Hydrogenation of Substituted Phthalic Anhydrides over Palladium

By **Alan J. McAlees, Robert McCrindle,*** and **David W. Sneddon**, Guelph-Waterloo Centre for Graduate Work in Chemistry, Guelph Campus, Department of Chemistry, University of Guelph, Guelph, Ontario, Canada

Catalytic hydrogenation of phthalic anhydride in ethyl acetate over 10% palladium–carbon gives *o*-toluic acid. Under similar conditions 3- and 4-substituted phthalic anhydrides give phthalides (8), and/or 2-(hydroxymethyl)benzoic acids (7) in addition to *o*-toluic acids (9). Mechanisms of formation of these products are discussed.

We have previously proposed [1] that the hydrogenation of cyclic anhydrides and *N*-acyl (or N-alkoxycarbonyl) imides over platinum involves nucleophilic attack by the catalyst on a carbonyl carbon atom (see Scheme 1). The stereochemistry of the products obtained is consistent with this mechanism. In the course of this work,[1] we observed that *N*-acyl- and *N*-alkoxycarbonyl-phthalimides (1a and b) are reduced to the corresponding 3-hydroxyisoindolin-1-ones (2a and b) over 10% palladium–charcoal. Subsequent studies have shown [2] that phthalimide and *N*-methylphthalimide (1c and d) resist hydrogenation under the latter conditions. These results are consistent with a mechanism for hydrogenation over palladium analogous to that proposed for platinum, the presence of an electron-withdrawing substituent on nitrogen being necessary to facilitate the initial nucleophilic attack of catalyst and resulting ring opening. We have now subjected a series of substituted phthalic anhydrides to hydrogenation over palladium (10% on carbon) in order to determine if attack on one carbonyl group in these derivatives is preferred and whether or not any such preference would be predictable on the basis of the anticipated effects of the substituents, assuming a mechanism similar to that outlined in Scheme 1.

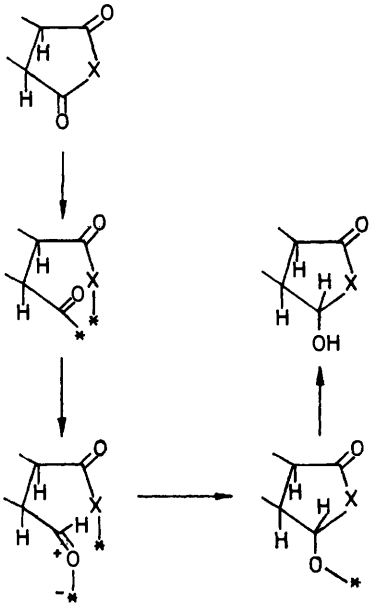
To our knowledge, there is no previous report of the reduction of phthalic anhydride over a palladium catalyst. We have found that this reaction proceeds smoothly in ethyl acetate solution to give *o*-toluic acid in high yield.† Indeed, the ease of this reaction led us

† Hydrogenation of phthalic anhydride over 5% palladium on carbon proceeded significantly more slowly and gave phthalide rather than *o*-toluic acid.

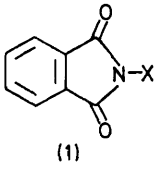
[1] A. J. McAlees and R. McCrindle, *J. Chem. Soc.* (*C*), 1969, 2425.

[2] A. J. McAlees, R. McCrindle, and D. W. Sneddon, *J.C.S. Perkin I*, 1977, 2038.

to choose phthalic anhydrides rather than the corresponding *N*-acylphthalimides for this investigation.

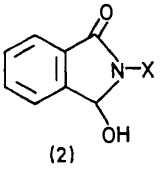


SCHEME 1 Mechanism proposed [1] to account for the products of hydrogenation of *N*-acyl imides and of cyclic anhydrides over platinum; X = O or NCOR; an asterisk denotes an adsorption site on the catalyst surface; charges are formal



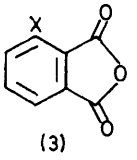
(1)

a; X = COR
b; X = CO_2R
c; X = H
d; X = Me



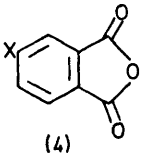
(2)

a; X = COR
b; X = CO_2R



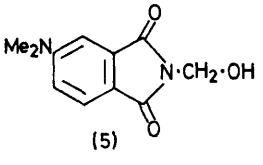
(3)

a; X = Me
b; X = CO_2Me
c; X = NMe_2
d; X = OMe

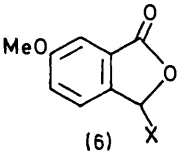


(4)

a; X = Me
b; X = CO_2Me
c; X = NMe_2
d; X = OMe



(5)

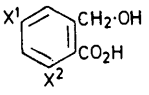


(6)

a; X = CCl_3
b; X = CO_2H

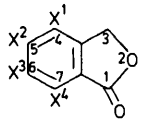
RESULTS

Substituted Phthalic Anhydrides.—Both 3-methyl- (3a) and 4-methyl- (4a) phthalic anhydride are commercial products. Reactions of hemimellitic and trimellitic anhydride acid chlorides with anhydrous methanol gave, respectively, 3-methoxycarbonyl- (3b) and 4-methoxycarbonyl- (4b) phthalic anhydride. 3-Dimethylaminophthalic anhydride (3c) was obtained both by the literature procedure [3] and, in one step, by reductive methylation of 3e nitrophthalic acid. The 4-isomer (4c) was prepared by reductive methylation of 4-nitrophthalimide, followed by



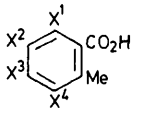
(7)

a; X^1 = OMe, X^2 = H
b; X^1 = NMe_2, X^2 = H
c; X^1 = H, X^2 = NMe_2



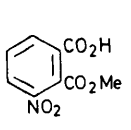
(8)

a; X^1 = NO_2, X^2 = X^3 = X^4 = H
b; X^3 = NO_2, X^1 = X^2 = X^4 = H
c; X^4 = NO_2, X^1 = X^2 = X^3 = H
d; X^2 = NMe_2, X^1 = X^3 = X^4 = H
e; X^2 = NH_2, X^1 = X^3 = X^4 = H
f; X^3 = OMe, X^1 = X^2 = X^4 = H
g; X^4 = CO_2Me, X^1 = X^2 = X^3 = H
h; X^1 = CO_2H, X^2 = X^3 = X^4 = H
i; X^1 = CO_2Me, X^2 = X^3 = X^4 = H
j; X^1 = NMe_2, X^2 = X^3 = X^4 = H
k; X^4 = NMe_2, X^1 = X^2 = X^3 = H
l; X^3 = NMe_2, X^1 = X^2 = X^4 = H
m; X^1 = OMe, X^2 = X^3 = X^4 = H
n; X^4 = OMe, X^1 = X^2 = X^3 = H
o; X^2 = OMe, X^1 = X^3 = X^4 = H
p; X^4 = Me, X^1 = X^2 = X^3 = H
q; X^1 = Me, X^2 = X^3 = X^4 = H

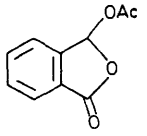


(9)

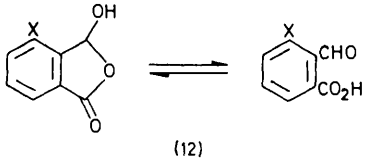
a; X^2 = NO_2, X^1 = X^3 = X^4 = H
b; X^2 = NMe_2, X^1 = X^3 = X^4 = H
c; X^1 = OMe, X^2 = X^3 = X^4 = H
d; X^4 = OMe, X^1 = X^2 = X^3 = H
e; X^3 = OMe, X^1 = X^2 = X^4 = H
f; X^2 = OMe, X^1 = X^3 = X^4 = H
g; X^3 = NMe_2, X^1 = X^2 = X^4 = H
h; X^4 = CO_2Me, X^1 = X^2 = X^3 = H
i; X^1 = CO_2Me, X^2 = X^3 = X^4 = H
j; X^2 = CO_2Me, X^1 = X^3 = X^4 = H
k; X^4 = Me, X^1 = X^2 = X^3 = H
l; X^1 = Me, X^2 = X^3 = X^4 = H
m; X^3 = Me, X^1 = X^2 = X^4 = H
n; X^2 = Me, X^1 = X^3 = X^4 = H
o; X^3 = CO_2Me, X^1 = X^2 = X^4 = H



(10)



(11)



(12)

a; X = Me
b; X = CO_2Me
c; X = H

hydrolysis of the resulting 4-dimethylamino-*N*-hydroxymethylphthalimide (5) with base and treatment of the dried

[3] R. M. Acheson and J. M. Vernon, *J. Chem. Soc.*, 1962, 1148.

salt with oxalyl chloride in benzene. Treatment of 3-methoxyphthalic acid, prepared by hydrolysis of 3-methoxy-*N*-methylphthalimide,[4] with acetic anhydride gave 3-methoxyphthalic anhydride (3d). Preparation of 4-methoxyphthalic anhydride (4d) involved condensation of *m*-anisic acid with chloral to give 6-methoxy-3-trichloromethylisobenzofuran-1(3*H*)-one [5] (6a), oxidation to 4-methoxyphthalic acid, and ring closure with acetic anhydride.

Products of Hydrogenation.—In contrast to phthalic anhydride itself, some of the substituted derivatives

Distribution of products and reaction times for the hydrogenation of substituted phthalic anhydrides

Substrate (substituted phthalic anhydride)	Products		Time to completion
	Substituted phthalides	Substituted benzoic acids	
3-Me	4-Me (8q) (10%)	2,3-Me_2 (9k) (58%)	30 h
	7-Me (8p) (3%)	2,6-Me_2 (9l) (29%)	
3-Me [a]	4-Me (8q) (69%)	2,3-Me_2 (9k) (16%)	23 h
	7-Me (8p) (13%)	2,6-Me_2 (9l) (2%)	
4-Me		2,4-Me_2 (9m) (47%) 2,5-Me_2 (9n) (53%)	3.5 h
4-Me [a]		2,4-Me_2 (9m) (37%) 2,5-Me_2 (9n) (63%)	3 h
3-OMe	4-MeO (8m) (5%)	3-MeO-2-Me (9d) (45%)	22 h
	7MeO (8n) (5%)	2-MeO-6-Me (9c) (45%)	
4-OMe		4-MeO-2-Me (9e) (50%) 5-MeO-2-Me (9f) (50%)	6 h
4-OMe	*b*	4-MeO-2-Me (9e) (15%) 5-MeO-2-Me (9f) (50%)	3 h [c]
3-NMe_2			>72 h [e]
	7-Me_2N (8k) (trace) [d]		
4-NMe_2	*f*	4-NMe_2-2-Me_2 (9g) (14%) 5-NMe_2-2-Me (9b) (57%)	24 h
3-CO_2Me	4-MeO_2C (8i) (18%) [g]	3-MeO_2C-2-Me (9h) (11%)	44 h
	7-MeO_2C (8g) (12%)	2-MeO_2C-6-Me (9i) (44%)	
4-CO_2Me		4-MeO_2C-2-Me (9o) (10%) 5-MeO_2C-2-Me (9j) (90%)	24 h

[a] In the presence of trifluoroacetic acid. [b] Product mixture contained 2-(hydroxymethyl)-4-methoxybenzoic acid (7a) (35%). [c] Not complete. [d] Product mixture also contained 6-dimethylamino-2-(hydroxymethyl)benzoic acid (7c) (major component), a substantial amount of substrate, and unidentified material. [e] Reaction worked up after 72 h. [f] Product mixture contained 4-dimethylamino-2-(hydroxymethyl)-benzoic acid (7b) (29%). [g] In addition, 4-carboxyphthalide (8h) (15%) was identified.

gave phthalides and/or 2-(hydroxymethyl)benzoic acids in addition to substituted *o*-toluic acids on hydrogenation. Thus, in the case of 4-methoxyphthalic anhydride (4d), some 2-(hydroxymethyl)-4-methoxybenzoic acid (7a) was detected on interruption of the reaction before the uptake of hydrogen was complete, and with 3- and 4-dimethylaminophthalic anhydrides [(3c) and (4c)] the corresponding 2-(hydroxymethyl)benzoic acids (7c and b) were present when uptake of hydrogen had virtually ceased. Products and relative yields are listed in the Table. Many of these compounds are new and we have synthesised several of them by independent routes in order to facilitate their identification and estimation in the product mixtures.

Reductive methylation of 4-nitro- (8a), 6-nitro- (8b), and 7-nitro- (8c) phthalide and of 2-methyl-5-nitrobenzoic acid (9a) gave the corresponding dimethylamines. All these nitro-compounds have been reported previously with the exception of 7-nitrophthalide, which we have obtained by reduction of 2-methyl hydrogen 3-nitrophthalate (10) with borane in tetrahydrofuran. Reduction of 3-nitrophthalic anhydride with sodium borohydride gave a high yield of 4-nitrophthalide (8a), previously obtained [6] as a minor by-product from nitration of phthalide. The fourth dimethylaminophthalide (8d) was prepared by reductive methylation of 5-aminophthalide [6] (8e). Two other known phthalides, 6-methoxyphthalide [7] (8f) and 7-methoxycarbonylphthalide [8] (8g), were found useful for analysis of the hydrogenation products. The former was prepared by decarboxylation [5] of 3-carboxy-6-methoxyphthalide (6b) and the latter by esterification of 7-carboxyphthalide (prepared in turn by treatment of 3-methylphthalic anhydride with *N*-bromosuccinimide and hydrolysis of the resulting bromomethylphthalic anhydride).

DISCUSSION

The only evidence clearly consistent with a mechanism analogous to that proposed [1] for platinum is the finding that the 3-substituted anhydrides react less rapidly than their 4-substituted counterparts. This suggests that anhydride ring opening is an important, rate-limiting step. The observed product distributions are not readily rationalised on the basis of the assumption of preferential nucleophilic attack of the catalyst on the more electrophilic carbonyl carbon atom although at first sight two substrates, 4-methoxycarbonyl-(4b) and 3-dimethylamino- (3c) phthalic anhydride appear to react in accord with this mechanism. The selectivity in the former case (4b) is higher than one would expect on the basis of substituent effects, and in the latter it is perhaps surprising in view of the results obtained for 4-dimethylaminophthalic anhydride. A closer consideration of the nature of the interaction of the substrate with the catalyst surface suggests that several complicating factors may come into play. (*a*) Interaction of the benzene ring with the catalyst will certainly modify the transmission of electronic effects from substituents through the ring to the carbonyl groups. By analogy with metal π-arene complexes (*cf. e.g.* the attenuation of electronic effects of substituents in tricarbonylchromium complexes of substituted benzoate esters [9]) the catalyst would be expected to act as a 'buffer' providing an electron sink or source depending on whether an electron-donating or electron-withdrawing substituent is present. (*b*) The electronic effect of the substituents may be modified by direct interaction with the catalyst, particularly in the case of the dimethylamino-derivatives. (*c*) If ring opening is a key step then the leaving ability of the carboxylate group as influenced by the substituent

[4] L. R. Caswell and T. L. Kao, *J. Heterocyclic Chem.*, 1966, **3**, 333.
[5] P. Fritsch, *Annalen*, 1897, **296**, 352.
[6] J. Tirouflet, *Bull. Soc. sci. Bretagne*, 1951, Spec. No. **26**, 7.
[7] S. Chakravarti and W. H. Perkin, *J. Chem. Soc.*, 1929, 196.
[8] E. Wenkert, D. B. R. Johnston, and K. G. Dave, *J. Org. Chem.*, 1964, **29**, 2534.
[9] G. Klompman and F. Calderazzo, *Inorg. Chem.*, 1967, **6**, 977.

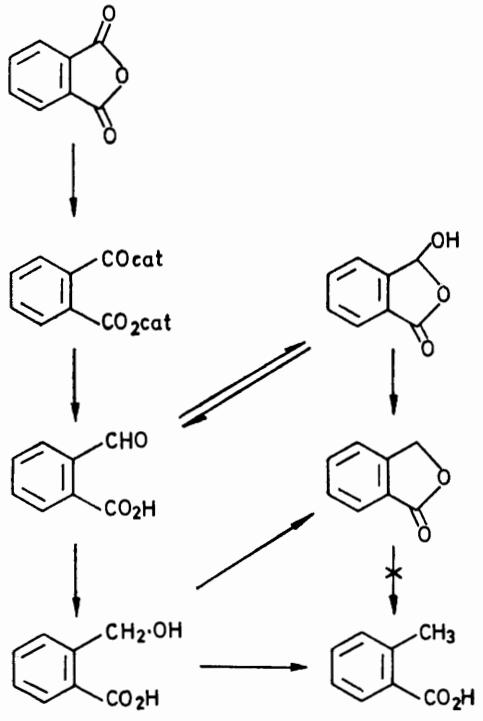
may be important. (*d*) Protonated species, the protons originating from acid in the catalyst [10] or from carboxylic acid products, may be involved.

As regards (*d*), it is well known that the presence of acid often results in a significant increase in the rate of hydrogenation of carbonyl compounds. In an attempt to determine if acid would affect the relative reactivities of the anhydride carbonyl groups to hydrogenation, we repeated the reactions of 3- and 4-methylphthalic anhydrides [(3a) and (4a)] in the presence of trifluoroacetic acid. The results (Table) show an *increase* in the tendency for reduction at that carbonyl group which is *ortho* or *para*, respectively, to the substituent. Thus, the relative reactivities of the two carbonyl groups in these substrates without added trifluoroacetic acid suggest the presence of an inherent source of protons (see later).

4-*Substituted Anhydrides*.—In the three derivatives carrying an electron-donating substituent (4a, c, and d), the tendency for reduction at the less electrophilic carbonyl is significantly greater than would be expected on the basis of a mechanism involving nucleophilic attack by catalyst. If such a mode of attack is operative, then the simplest explanation for this observation is that protonated species are involved, at least to some extent. Thus, in the case of 4-methylphthalic anhydride (4a), it would be expected that protonation of the carbonyl group *para* to the methyl group should be preferred, leading to an increase in the relative rate of nucleophilic attack of catalyst at this group. In the 4-methoxy and 4-dimethylamino-derivatives (4d and c), the expected preference for protonation at the carbonyl group *para* to the substituent should be offset to some extent by adsorption of the aromatic ring *and the substituents*, thus explaining the lack of specificity of reduction of these anhydrides. The influence of added acid on the hydrogenation of the methylphthalic anhydrides (see before) lends credence to the proposed role of protonation.

3-*Substituted Anhydrides*.—In the case of the 3-substituted anhydrides, the complexity of the reaction is compounded by steric effects. Indeed, these compounds undergo hydrogenation at a significantly lower rate than their 4-isomers. It appears unlikely that adsorption of the aromatic ring and the anhydride carbonyl groups on the catalyst will be adversely affected by the presence of these 3-substituents, with the possible exception of the methoxycarbonyl group. Thus, the reduced reactivity may be rationalised most readily by postulating that ring opening accompanies attack by the catalyst on the relevant carbonyl group.

The observed product distributions could result from an interplay of steric and electronic factors, as follows. For 3-methylphthalic anhydride (3a), the electronic influence of the substituent would be expected to militate against nucleophilic attack at the *ortho*-carbonyl group. The observation that attack on this carbonyl group is preferred would be explained by invoking the intervention of protonated intermediates, as discussed above. In addition, nucleophilic attack at the *ortho*-carbonyl carbon atom would relieve steric compression between the methyl group and carbonyl oxygen atom as it rotates away from the catalyst. Attack at the *meta*-carbonyl group would lead to increased steric compression as the departing (*ortho*) carboxylate would, of necessity, move closer to the methyl group. For 3-dimethylaminophthalic anhydride (3c) the molecule may be adsorbed through the aromatic ring, the anhydride group, and the nitrogen lone pair, in such a way that the *N*-methyl groups lie on the opposite side of the ring from the catalyst. Rotation of the oxygen atom of the *ortho*-carbonyl group away from the catalyst would be hindered by increasing interaction with an *N*-methyl group because of the proximity of these two groups.* For 3-methoxyphthalic anhydride (3d) it is not surprising that the reaction selectivity falls between those of the



SCHEME 2 Possible intermediates in the hydrogenation of phthalic anhdrides

3-dimethylamino and 3-methyl analogues. The electron-withdrawing character of the substituent in 3-methoxycarbonylphthalic anhydride (3d) might lead one to predict that attack at the *ortho*-carbonyl group of the anhydride would be preferred. However, steric interaction between these two functions will decrease the conjugation of the methoxycarbonyl group with the aromatic ring, both reducing the resonance effect of the former and also blocking access of the catalyst to the *ortho*-carbonyl group of the anhydride.

* The adsorption of these two groups on the catalyst could produce a species resembling a metal chelate which may be particularly resistant to nucleophilic attack. On the other hand, attack at the *ortho*-carbonyl group produces an *ortho*-amino-carboxylate.

[10] *Cf.* R. Baltzly, *J. Org. Chem.*, 1976, **41**, 920.

Reaction Routes.—If it is accepted that the initial reaction in the hydrogenation of the substituted phthalic anhydrides over palladium involves nucleophilic attack of the catalyst on a carbonyl carbon atom with concomitant ring opening, then Scheme 2 shows possible routes to the products isolated. On the basis of the following observations we favour the route *via* the formyl- and hydroxy-acids in most cases. First, under the conditions of hydrogenation, phthalide gives no *o*-toluic acid. Secondly, 3-acetoxyphthalide (11) undergoes *slow* hydrogenolysis to phthalide, whereas phthalaldehydic acid (12c) is rapidly reduced to *o*-toluic acid.* Thirdly, in three instances (see before) 2-(hydroxymethyl)benzoic acids (7a—c) were observed as products of hydrogenation of substituted phthalic anhydrides.

In the case of 3-substituted phthalic anhydrides, buttressing effects will tend to make ring closure of the intermediate 2-(hydroxymethyl)benzoic acids competitive with hydrogenolysis. It is likely that at least a portion of the phthalides is derived from hydrogenolysis of lactols [*e.g.* (12a)] which will also be stabilised by the 3-substituents. The absence of lactones in the products from 4-substituted phthalic anhydrides is consistent with the reports [11] that 4- and 5-substituents in 2-(hydroxymethyl)benzoic acids retard lactonisation whereas 3- and 6-substituents accelerate it. The increase in the proportion (see Table) of phthalides observed upon hydrogenation of 3-methylphthalic anhydride in the presence of trifluoroacetic acid may be explained as follows. Either ring closure of the 2-(hydroxymethyl)benzoic acids is promoted to a greater extent than hydrogenolysis of these intermediates, or hydrogenolysis of the lactols becomes more important. Evidence for participation of both lactol and 2-(hydroxymethyl)benzoic acid in the formation of a phthalide comes from the observation that 3-methoxycarbonylphthalic anhydride (3b) gives 4-carboxyphthalide (8h) in addition to 4-methoxycarbonylphthalide (8i). Since 2-(hydroxymethyl)-3-methoxycarbonylbenzoic acid would be expected to undergo lactonisation with the ester function † in preference to the carboxy-group, it is likely that the ester phthalide (8i) is formed by hydrogenolysis of 3-hydroxy-4-methoxycarbonylphthalide (12b).

In conclusion, although it is difficult to rationalise the observed selectivity of reduction of these anhydrides in terms of an initial nucleophilic attack of the catalyst in a rate-limiting step, closer consideration of the factors involved indicates that such a mechanism cannot be discounted on the basis of these results. Indeed, the relative rates of reduction of isomeric pairs of anhydrides appear to be more consistent with a mechanism involving initial opening of the anhydride ring than with one [1] requiring addition of hydrogen to a carbonyl function.‡ For a reaction of the latter type steric hindrance would not be expected to cause significant retardation of hydrogenation of the 3-substituted isomers, at least in the case of the methyl or methoxy-derivatives (3a and d) and when attack occurs at the carbonyl group remote from the substituent.

* The hydrogenation (10% palladium–carbon) of phthalic anhydride in the presence of acetic anhydride gave exclusively phthalide, presumably *via* the hydroxy-acid and the mixed anhydride derived therefrom.

† We have observed that although 4-dimethylamino-2-(hydroxymethyl)benzoic acid (7b) is stable, spontaneous lactonisation occurs upon treatment with diazomethane.

‡ This is true only if it can be assumed that the 4-substituted anhydrides, and intermediates and products derived therefrom in the course of the reaction, are not desorbed from the catalyst surface at a significantly greater rate than their 3-substituted counterparts.

EXPERIMENTAL

M.p.s were determined with a Kofler hot stage apparatus. I.r. spectra were recorded for Nujol mulls with a Beckmann IR-5A spectrophotometer and n.m.r. spectra with a Varian A-60A spectrometer for solutions in [$^2H_6$]acetone unless otherwise indicated. N.m.r. spectra (220 MHz) were run at the Canadian 220 MHz NMR Centre, Ontario Research Foundation, Sheridan Park, Ontario. Microanalyses were performed by Mr. S. H. McKinnon. T.l.c. plates were spread with Kieselgel G (Merck) and developed with ethyl acetate–light petroleum (1 : 1); spots were located by u.v. illumination (340 nm) or exposure to iodine vapour. G.l.c. analyses were carried out with a Varian Aerograph 1200 gas chromatograph [stainless steel column ($\frac{1}{8}$ in × 10 ft) containing 5% SE-30; nitrogen gas flow rate *ca.* 25 ml min^{-1}]. Light petroleum refers to the fraction of b.p 60–80 °C. Hydrogenations were carried out at ambient temperature and pressure in ethyl acetate which had been distilled and then stored over molecular sieves. Palladium–carbon catalyst was obtained from Matheson, Coleman, and Bell, Norwood, Ohio, U.S.A.

Preparation of Substituted Phthalic Anhydrides.—*3- and 4-Methoxycarbonylphthalic anhydrides* [(3b) *and* (4b)]. Dry methanol (1.1 ml) was added dropwise during 0.5 h to an ice-cooled solution of the appropriate anhydride acid chloride (5.5 g) in dry ether (150 ml). Refrigeration overnight gave crystalline material (2—2.3 g). The 3-methoxycarbonylphthalic anhydride (3b) had m.p. 139—142° (from dry acetone–light petroleum) (lit.,[8] 143°). The 4-isomer (4b) had m.p. 103—105° (lit.,[12] 99°) (from carbon tetrachloride).

Higher yields of (3b) were obtained by addition of hemimellitic anhydride acid chloride (0.2 g) to an excess of dry methanol (1 ml) and rapid removal of the resulting crystalline precipitate (3b), (0.16 g) by filtration.

3-Dimethylaminophthalic anhydride (3c). A solution of 3-nitrophthalic acid (4.2 g) in ethanol (120 ml) containing aqueous formaldehyde (30%; 15 ml) was hydrogenated over 10% palladium–carbon (0.8 g) for 80 h at 100 °C and 500 lb in^{-2}. Crystallisation of the residue obtained by removal of catalyst and solvent from ethanol gave bright yellow plates (3c) (1.6 g), m.p. 141—143° (lit.,[3] 140—141°).

4-Dimethylaminophthalic anhydride (4c). Attempts to prepare this compound by the method of Inagaki [13] gave poor yields. For example, 24.0 g of 4-bromophthalic acid gave only 1.4 g of (4c).

Hydrogenation of 4-nitrophthalimide (5.4 g) in ethanol (125 ml) containing aqueous formaldehyde (30%; 25 ml)

[11] J. Tirouflet, *Bull. Soc. chim. France*, 1954, 799; J. F. Bunnett and C. F. Hauser, *J. Amer. Chem. Soc.*, 1965, **87**, 2214.

[12] R. Wegscheider, H. F. Perndanner, and O. Auspitzer, *Monatsh.*, 1910, **31**, 1253.

[13] K. Inagaki, Jap. P. 12,783/1965 (*Chem. Abs.*, 1966, **64**, 8097f).

over 10% palladium–carbon (1.1 g) for 48 h at 100 °C and 800 lb in^{-2} gave 4-*dimethylamino*-N-(*hydroxymethyl*)*phthalimide* (5) (4.0 g), which formed needles, m.p. 131—133° (from ethanol); $\nu_{max.}$ 3 300, 1 750, and 1 700 cm^{-1}; τ 2.42 (1 H, d, *J* 9 Hz), 3.10 (2 H, m), 4.90br (3 H, s, CH_2OH; 1 H lost by D_2O equilibration), and 6.92 (6 H, s, NMe_2) (Found: C, 60.0; H, 5.6; N, 12.9. $C_{11}H_{12}N_2O_3$ requires C, 60.0; H, 5.5; N, 12.7%).

A solution of compound (5) (2.2 g) and sodium hydroxide (0.8 g) in water (20 ml) was boiled until evolution of ammonia ceased and evaporated to dryness; the residue was heated in refluxing acetic anhydride (30 ml) for 2 h. The yellow needles obtained on cooling were recrystallised from acetic anhydride to give the anhydride (4c) (1.7 g), m.p. 201—202° (lit.,[13] 202°).

3-*Methoxyphthalic anhydride* (3d). A solution of 3-methoxy-*N*-methylphthalimide [4] (1.85 g) and sodium hydroxide (2.0 g) in water (60 ml) was heated for 48 h at 150 °C in a bomb, then evaporated to dryness. The residue was redissolved in water and acidified with hydrochloric acid, and the solution was evaporated to dryness. Extraction (Soxhlet) of the residual solid with ether gave crude 3-methoxyphthalic acid (1.2 g), m.p. 165—170° (lit.,[14] 173°). A sample of this material (1.0 g) was heated in refluxing acetic anhydride (4 ml) for 2 h. The precipitate obtained on cooling crystallised from ethanol to give the anhydride (3d) (0.45 g), m.p. 161—162° (lit.,[14] 160—161°).

4-*Methoxyphthalic anhydride* (4d). A solution of 6-methoxy-3-trichloromethylphthalide [5] (6a) (6.0 g) and sodium hydroxide (6.0 g) in water (50 ml) was heated on a steam-bath for 15 min and then cooled in an ice-bath. Potassium permanganate (2.5 g) in water (125 ml) was added dropwise during 1.5 h, aqueous sodium hydroxide (1M; 20 ml) being added all at once when about half the oxidising agent had been added. After stirring for 18 h at 25 °C, the mixture was acidified with concentrated hydrochloric acid and then saturated with sulphur dioxide. A precipitate of 4-methoxyphthalic acid (0.8 g) was filtered off and the filtrate evaporated to dryness. The residue was resubmitted to the oxidation conditions described above to give more 4-methoxyphthalic acid (2.8 g). The combined product had m.p. 165—167° (from water) (lit.,[15] 167°). A sample of this material (1.0 g) was heated in refluxing acetic anhydride (2 ml) for 1 h. The crystalline precipitate obtained on cooling gave the anhydride (4d) as plates (0.61 g), m.p. 94—95° (from ethanol) (lit.,[5] 97°).

Preparation of Standards for Comparison with Hydrogenation Products.—4-*Dimethylaminophthalide* (8j). A solution of 3-nitrophthalic anhydride (2.0 g) in dry tetrahydrofuran (10 ml) was added dropwise to a suspension of sodium borohydride (0.4 g) in the same solvent (5 ml) at 0 °C and the mixture was then stirred for 90 min at 20 °C. Acidification with dilute hydrochloric acid gave 4-nitrophthalide (8a) (1.5 g), which crystallised from ethanol as pale yellow rods, m.p. 134—136° (lit.,[6] 136°). Hydrogenation of this nitrophthalide (0.6 g) over 10% palladium–carbon (0.09 g) in ethanol (20 ml) and ethyl acetate (10 ml) containing aqueous formaldehyde (40%; 0.7 ml) at 45 lb in^{-2} for 9 h gave 4-*dimethylaminophthalide* (8j) (0.4 g), needles, m.p. 134—136° (from aqueous ethanol); τ 2.50—3.05 (3 H, m), 4.55 (2 H, s), and 7.05 (6 H, s) (Found: C, 67.55; H, 6.45; N, 8.05. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.25; N, 7.9%).

7-*Dimethylaminophthalide* (8k). Borane–tetrahydrofuran adduct (1M; 15 ml) was added dropwise with stirring to an ice-cold solution of 2-methyl hydrogen 3-nitrophthalate (3.0 g) in dry ether (75 ml). After stirring for 20 h at 20 °C the solution was diluted with aqueous methanol and then evaporated to small volume. Acidification with dilute hydrochloric acid and warming for 0.5 h on a steam-bath gave 7-*nitrophthalide* (8c) (1.7 g), pale yellow needles, m.p. 164—166° (from aqueous ethanol) (Found: C, 53.95; H, 3.0; N. 7.9. $C_8H_5NO_4$ requires C, 53.65; H, 2.8; N, 7.8%). Reductive methylation (see above) of (8c) (1.0 g) at 60 lb in^{-2} and 50 °C for 48 h gave a mixture, separated by column chromatography over silica gel (35 g). Elution with ethyl acetate–light petroleum (9 : 1) gave first 7-methylaminaphthalide (0.1 g), identified by n.m.r., and then 7-*dimethylaminophthalide* (8k) (0.5 g), prisms, m.p. 56—57° (from ether–light petroleum); τ ($CDCl_3$) 2.55 (1 H, m, H-5), 3.20 (2 H, m, H-4 + -6), 4.85 (2 H, s), and 7.00 (6 H, s) (Found: C, 67.7; H, 6.45; N, 7.9. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.25; N, 7.9%).

5-*Dimethylaminophthalide* (8d). Reductive methylation (see before) of 5-aminophthalide [6] (2.0 g) at 60 lb in^{-2} and 60 °C for 110 h gave 5-*dimethylaminophthalide* (8d) (0.95 g), needles, m.p. 117—118° (from aqueous ethanol); τ ($CDCl_3$) 2.33 (1 H, d, H-7, *J* 8.5 Hz), 3.26 (1 H, dd, H-6, *J* 8.5 and 2.0 Hz), 3.43br (1 H, s, H-4), 4.83 (2 H, s), and 6.95 (6 H, s) (Found: C, 67.55; H, 6.15; N, 7.75. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.25; N, 7.9%).

6-*Dimethylaminophthalide* (8l). Reductive methylation (see before) of 6-nitrophthalide (1.8 g); (prepared by nitration of phthalide) at 45 lb in^{-2} and 20 °C for 6 h gave 6-*dimethylaminophthalide* (8l) (1.75 g), needles, m.p. 121—122° (from aqueous ethanol); τ 2.57 (1 H, d, H-4, *J* 8.5 Hz), 2.88 (1 H, dd, H-5, *J* 8.5 and 2.5 Hz), 2.97br (1 H, s, H-7), 4.78 (2 H, s), and 7.00 (6 H, s) (Found: C, 67.65; H, 6.3; N, 7.85. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.25; N, 7.9%).

7-*Methoxycarbonylphthalide* (8g). A solution of 3-methylphthalic anhydride (3.24 g) and *N*-bromosuccinimide (3.92 g) in dry carbon tetrachloride (120 ml) was heated at reflux for 15 h while being irradiated with a tungsten lamp. The residue obtained after removal of the succinimide and evaporation was treated with warm dilute hydrochloric acid (10 ml). The resulting mixture upon cooling gave 7-carboxyphthalide (0.8 g), m.p. 170—171° (lit.,[8] 170—172°) (from methanol). Methylation with diazomethane gave the ester (8g), m.p. 105—106° (lit.,[8] 106—108°) (from methanol); τ 2.1—2.3 (3 H, m), 4.57 (2 H, s), and 6.08 (3 H, s).

6-*Methoxyphthalide* (8f). Attempts to prepare this compound by the method of Chakravarti and Perkin [7] gave mixtures (*cf.* Numata *et al.*[16]). The phthalide was prepared by decarboxylation [5] of 3-carboxy-6-methoxyphthalide (6b) and had m.p. 117—120° (lit.,[7] 120°) (from methanol); τ (C_6D_6) 2.80 (1 H, d, H-7, *J* 2.2 Hz), 3.07 (1 H, dd, H-5, *J* 8.5 and 2.2 Hz), 3.37 (1 H, d, H-4, *J* 8.5 Hz), 5.47 (2 H, s), and 6.74 (3 H, s).

5-*Dimethylamino*-2-*methylbenzoic acid* (9b). Reductive methylation (see before) of 2-methyl-5-nitrobenzoic acid [17] (9a) (0.53 g) at 60 lb in^{-2} and 20 °C for 16 h gave 5-*dimethylamino*-2-*methylbenzoic acid* (9b) (0.46 g), needles, m.p. 148—150° (from aqueous ethanol); τ 2.65 (1 H, d, H-6, *J* 2.3 Hz), 2.87 (1 H, d, H-3, *J* 8.5 Hz), 3.15 (1 H, dd, *J* 8.5

[14] W. H. Bentley, R. Robinson, and C. Weizmann, *J. Chem. Soc.*, 1907, **91**, 104.

[15] J. F. Eijkman, *Chem. Zentr.*, 1904, **1**, 1597.

[16] A. Numata, K. Ono, H. Irie, and S. Ueo, *Yakugaku Zasshi*, 1968, **88**, 1151.

[17] O. Jacobsen and F. Wierss, *Ber.*, 1883, **16**, 1956.

and 2.3 Hz), 7.08 (6 H, s), and 7.55 (3 H, s) (Found: C, 67.3; H, 7.4; N, 7.95. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%).

Hydrogenations.—Unless otherwise stated, the anhydride (0.5 g) was stirred in ethyl acetate (50 ml) with the catalyst [10% palladium–carbon (0.5 g)] under hydrogen at ambient temperature and pressure until uptake appeared to have ceased. Product compositions (see Table) were determined, where possible, by integration of n.m.r. spectra of solutions of the residue obtained by removal of catalyst and solvent. In some cases (see later) at least partial separation was necesary because of the complex nature of the mixture obtained.

Phthalic anhydride. This anhydride absorbed *ca.* 3 mol. equiv. of hydrogen within 1 h. Work-up gave *o*-toluic acid (0.35 g) and a small amount of phthalic acid.

3-*Methoxyphthalic anhydride* (3d). Approximately 3 mol. equiv. of hydrogen were absorbed during 22 h. Work-up gave products (423 mg) which showed τ (C_6D_6) 2.17—3.75 (m, aromatic), 5.28 (s, OCH_2) (8m), 5.49 (s, OCH_2), (8n), 6.54 (s, OCH_3), (8n), 6.70 (s, OCH_3), [(9c) + (9d)], 6.73 (s, OCH_3), (8m), 7.39 (s, aromatic CH_3), (9d), and 7.68 (s, aromatic CH_3), (9c).

4-*Methoxyphthalic anhydride* (4d). The absorption of *ca.* 3 mol. equiv. of hydrogen required 6 h. Work-up gave products (405 mg) which showed τ 1.95—3.30 (m, aromatic), 6.13 and 6.18 (both s, OCH_3), and 7.39 and 7.48 (both s, aromatic CH_3). When the hydrogenation was terminated after 3 h the residue showed τ 1.85—3.30 (m, aromatic), 5.07 (s, CH_2OH), (7a), 6.10 (s, OCH_3), (7a), 6.13 (s, OCH_3), (9e), 6.18 (s, OCH_3), (9f), 7.38 (s, aromatic CH_3), (9e), and 7.48 (s, aromatic CH_3), (9f). Upon treatment of the residue with dilute hydrochloric acid the singlet at τ 5.07 disappeared and was replaced by one at τ 4.71 (phthalide CH_2), (8o). Direct comparison by t.l.c. indicated the absence of 6-methoxyphthalide (8f).

3-*Dimethylaminophthalic anhydride* (3c). This anhydride absorbed *ca.* 2 mol. equiv. of hydrogen during 72 h. The residue (470 mg) showed τ 2.35 (s, aromatic) (8k), 2.4—3.0 (m, aromatic), 4.75 (s, phthalide CH_2), (8k), 5.08 (s, CH_2-OH), (7c), 6.79 (s, NMe_2) (3c), 7.12 (s, NMe_2) (7c), and six low intensity singlets between 6.9 and 7.45. When this hydrogenation was repeated in the presence of acetic anhydride no (7c) was detected. The major product was shown (n.m.r. and t.l.c.) to be (8k).

4-*Dimethylaminophthalic anhydride* (4c). This anhydride consumed *ca.* 2.5 mol. equiv. of hydrogen over 24 h, after which reaction appeared to have stopped. The residue (405 mg) showed τ 1.9—3.5 (m, aromatic), 5.13 (s, CH_2OH), (7b), 6.93 (s, NMe_2) (7b), 6.97 (s, NMe_2) (9g), 7.07 (s, NMe_2) (9b), 7.40 (s, aromatic CH_3), (9g), and 7.52 (s, aromatic CH_3), (9b); three components were observed on t.l.c., the one of intermediate polarity having an R_F value identical with that of authentic (9b). T.l.c. after treatment with ethereal diazomethane again showed three components, those of intermediate and greatest polarities having the same mobilities as methyl 5-dimethylamino-2-methylbenzoate and (8d), respectively. The ratio of methyl esters determined by g.l.c. (150 °C) coincided with that found for the related acids by n.m.r. integration (see Table).

3-*Methoxycarbonylphthalic anhydride* (3d). This anhydride consumed 2.75 mol. equiv. of hydrogen during 44 h. The residue (340 mg) was extracted with aqueous sodium hydrogen carbonate. The insoluble fraction (85 mg) showed τ 1.6—2.4 (m, aromatic), 4.38 (s, phthalide CH_2), (8i), 4.57 (s, phthalide CH_2), (8g) 6.03 (s, OCH_3), (8i), and 6.08 (s, OCH_3), (8g). The soluble fraction (185 mg) showed τ 1.8—2.85 (m, aromatic), 4.37 (s, phthalide CH_2), (8h), 6.11 and 6.16 (both s, OCH_3), 7.30 (s, aromatic CH_3), (9h), and 7.62 (s, aromatic CH_3), (9i). A sample (45 mg) of this fraction was treated with dilute aqueous sodium hydroxide at 60 °C for 10 min. Acidificaton gave a crystalline precipitate (30 mg), the n.m.r. spectrum of which was essentially identical with that of 3-methylphthalic acid. The mother liquors on evaporation to dryness afforded a residue which crystallised from water to give 4-carboxyphthalide (8h), (8 mg), m.p. 243—246° (lit.,[8] 246°).

4-*Methoxycarbonylphthalic anhydride* (4b). This anhydride absorbed 3 mol. equiv. of hydrogen during 24 h. The residue (443 mg) consisted largely of 5-methoxycarbonyl-2-methylbenzoic acid (9j), τ 1.62 (d, H-6, *J* 2 Hz), 2.22 (dd, H-4, *J* 2 and 8 Hz), 2.33 (s, aromatic) (minor product), 2.86 (d, H-3, *J* 8 Hz), 6.36 (s, OCH_3), and 7.59 (aromatic CH_3). Esterification with an excess of ethereal diazomethane and crystallisation from methanol gave dimethyl 4-methylisophthalate, m.p. 76° (lit.,[18] 80°). G.l.c. (135 °C) of the initial product of esterification showed the presence of a minor component (*ca.* 10%; dimethyl methylterephthalate?).

3-*Methylphthalic anhydride* (3a). Approximately 3 mol. equiv. of hydrogen were absorbed by this anhydride during 30 h. The residue (490 mg) was dissolved in ether and extracted with aqueous sodium hydrogen carbonate. The hydrogen carbonate-soluble fraction (420 mg) showed τ ($CDCl_3$) 2.15 (dd, H-6, *J* 2 and 7 Hz), (9k), 2.57—3.05 (m, aromatic), 7.48 and 7.70 (both s, aromatic CH_3), (9k), and 7.60 (s, aromatic CH_3) (9l). The insoluble fraction (60 mg) showed τ ($CDCl_3$) 2.15—2.75 (m, aromatic), 4.72 (s, phthalide CH_2) [(8p) + (8q)], 7.30 (s, aromatic CH_3), (8p), and 7.62 (s, aromatic CH_3), (8q).

When this hydrogenation was repeated in the presence of trifluoroacetic acid (2.5 ml) and molecular sieves (4A; 0.5 g) 3 mol. equiv. of hydrogen were absorbed during 23 h. Analysis of the residue as above gave the results shown in the Table.

4-*Methylphthalic anhydride* (4a). This anhydride absorbed 3 mol. equiv. of hydrogen during 3.5 h. The residue (400 mg) showed τ ($CDCl_3$; 220 MHz) 2.03 (d, H-6, *J* 8.5 Hz), (9m), 2.11 (d, H-6, *J* 1.7 Hz), (9n), 2.77 (dd, H-4, *J* 1.7 and 7.5 Hz), (9n), 2.86 (d, H-3, *J* 7.5 Hz), (9n), 2.94 (m, H-3 + -5), (9m), 7.38 and 7.40 (both s, 2 aromatic CH_3), and 7.65 (s, 2 aromatic CH_3).

When this hydrogenation was repeated in the presence of trifluoroacetic acid (2.5 ml) and molecular sieves (4A; 0.5 g) 3 mol. equiv. of hydrogen were absorbed during 3 h. Analysis of the residue (220 MHz n.m.r.) gave the results shown in the Table.

Phthaldehydic acid (12c). This compound absorbed 2 mol. equiv. of hydrogen within 20 min to give *o*-toluic acid (400 mg).

3-*Acetoxyphthalide* (11). This compound absorbed 1 mol. equiv. of hydrogen during 15 h to give phthalide.

Phthalide. This compound absorbed *ca.* 0.5 mol. equiv. during 66 h. The residue contained substrate and a small amount (<10%) of hexahydrophthalide.

We thank the National Research Council of Canada for an operating grant.

[7/261 *Received*, 14*th February*, 1977]

[18] W. H. Bentley and W. H. Perkin, *J. Chem. Soc.*, 1897, **71**, 176.