–70 °C (lit.,² m.p. 68–70 °C), λ_{max.} 321, 308, 282infl., 272, 237, and 221 nm; ν_{max.} 1 770, 1 695, and 1 640 cm⁻¹; τ 0.94 (dd, *J* 8 and 2, 4-H), 1.91–2.31 (m, 3 H), 3.87 (:CHCO₂Et), 5.68 (q, *J* 7, CH₂CH₃), and 8.66 (t, *J* 7, CH₂CH₃) (Found: C, 66.2; H, 4.7. C₁₂H₁₀O₄ requires C, 66.1; H, 4.6%).

3-Ethoxycarbonylmethylphthalide (13; R = H).—By the general procedure, hydrogenation of 3-ethoxycarbonylmethylidenephthalide (0.05 g) gave the phthalide (0.04 g) which crystallised from petroleum as needles, m.p. 74–75 °C, λ_{max.} 280, 272, and 227 nm; ν_{max.} 1 748 and 1 712 cm⁻¹; τ 2.07 (dd, *J* 8 and ca. 2, 7-H), 2.19–2.57 (m, 3 H), 4.11 (t, *J* 7.5, CHCH₂), 5.78 (q, *J* 7, CH₂CH₃), 7.10 (d, *J* 7.5, CHCH₂), and 8.75 (t, *J* 7, CH₂CH₃); *m/e* 220(2%), 195(100),

167(9), 146(9), 133(8), and 77(30) (Found: C, 65.4; H, 5.5. $C_{12}H_{12}O_4$ requires C, 65.5; H, 5.5%).

Reaction between 3-Methoxyphthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 3-methoxyphthalic anhydride (0.14 g) and the phosphorane (0.27 g) followed by silica-gel chromatography in chloroform gave the following: (i) (*E*)-3-ethoxycarbonylmethylidene-7-methoxyphthalide (11aA) (eluted first) which crystallised from chloroform–benzene as needles, m.p. 119–120 °C, λ_{\max} 343, 288infr., 279, 271infr., 242infr., and 232 nm; ν_{\max} 1778, 1700, and 1646 cm^{-1} ; τ 1.30 (d, J 8, 4-H), 2.20 (t, J 8, 5-H), 2.78 (d, J 8, 6-H), 3.88 (:CHCO₂Et), 5.68 (q, J 7, CH₂CH₃), 5.94 (OMe), and 8.68 (t, J 7, CH₂CH₃); *m/e* 248(20%), 203(40), and 176(100) (Found: C, 62.9; H, 4.7. $C_{13}H_{12}O_5$ requires C, 62.9; H, 4.9%); (ii) (*Z*)-3-ethoxycarbonylmethylidene-4-methoxyphthalide (12bA) (eluted second) which crystallised from chloroform–petroleum as prisms, m.p. 154–155 °C, λ_{\max} 338, 308, 283infr., 273, 236infr., and 227 nm; ν_{\max} 1792, 1710, and 1658 cm^{-1} ; τ 2.36–2.52 (m, 2 H), 2.76 (dd, J 8 and 2), 3.74 (:CHCO₂Et), 5.71 (q, J 7, CH₂CH₃), 5.98 (OMe), and 8.68 (t, J 7, CH₂CH₃); *m/e* 248(9%), 203(36), and 176(100) (Found: C, 62.9; H, 4.9%); and (iii) (*Z*)-3-ethoxycarbonylmethylidene-7-methoxyphthalide (11bA) (eluted last), which crystallised from methanol as needles m.p. 132–133 °C, λ_{\max} 340, 284infr., 276, 270infr., 244infr., and 230 nm; ν_{\max} 1794, 1705, and 1668 cm^{-1} ; τ 2.28 (t, J 8, 5-H), 2.73 (d, J 8), 2.92 (d, J 8), 4.17 (:CHCO₂Et), 5.70 (t, J 7, CH₂CH₃), 5.98 (OMe), and 8.69 (t, J 7, CH₂CH₃); *m/e* 248(14%), 203(53), and 176(100) (Found: C, 62.5; H, 4.6%).

Hydrogenation of Products from 3-Methoxyphthalic Anhydride.—By the general procedure, hydrogenation of (*E*)- or (*Z*)-3-ethoxycarbonylmethylidene-7-methoxyphthalide (11aA) or (11bA) gave 3-ethoxycarbonylmethyl-7-methoxyphthalide (13A), a colourless oil showing λ_{\max} 296 and 234 nm; ν_{\max} 1758 and 1710 cm^{-1} ; τ 2.37 (t, J 8, 5-H), 2.96 (d, J 8), 3.04 (d, J 8), 4.20 (t, J 7.5, CHCH₂), 5.79 (q, J 7, CH₂CH₃), 6.01 (OMe), 7.16 (d, J 7.5, CHCH₂), and 8.75 (t, J 7, CH₂CH₃) (Found: M^+ , 250.0840. $C_{13}H_{14}O_5$ requires M , 250.0841).

By contrast, hydrogenation of (*Z*)-3-ethoxycarbonylmethylidene-4-methoxyphthalide (12bA) gave 3-ethoxycarbonylmethyl-4-methoxyphthalide (14A) as an oil, with λ_{\max} 295 and 232 nm; ν_{\max} 1760 and 1714 cm^{-1} ; τ 2.45–2.52 (m, 2 H), 2.88 (dd, J 8 and 2), 4.11 (dd, J 9 and 4, CHCH₂), 5.83 (q, J 7, CH₂CH₃), 6.09 (OMe), 6.71 (dd, J 16 and 4, CHCH_aH_b), 7.40 (dd, J 16 and 9, CHCH_aH_b), and 8.79 (t, J 7, CH₂CH₃) (Found: M^+ , 250.0846).

Reaction between 3-Dimethylaminophthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 3-dimethylaminophthalic anhydride (0.63 g) and the phosphorane (1.16 g) gave a mixture of two isomers (0.70 g) which were separated by silica-gel chromatography in petroleum–ether (1 : 1) to give the following: (i), (*E*)-7-dimethylamino-3-ethoxycarbonylmethylidene-phthalide (11aB) (eluted first) which crystallised from methanol as fine yellow needles, m.p. 82–83 °C, λ_{\max} 422, 366, and 276 nm; ν_{\max} 1784, 1716, and 1660 cm^{-1} ; τ 1.54 (d, J 8 4-H), 2.46 (t, J 8, 5-H), 3.03 (d, J 8, 6-H), 4.02 (:CHCO₂Et), 5.76 (q, J CH₂CH₃), 6.93 (NMe₂), and 8.70 (t, J 7, CH₂CH₃); *m/e* 261 (91%), 246(33), 216(22), and 188(100) (Found: N, 5.2. $C_{14}H_{15}NO_4$ requires N, 5.4%); and (ii) (*Z*)-7-dimethylamino-3-ethoxycarbonylmethylidene-phthalide (11bB) (eluted second) which crystallised from methanol as yellow prisms partially melting at 82–83 °C (thermal isomerisation?) and com-

pletely at 97–98 °C [mixed m.p. of (*E*)- and (*Z*)-isomers, 69–79 °C], λ_{\max} 420, 368, and 273 nm; ν_{\max} 1781, 1714, and 1665 cm^{-1} ; τ 2.50 (t, J 8, 5-H), 2.96 (d, J 8), 3.10 (d, J 8), 4.23 (:CHCO₂Et), 5.74 (q, J 7, CH₂CH₃), 6.91 (NMe₂), and 8.69 (t, J 7, CH₂CH₃); *m/e* 261(48%), 246(35), 216(17), and 188(100) (Found: C, 64.7; H, 5.5; N, 5.6. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.7; N, 5.4%).

Hydrogenation of the Products from 3-Dimethylaminophthalic Anhydride.—By the general procedure, hydrogenation of either (*E*)-7-dimethylamino-3-ethoxycarbonylmethylidene-phthalide (11aB) or its (*Z*)-isomer (11bB) gave 7-dimethylamino-3-ethoxycarbonylmethylphthalide (13B) as a viscous yellow oil which resisted attempts at crystallisation, and which showed λ_{\max} 326 and 252 nm; ν_{\max} 1756 and 1738 cm^{-1} ; τ 2.57 (t, J 8, 5-H), 3.20 (d, J 8), 3.24 (d, J 8), 4.30 (t, J 7.5, CHCH₂), 5.82 (q, J 7, CH₂CH₃), 6.92 (NMe₂), 7.17 (d, J 7.5 CHCH₂), and 8.73 (t, J 7, CH₂CH₃); *m/e* 263(100%), 248(22), 190(89), 176(60), and 172(25) (Found: M^+ , 263.1142. $C_{14}H_{17}NO_4$ requires M , 263.1157).

Reaction between 3-Methylphthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 3-methylphthalic anhydride (1.62 g) and the phosphorane (3.48 g) gave a mixture of two isomers (1.98 g) which were separated by chromatography over silica gel eluted with petroleum–ether (1 : 1) to give the following: (i) (*E*)-3-ethoxycarbonylmethylidene-7-methylphthalide (11aC) (eluted first) which crystallised from methanol as thick, colourless needles, m.p. 78–79 °C, λ_{\max} 331, 317, 285infr., 275, and 241 nm; ν_{\max} 1768, 1694, and 1637 cm^{-1} ; τ 1.09 (dd, J 8 and 2, 4-H), 2.32 (t, J 8, 5-H), 2.55 (d, J 8, 6-H), 3.91 (:CHCO₂Et), 5.74 (q, J 7, CH₂CH₃), 7.32 (CH₃), and 8.68 (t, J 7, CH₂CH₃); *m/e* 232(33%), 187(100), 186(50), 160(31), and 103(29) (Found: C, 67.2; H, 5.1. $C_{13}H_{12}O_4$ requires C, 67.2; H, 5.2%); and (ii), (*Z*)-3-ethoxycarbonylmethylidene-7-methylphthalide (11bC) which crystallised from methanol as colourless cubes, m.p. 92–93 °C (with softening at 80 °C), λ_{\max} 328, 315, 283infr., 273, and 250 nm; ν_{\max} 1779, 1690, and 1659 cm^{-1} ; τ 2.3–2.6 (m, 3 H), 4.17 (:CHCO₂Et), 5.70 (q, J 7, CH₂CH₃), 7.33 (CH₃), and 8.68 (t, J 7, CH₂CH₃); *m/e* 232(24%), 187(100), 186(41), 160(33), and 103(20) (Found: C, 67.3; H, 5.2%). A trace of a third compound, probably the (*Z*)-4-methyl isomer was also detected [τ 4.09 (:CHCO₂Et) and 7.41 (CH₃)].

3-Ethoxycarbonylmethyl-7-methylphthalide (13C).—Hydrogenation, by the general procedure, of either the (*E*)-7-methylphthalide (11aC) or the (*Z*)-7-methylphthalide (11bC) gave the *phthalide* (13C) as a colourless, viscous oil, λ_{\max} 286, 278, and 230 nm; ν_{\max} 1750 and 1726 cm^{-1} ; τ 2.39–2.83 (m, 3 H), 4.21 (t, J 7.5, CHCH₂), 5.81 (q, J 7, CH₂CH₃), 7.17 (d, J 7.5, CHCH₂), 7.33 (CH₃), and 8.76 (t, J 7, CH₂CH₃) (Found: M^+ , 234.0890. $C_{13}H_{14}O_4$ requires M , 234.0892).

Reaction between 3-Methoxycarbonylphthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 3-methoxycarbonylphthalic anhydride (0.68 g) and the phosphorane (1.16 g) gave a mixture of two isomers (0.78 g) which were separated by silica-gel chromatography in petroleum–ether (3 : 2) to give the following: (i) (*E*)-3-ethoxycarbonylmethylidene-7-methoxycarbonylphthalide (11aD) (eluted first) which crystallised from methanol as fine needles, m.p. 105–106 °C, λ_{\max} 324, 317.5infr., 314, 282, 273, 248, and 226 nm; ν_{\max} 1793, 1720, 1700, and 1652 cm^{-1} ; τ 1.05 (dd, J 8 and 2, 4-H), 2.32–2.49 (m, 2 H), 4.04 (:CHCO₂Et), 5.82 (q, J 7, CH₂CH₃), 6.07 (OMe), and 8.67 (t, J 7, CH₂CH₃); *m/e* 276(23%), 232(11), 231(100), and 204(41)

(Found: C, 60.8; H, 4.5. $C_{14}H_{12}O_6$ requires C, 60.9; H, 4.4%); and (ii) (*Z*)-3-ethoxycarbonylmethylidene-4-methoxycarbonylphthalide (12bD) (eluted second) which crystallised from methanol as fine needles, m.p. 122—123 °C, λ_{\max} 320infr., 308infr., 283, 253infr., and 242 nm; ν_{\max} 1 800, 1 723, 1 699, and 1 658 cm^{-1} ; τ 1.90 (d, *J* 8, 5-H), 2.09 (d, *J* 8, 7-H), 2.51 (t, *J* 8, 6-H), 3.12 (:CHCO₂Et), 5.78 (q, *J* 7, CH₂CH₃), 6.06 (OMe), and 8.67 (t, *J* 7, CH₂CH₃); *m/e* 276(4%), 231(100), and 204(45) (Found: C, 60.7; H, 4.3%).

Hydrogenation of Products from 3-Methoxycarbonylphthalic Anhydride.—Hydrogenation of (*E*)-3-ethoxycarbonylmethylidene-7-methoxycarbonylphthalide (11aD) (50 mg) by the general procedure gave 3-ethoxycarbonylmethyl-7-methoxycarbonylphthalide (13D) (45 mg) as a colourless oil, showing λ_{\max} 282 nm; ν_{\max} 1 778 and 1 734 cm^{-1} ; τ 2.42—2.64 (m, 3 H), 4.30 (t, *J* 7.5, CHCH₂), 5.83 (q, *J* 7, CH₂CH₃), 6.10 (CO₂Me), 7.17 (d, *J* 7.5, CHCH₂), and 8.77 (t, *J* 7, CH₂CH₃); *m/e* 278(14%), 204(69), and 191(100) (Found: M^+ , 278.078. $C_{14}H_{14}O_6$ requires *M*, 278.079).

Hydrogenation of (*Z*)-3-ethoxycarbonylmethylidene-4-methoxycarbonylphthalide (12bD) (28 mg) gave 3-ethoxycarbonylmethyl-4-methoxycarbonylphthalide (14D) (26 mg) as colourless prisms, m.p. 54—55 °C (ether-petroleum), λ_{\max} 290 and 281 nm; ν_{\max} 1 775 and 1 736 cm^{-1} ; τ 2.06 (d, *J* 8, 5-H), 2.27 (d, *J* 8, 7-H), 2.70 (t, *J* 8, 6-H), 4.07 (dd, *J* 7 and 4, CHCH₂), 5.96 (q, *J* 7, CH₂CH₃), 6.08 (CO₂Me), 6.78 (dd, *J* 16.5 and 4, CHCH_aH_b), 7.42 (dd, *J* 16.5 and 7, CH·CH_aH_b), and 8.89 (t, *J* 7, CH₂CH₃); *m/e* 278(2%), 204(81), and 191(100) (Found: C, 60.4; H, 4.9. $C_{14}H_{14}O_6$ requires C, 60.4; H, 5.1%). The two compounds were readily distinguished by t.l.c.; e.g. in hexane-ether (3 : 2). (13D) had R_F 0.09 while (14D) had R_F 0.18.

Reaction between 3-Nitrophthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 3-nitrophthalic anhydride (1.93 g) and the phosphorane (3.48 g), gave a mixture of three isomers (2.1 g). Chromatography of the mixture over silica gel eluted with chloroform gave the following: (i) (*E*)-3-ethoxycarbonylmethylidene-7-nitrophthalide (11aE) (eluted first) which crystallised from methanol as needles, m.p. 105—106 °C, λ_{\max} 321, 304infr., 267infr., and 225 nm; ν_{\max} 1 793, 1 703, and 1 650 cm^{-1} ; τ 0.60 (dd, *J* 8 and 2, 4-H), 1.90—2.10 (m, 2 H), 3.73 (:CHCO₂Et), 5.76 (q, *J* 7, CH₂CH₃), and 8.71 (t, *J* 7, CH₂CH₃); *m/e* 263(35%), 219(27), and 218(100) (Found: C, 54.7; H, 3.9; N, 5.4. $C_{12}H_9NO_6$ requires C, 54.8; H, 3.4; N, 5.3%); (ii) (*Z*)-3-ethoxycarbonylmethylidene-4-nitrophthalide (12bE) (eluted last), which crystallised from methanol or ethyl acetate as prisms, m.p. 134—135 °C, λ_{\max} 320.5, 286infr., 256, and 222 nm; ν_{\max} 1 792, 1 709, and 1 649 cm^{-1} ; τ 1.58 (d, *J* 8), 1.70 (d, *J* 8), 2.11 (t, *J* 8), 3.38 (:CHCO₂Et), 5.69 (q, *J* 7, CH₂CH₃), and 8.67 (t, *J* 7, CH₂CH₃); *m/e* 263(25%), 219(19), and 218(100) (Found: C, 54.6; H, 3.5; N, 5.1%); and (iii) a mixture of (11aE) and (*Z*)-3-ethoxycarbonylmethylidene-7-nitrophthalide (11bE) (eluted second) which was not further separated; (11bE) showed a characteristic resonance at τ 3.60 (:CHCO₂Et).

The (*Z*)-4-nitrophthalide (12bE) was also partly separated from the mixture of isomers by fractional crystallisation with ethyl acetate.

Hydrogenation of the Products from 3-Nitrophthalic Anhydride.—By the general procedure, hydrogenation of (*E*)-3-ethoxycarbonylmethylidene-7-nitrophthalide (11aE) or a mixture of (11aE) and its (*Z*)-isomer (11bE) [see (iii) above] resulted in reduction of the nitro-group as well as the

exocyclic double-bond and gave 7-amino-3-ethoxycarbonylmethylphthalide (13; R = NH₂) as a viscous oil showing ν_{\max} 3 370, 1 738, and 1 710 cm^{-1} ; τ 2.58—2.79 (m, 2 H), 3.39 (dd, *J* 8 and 2), 4.24 (t, *J* 7, CHCH₂), 5.82 (q, *J* 7, CH₂CH₃), 7.20 (d, *J* 7, CHCH₂), and 8.76 (t, *J* 7, CH₂CH₃) (Found: M^+ , 235.0838. $C_{12}H_{13}NO_4$ requires *M*, 235.0845).

Similar reduction of the (*Z*)-4-nitrophthalide (12bE) gave 4-amino-3-ethoxycarbonylmethylphthalide (14; R = NH₂) as yellow needles, m.p. 134—135 °C (EtOH), λ_{\max} 392 and 321 nm; ν_{\max} 3 400, 1 752, and 1 718 cm^{-1} ; τ 2.48—2.68 (m, 2 H), 3.01 (m, 1 H), 4.06 (apparent, *J* 7, CHCH₂), 5.74 (q, *J* 7, CH₂CH₃), 6.87 (dd, *J* 17 and 6, CH·CH_aH_b), 7.20 (dd, *J* 17 and 7, CHCH_aH_b), and 8.74 (t, *J* 7, CH₂CH₃); *m/e* 235(42%), 161(65), 148(100), and 120(17) (Found: C, 61.7; H, 5.5; N, 5.9. $C_{12}H_{13}NO_4$ requires C, 61.3; H, 5.5; N, 6.0%).

Reaction between 3-Chlorophthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 3-chlorophthalic anhydride (0.91 g) and the phosphorane (1.74 g) gave a mixture of two isomers (1.1 g) which were separated by silica-gel chromatography in petroleum-ether (2 : 3) to give the following: (i) (*E*)-7-chloro-3-ethoxycarbonylmethylidene-phthalide (11aF) (eluted first) which crystallised from methanol as needles, m.p. 116—117 °C, λ_{\max} 336, 321.5, 283infr., 275, and 228 nm; ν_{\max} 1 790, 1 710, and 1 658 cm^{-1} ; τ 1.02 (dd, *J* 8 and 2, 4-H), 2.20—2.45 (m, 2 H), 3.87 (:CHCO₂Et), 5.74 (q, *J* 7, CH₂CH₃), and 8.68 (t, *J* 7, CH₂CH₃); *m/e* 254(4%), 252(13), 209(24), 207(100), 180(36), and 123(16) (Found: C, 57.0; H, 3.6. $C_{12}H_9ClO_4$ requires C, 57.0; H, 3.6%); and (ii) (*Z*)-7-chloro-3-ethoxycarbonylmethylidene-phthalide (11bF) which crystallised from ethanol as needles, m.p. 121—122 °C, λ_{\max} 323.5, 292, 265, 256.5, and 233 nm; ν_{\max} 1 800, 1 710, and 1 662 cm^{-1} ; τ 2.10 (dd, *J* 8 and 2), 2.38—2.55 (m, 2 H), 3.41 (:CHCO₂Et), 5.71 (q, *J* 7, CH₂CH₃), and 8.68 (t, *J* 7, CH₂CH₃); *m/e* 254(2%), 252(6), 209(23), 207(100), 180(32), and 123(25) (Found: C, and 56.9; H, 3.7%).

A small amount of a third isomer (*Z*)-4-chloro-3-ethoxycarbonylmethylidene-phthalide (12bF) was also detected, τ 2.30—2.36 (bs, 3 H), 4.10 (:CHCO₂Ft), 5.68 (q, *J* 7 CH₂CH₃), and 8.66 (t, *J* 7, CH₂CH₃); *m/e* 254(6%), 252(20), 209(20), and 207(100).

Hydrogenation of the Products from 3-Chlorophthalic Anhydride.—By the general procedure, hydrogenation of either (*E*)- or (*Z*)-7-chloro-3-ethoxycarbonylmethylidene-phthalide [(11aF) or (11bF)] gave 7-chloro-3-ethoxycarbonylmethylphthalide (13F), as colourless needles (from petroleum-ether), m.p. 160—161 °C, λ_{\max} 279.5, and 272 nm; ν_{\max} 1 759 and 1 727 cm^{-1} ; τ 2.08 (dd, *J* 8 and 2), 2.28—2.58 (m, 2 H), 4.12 (t, *J* 7.5, CHCH₂), 5.79 (q, *J* 7, CH₂CH₃), 7.12 (d, *J* 7.5, CHCH₂), and 8.74 (t, *J* 7, CH₂CH₃); *m/e* 256(<1%), 254(1), 182(11), 180(31), 169(7), 167(26), and 146(100) (Found: M^+ , 254.031; $C_{12}H_{11}^{35}ClO_4$ requires *M*, 254.035) (Found: C, 56.7; H, 4.0. $C_{12}H_{11}ClO_4$ requires C, 56.6; H, 4.3%).

(*E*)-7-Bromo-3-ethoxycarbonylmethylidene-phthalide (11aG).—By the general procedure, reaction between 3-bromophthalic anhydride (0.23 g) and the phosphorane (0.35 g) followed by crystallisation of the product from methanol gave the phthalide (11aG) (0.2 g) as prisms, m.p. 107—108 °C, λ_{\max} 334, 321, 282infr., 274, and 230 nm; ν_{\max} 1 781, 1 700, and 1 640 cm^{-1} ; τ 0.97 (dd, *J* 8, and 2, 4-H), 2.1—2.4 (m, 2 H), 3.91 (:CHCO₂Et), 5.77 (q, *J* 7, CHCH₂), and 8.70 (t, *J* 7, CH₂CH₃); *m/e* 298(31%), 296(33), 270(15), 268(16), 253(98), 251(100), 226(57), and 224(65) (Found: C, 48.8; H, 3.1. $C_{12}H_9BrO_4$ requires C, 48.5; H, 3.0%).

Reaction between 4-Methoxyphthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 4-methoxyphthalic anhydride (0.09 g) and the phosphorane (0.174 g) gave a mixture of three isomers (0.11 g). Chromatography over silica gel eluted with petroleum-ether (1 : 1) gave the following: (i) (*E*)-3-ethoxycarbonylmethylidene-5-methoxyphthalide (12cA) (eluted first) which crystallised from methanol as plates, m.p. 112–113 °C, λ_{\max} 327, 295, 274infr., 265, and 241 nm; ν_{\max} 1 786, 1 706, and 1 650 cm^{-1} ; τ 1.39 (d, *J* 2, 4-H), 2.17 (d, *J* 8, 7-H), 2.83 (dd, *J* 8 and 2, 6-H), 3.91 (:CHCO₂Et), 5.74 (q, *J* 7, CH₂CH₃), 6.06 (OMe), and 8.68 (t, *J* 7, CH₂CH₃); *m/e* 248(12%), 220(9), 203(58), and 176(100) (Found: C, 62.8; H, 4.8. C₁₃H₁₂O₅ requires C, 62.9; H, 4.9%); (ii) (*Z*)-3-ethoxycarbonylmethylidene-5-methoxyphthalide (12dA) (eluted last) which crystallised from methanol as thick needles, m.p. 146–147 °C, λ_{\max} 320infr., 292, 271infr., 263, and 224 nm; ν_{\max} 1 794, 1 704, and 1 665 cm^{-1} ; τ 2.16 (d, *J* 8, 7-H), 2.80 (dd, *J* 8 and 2, 6-H), 2.86 (d, *J* 2, 4-H), 4.19 (:CHCO₂Et), 5.71 (q, *J* 7, CH₂CH₃), 6.08 (OMe), and 8.69 (t, *J* 7, CH₂CH₃); *m/e* 248(12%), 220(8), 203(60), and 176(100) (Found: C, 62.7; H, 4.7%); and (iii) a mixture of (12cA) and (*E*)-3-ethoxycarbonylmethylidene-6-methoxyphthalide (11cA) (eluted second); the latter showed τ 1.06 (d, *J* 8, 4-H), 2.63 (d, *J* 2, 7-H), 2.66 (dd, *J* 8 and 2, 5-H), and 3.99 (:CHCO₂Et). A very small trace of a fourth compound probably the (*Z*)-6-methoxyisomer (11dA), was also detected [τ 4.26 (:CHCO₂Et)].

3-Ethoxycarbonylmethyl-5-methoxyphthalide (16A).—By the general procedure, hydrogenation of either (*E*)- or (*Z*)-3-ethoxycarbonylmethylidene-5-methoxyphthalide [(12cA) or (12dA)] gave the *phthalide* (16A), λ_{\max} 284, 255, 247, and 220 nm; ν_{\max} 1 740 and 1 718 cm^{-1} ; τ 2.18 (d, *J* 8, 7-H), 2.95 (dd, *J* 8 and 2, 6-H), 3.07 (d, *J* 2, 4-H), 4.19 (t, *J* 7, CHCH₂), 5.77 (q, *J* 7, CH₂CH₃), 6.11 (OMe), 7.13 (dd, *J* 7 and 2, CHCH₂), and 8.72 (t, *J* 7, CH₂CH₃) (Found: *M*⁺, 250.0836. C₁₃H₁₄O₅ requires *M*, 250.0841).

Reaction between 4-Dimethylaminophthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 4-dimethylaminophthalic anhydride (0.24 g) and the phosphorane (0.44 g) gave a mixture of mainly two isomers (0.28 g) which were separated by silica-gel chromatography in petroleum-ether (1 : 2), to give the following: (i) (*E*)-5-dimethylamino-3-ethoxycarbonylmethylidene-*phthalide* (12cB) (eluted first) which crystallised from ethanol as fine yellow needles, m.p. 138–139 °C; λ_{\max} 398, 307infr., and 291.5 nm; ν_{\max} 1 766, 1 699, and 1 645 cm^{-1} ; τ 1.80 (d, *J* 2, 4-H), 2.43 (d, *J* 8, 7-H), 3.29 (dd, *J* 8 and 2, 6-H), 4.09 (:CHCO₂Et), 5.78 (q, *J* 7, CH₂CH₃), 6.88 (NMe₂), and 8.67 (t, *J* 7, CH₂CH₃); *m/e* 261(100%), 216(29), 189(77), and 188(22) (Found: C, 64.5; H, 5.6. C₁₄H₁₅NO₄ requires C, 64.4; H, 5.7%); and (ii) (*Z*)-5-dimethylamino-3-ethoxycarbonylmethylidene-*phthalide* (12dB) (eluted second) which crystallised from methanol as yellow prisms, m.p. 162–163 °C, λ_{\max} 386, 317.5infr., 305infr., and 290 nm; ν_{\max} 1 784, 1 691, and 1 667 cm^{-1} ; τ 2.35 (d, *J* 8, 7-H), 3.20 (dd, *J* 8 and 2, 6-H), 3.30 (d, *J* 2, 4-H), 4.26 (:CHCO₂Et), 5.74 (q, *J* 7, CH₂CH₃), 6.84 (NMe₂), and 8.65 (t, *J* 7, CH₂CH₃); *m/e* 261(100%), 216(39), 189(77), and 188(31) (Found: C, 64.6; H, 5.8%).

Small traces (<5%) of the (*E*)- and (*Z*)-6-dimethylaminoisomers [(11cB) and (11dB)] were also detected [τ 2.32 (d, *J* 8, 4-H) and 4.38 (:CHCO₂Et) respectively].

Hydrogenation of the Products from 4-Dimethylaminophthalic Anhydride.—By the general procedure, hydrogenation of either (*E*)- or (*Z*)-5-dimethylamino-3-ethoxycar-

bonylmethylidene-*phthalide* [(12cB) or (12dB)] gave 5-dimethylamino-3-ethoxycarbonylmethyl-*phthalide* (16B) which crystallised from ether-cyclohexane as prisms, m.p. 67–68 °C, λ_{\max} 312 and 298infr. nm; ν_{\max} 1 752 and 1 740 cm^{-1} ; τ 2.45 (d, *J* 8, 7-H), 3.37 (dd, *J* 8 and 2, 6-H), 3.58 (d, *J* 2, 4-H), 4.39 (t, *J* 7.5, CHCH₂), 5.88 (q, *J* 7, CH₂CH₃), 7.00 (NMe₂), 7.24 (d, *J* 7.5, CHCH₂), and 8.77 (t, *J* 7, CH₂CH₃); *m/e* 263(97%), 190(30), 189(59), 176(100), and 148(25) (Found: C, 64.1; H, 6.5. C₁₄H₁₇NO₄ requires C, 63.9; H, 6.5%).

Reaction between 4-Methylphthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 4-methylphthalic anhydride (1.62 g) and the phosphorane (3.48 g) gave a mixture of all four possible isomers (2.01 g), chromatography of which over silica gel eluted with ether-petroleum (2 : 3) resulted in the complete resolution of the (*E*)-isomers from the (*Z*) isomers but only gave a partial separation of the individual components. Crystallisation of one fraction from methanol gave a sample of pure (*E*)-3-ethoxycarbonylmethylidene-6-methyl-*phthalide* (11cC), as fine, colourless needles, m.p. 119–120 °C, λ_{\max} 325.5, 313.5, 286, 276, and 240 nm; ν_{\max} 1 790, 1 704, and 1 652 cm^{-1} ; τ 1.05 (d, *J* 8, 4-H), 2.14 (d, *J* 2, 7-H), 2.36 (dd, *J* 8 and 2, 5-H), 3.92 (:CHCO₂Et), 5.68 (q, *J* 7, CH₂CH₃), 7.49 (CH₃), and 8.66 (t, *J* 7, CH₂CH₃); *m/e* 232(27%), 204(9), 187(100), and 160(58) (Found: C, 67.3; H, 5.2. C₁₃H₁₂O₄ requires C, 67.3; H, 5.2%). The remaining mixtures were not further separated.

Reaction between 4-Methoxycarbonylphthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 4-methoxycarbonylphthalic anhydride (1.03 g) and the phosphorane (1.74 g) gave a mixture of three isomers (1.2 g) which were separated by chromatography over silica gel eluted with petroleum-ether (1 : 1) to give the following: (i) (*E*)-3-ethoxycarbonylmethylidene-6-methoxycarbonyl-*phthalide* (11cD) (eluted first) which crystallised from ethanol as prisms, m.p. 136–137 °C, λ_{\max} 335, 323, 284, 274, 254, and 231 nm; ν_{\max} 1 791, 1 720, 1 703, and 1 658 cm^{-1} ; τ 0.88 (d, *J* 8, 4-H), 1.42 (d, *J* 2, 7-H), 1.57 (dd, *J* 8, and 2, 5-H), 3.81 (:CHCO₂Et), 5.71 (q, *J* 7, CH₂CH₃), 6.05 (OMe), and 8.70 (t, *J* 7, CH₂CH₃); *m/e* 276(21%), 248(16), 245(12), 232(16), 231(100), and 204(60) (Found: C, 61.1; H, 4.1. C₁₄H₁₂O₆ requires C, 60.9; H, 4.4%); (ii) (*E*)-3-ethoxycarbonylmethylidene-5-methoxycarbonyl-*phthalide* (12cD) (eluted second), which crystallised from methanol as prisms, m.p. 119–120 °C, λ_{\max} 326.5, 313.5, 294, 283, 274infr., and 232 nm; ν_{\max} 1 796, 1 722, 1 705, and 1 660 cm^{-1} ; τ 0.35 (d, *J* 2, 4-H), 1.65 (dd, *J* 8 and 2, 6-H), 1.97 (d, *J* 8, 7-H), 3.83 (:CHCO₂Et), 5.69 (q, *J* 7, CH₂CH₃), 6.03 (OMe), and 8.69 (t, *J* 7, CH₂CH₃); *m/e* 276(23%), 248(18), 245(10), 232(16), 231(100), and 204(65) (Found: C, 60.9; H, 4.2%); and (iii) (*Z*)-3-ethoxycarbonylmethylidene-6-methoxycarbonyl-*phthalide* (11dD) (eluted last), which showed λ_{\max} 324, 310, 292, 283, and 234 nm; ν_{\max} 1 791, 1 722, 1 705, and 1 660 cm^{-1} ; τ 1.38 (d, *J* 2, 7-H), 1.55 (dd, *J* 8, and 2, 5-H), 2.16 (d, *J* 8, 4-H), 4.04 (:CHCO₂Et), 5.68 (q, *J* 7, CH₂CH₃), 6.03 (OMe), and 8.68 (t, *J* 7, CH₂CH₃); *m/e* 276(70%), 232(20), 231(100), and 204(90) (Found: *M*⁺, 276.0639. C₁₄H₁₂O₆ requires *M*, 276.0634).

Reaction between 4-Nitrophthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 4-nitrophthalic anhydride (0.193 g) and the phosphorane (0.348 g) gave a mixture of three isomers which were separated by high-pressure liquid chromatography using chloroform-cyclohexane (1 : 1) as eluant to give the following: (i) (*E*)-3-ethoxycarbonylmethylidene-6-nitro-*phthalide* (11cE) (eluted first) which crystallised from ethanol as

needles, m.p. 111—112 °C, λ_{\max} 325, 308, 286, 256, and 224 nm; ν_{\max} 1 793, 1 710, and 1 660 cm^{-1} ; τ 0.72 (d, J 8, 4-H), 1.28 (d, J 2, 7-H), 1.38 (dd, J 8 and 2, 5-H), 3.70 (:CHCO₂Et), 5.67 (q, J 7, CH₂CH₃), and 8.63 (t, J 7, CH₂CH₃); *m/e* 263(3%), 234(32), 218(100), 191(94), and 172(91) (Found: C, 54.7; H, 3.5; N, 5.4. C₁₂H₉NO₆ requires C, 54.8; H, 3.4; N, 5.3%); (ii) (E)-3-ethoxycarbonylmethylidene-5-nitrophthalide (12cE) (eluted second) which crystallised from benzene-chloroform as prisms, m.p. 96—97 °C, λ_{\max} 327, 310, 290, 255, and 221 nm; ν_{\max} 1 791, 1 702, and 1 647 cm^{-1} ; τ 0.11 (d, J 2, 4-H), 1.47 (dd, J 8, and 2, 6-H), 1.86 (d, J 8, 7-H), 3.74 (:CHCO₂Et), 5.65 (q, J 7, CH₂CH₃), and 8.63 (t, J 7, CH₂CH₃); *m/e* 263(34%), 234(15), 218(100), 191(47), and 172(65) (Found: C, 54.4; H, 3.6; N, 5.0%); and (iii) (Z)-3-ethoxycarbonylmethylidene-6-nitrophthalide (11dE) (eluted last) which showed ν_{\max} 1 790, 1 709, and 1 658 cm^{-1} ; τ 1.20 (d, J 2, 7-H), 1.36 (dd, J 8 and 2, 5-H), 2.08 (d, J 8, 4-H), 3.86 (:CHCO₂Et), 5.65 (q, J 7, CH₂CH₃), and 8.62 (t, J 7, CH₂CH₃) (Found: *M*⁺, 263.0419. C₁₂H₉NO₆ requires *M*, 263.0430).

Reaction between 4-Chlorophthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 4-chlorophthalic anhydride (1.83 g) and the phosphorane (3.48 g) gave a mixture of three isomers (2.0 g). Chromatography over silica gel eluted with n-hexane-ether (9 : 1) gave (i) (E)-6-chloro-3-ethoxycarbonylmethylidene-phthalide (11cF) (eluted first), which crystallised from methanol as soft plates, m.p. 111—113 °C; λ_{\max} 325, 313.5, 285infr., and 275 nm; ν_{\max} 1 788, 1 705, and 1 652 cm^{-1} ; τ 1.31 (d, J 8, 4-H), 2.38 (d, J 2, 7-H), 2.55 (dd, J 8 and 2, 5-H), 4.06 (:CHCO₂Et), 5.85 (q, J 7, CH₂CH₃), and 8.66 (t, J 7, CH₂CH₃); *m/e* 254(3%), 252(18), 226(2), 224(9), 209(31), 207(100), 182(15), and 180(52) (Found: C, 56.7; H, 3.5. C₁₂H₉ClO₄ requires C, 57.0; H, 3.6%); (ii) (E)-5-chloro-3-ethoxycarbonylmethylidene-phthalide (12cF) (eluted second), which crystallised from methanol as needles, m.p. 120—121 °C, λ_{\max} 323, 310, 286infr., and 278 nm; ν_{\max} 1 794, 1 711, and 1 660 cm^{-1} ; τ 1.25 (d, J 2, 4-H), 2.38 (d, J 8, 7-H), 2.61 (dd, J 8 and 2, 6-H), 4.05 (:CHCO₂Et), 5.84 (q, J 7, CH₂CH₃), and 8.66 (t, J 7, CH₂CH₃); *m/e* 254(4%), 252(19), 226(2), 224(10), 209(30), 207(100), 182(16), and 180(52) (Found: C, 57.0; H, 3.4%); and (iii) (Z)-5-chloro-3-ethoxycarbonylmethylidene-phthalide (12dF) (eluted last) which crystallised from methanol as needles, m.p. 110—111 °C, λ_{\max} 321.5, 310, 284infr., and 276 nm; ν_{\max} 1 804, 1 719, and 1 666 cm^{-1} ; τ 2.36 (d, J 8, 7-H), 2.54 (d, J 2, 4-H), 2.62 (dd, J 8 and 2, 6-H), 4.31 (:CHCO₂Et), 5.83 (q, J 7, CH₂CH₃), and 8.68 (t, J 7, CH₂CH₃); *m/e* 254(2%), 252(5), 209(14), 207(100), 182(9), and 180(50) (Found: C, 57.4; H, 3.4%).

Hydrogenation of the Products from 4-Chlorophthalic Anhydride.—By the general procedure, hydrogenation of (E)-6-chloro-3-ethoxycarbonylmethylidene-phthalide (11cF) (21 mg) over 10% Pd-C gave the expected 6-chloro-3-ethoxycarbonylmethylphthalide (15F) (17 mg) which recrystallised from n-hexane-ether (ca. 10 : 1) as clusters of thick, colourless needles, m.p. 95—96 °C, λ_{\max} 291, 283, and 278infr. nm; ν_{\max} 1 764 and 1 727 cm^{-1} ; τ 2.18 (d, J 2, 7-H), 2.40 (dd, J 8, and 2, 5-H), 2.58 (d, J 8, 4-H), 4.18 (t, J 7.5, CHCH₂), 5.82 (q, J 7, CH₂CH₃), 7.11 (bd, J 7.5, CHCH₂), and 8.73 (t, J 7, CH₂CH₃); *m/e* 256(6%), 254(17), 182(35), 180(100), 169(19), 167(73), and 146(22) (Found: C, 56.1; H, 4.0. C₁₂H₁₁ClO₄ requires C, 56.6; H, 4.3%) (Found: *M*⁺, 254.033. C₁₂H₁₁³⁵ClO₄ requires *M*, 254.035).

Hydrogenation of either (E)- or (Z)-5-chloro-3-ethoxycarbonylmethylidene-phthalide [(12cF) or (12dF)] gave 5-

chloro-3-ethoxycarbonylmethylphthalide (16F) which crystallised from petroleum-ether as small, colourless needles, m.p. 105—106 °C, λ_{\max} 291.5infr., 283, and 275.5 nm; ν_{\max} 1 766 and 1 730 cm^{-1} ; τ 2.10 (d, J 8, 7-H), 2.26 (dd, J 8 and 2, 6-H), 2.45 (d, J 2, 4-H), 4.16 (t, J 7.5, CHCH₂), 5.78 (q, J 7, CH₂CH₃), 7.09 (d, J 7.5, CHCH₂), and 8.71 (t, J 7, CH₂CH₃); *m/e* 256(8%), 254(60), 182(36), 180(100), 169(16), 167(61), and 146(47) (Found: C, 56.4; H, 4.2%).

Reaction between 4-Bromophthalic Anhydride and the Phosphorane.—By the general procedure, reaction between 4-bromophthalic anhydride (0.23 g) and the phosphorane (0.35 g) gave a mixture of two isomers (0.24 g) which were separated by h.p.l.c. using chloroform-petroleum (1 : 19) as eluant to give the following (i) (E)-6-bromo-3-ethoxycarbonylmethylidene-phthalide (11cG) (eluted first) which crystallised from methanol as needles, m.p. 114—115 °C, λ_{\max} 326, 312, 287infr., 277infr., 265infr., 238infr., and 217 nm; ν_{\max} 1 778, 1 700, and 1 642 cm^{-1} ; τ 1.06 (d, J 8, 4-H), 1.93 (d, J 2, 7-H), 2.08 (dd, J 8 and 2, 5-H), 3.86 (CH:CO₂Et), 5.70 (q, J 7, CH₂CH₃), and 8.64 (t, J 7, CH₂CH₃); *m/e* 298(25%), 296(25), 254(23), 253(100), 252(25), 251(100), 226(70), and 224(71) (Found: C, 48.3; H, 2.8. C₁₂H₉BrO₄ requires C, 48.5; H, 3.0%); and (ii) (E)-5-bromo-3-ethoxycarbonylmethylidene-phthalide (12cG), which crystallised from methanol as needles, m.p. 140—141 °C, λ_{\max} 324, 311, 288infr., 277, 253infr., 234, and 207nm; ν_{\max} 1 780, 1 698, and 1 644 cm^{-1} ; τ 0.78 (4-H), 2.20 (6- and 7-H), 3.86 (:CHCO₂Et), 5.68 (q, J 7, CH₂CH₃), and 8.64 (t, J 7, CH₂CH₃); *m/e* 298(32%), 296(32), 254(18), 253(100), 252(27), 251(100), 226(69), and 224(72) (Found: C, 48.4; H, 3.0%). Traces of the two possible (Z) isomers were also detected, τ 3.99 (:CHCO₂Et) and 4.03 (:CHCO₂Et).

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