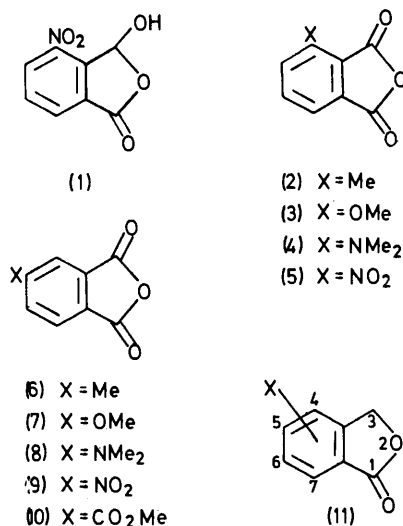


Reduction of Substituted Phthalic Anhydrides with Sodium Borohydride

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The reduction of a series of substituted phthalic anhydrides to phthalides with sodium borohydride has been studied. Preferential reduction of the carbonyl function adjacent to 3-substituents is observed. In the 4-substituted analogues, selectivity of reduction is found only when the substituent is electron-donating.

We have proposed¹ a mechanism, involving nucleophilic attack of catalyst on a carbonyl carbon atom, for the hydrogenation of cyclic anhydrides and imides over platinum. In an attempt to determine whether a similar mechanism applies for reactions of palladium, a series of substituted phthalic anhydrides was subjected



to hydrogenation.² Although the relative rates of reduction of 3- and 4-substituted phthalic anhydrides, to phthalides and/or *o*-toluic acids, were consistent with such a mechanism, the relative susceptibilities to reaction of the two carbonyl groups in each substrate could not be rationalised readily in terms of electronic effects of the substituents. We have suggested² that this may be due to direct interaction between substituents and catalyst, adsorption of the aromatic ring, and the participation of protonated species. In order to determine if the electronic effect of substituents can play a role in directing nucleophilic attack preferentially to one carbonyl group, we have examined the distribution of products from the reduction of substituted phthalic anhydrides with sodium borohydride. In this case nucleophilic attack by hydride ion on a carbonyl carbon atom is presumably involved.³

Reductions of several cyclic anhydrides, including 3-nitro- and 3-methyl-phthalic anhydrides, by sodium borohydride have been reported,⁴⁻⁶ usually to lactones,

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

² A. J. McAlees, R. McCrindle, and D. W. Sneddon, preceding paper.

³ H. O. House, 'Modern Synthetic Reactions,' 2nd edn., Benjamin, Menlo Park, California, 1972, p. 51.

⁴ D. M. Bailey and R. E. Johnson, *J. Org. Chem.*, 1970, **35**, 3574.

the former giving⁵ the nitrophthalaldehydic acid (1) and the latter⁶ a 1 : 1 mixture of 4- and 7-methylphthalides. In the present investigation, addition of the anhydrides (2)—(10)² to a suspension of sodium borohydride in dry tetrahydrofuran followed by work-up with aqueous acid gave only phthalides (11), in the absolute and relative yields recorded in the Table.

Product yields and distributions of the phthalide isomers obtained by reduction of phthalic anhydrides with sodium borohydride

Phthalic anhydride reduced ^a	Phthalides (11) produced ^a	Overall yields of phthalides (%)
3-Me	4-Me (57%) ^b 7-Me (43%) ^b	77
4-Me	5-Me (67%) ^{c,d} 6-Me (33%) ^{c,d}	55
3-MeO	4-MeO (87%) ^e 7-MeO (13%)	52
4-MeO	5-MeO (70%) ^b 6-MeO (30%) ^b	67
3-Me ₂ N	4-Me ₂ N (80%) 7-Me ₂ N (20%)	45
4-Me ₂ N	5-Me ₂ N (100%) ^f 6-Me ₂ N (—)	54
3-NO ₂	4-NO ₂ (100%) 7-NO ₂ (—)	81
4-NO ₂	5-NO ₂ (50%) ^b 6-NO ₂ (50%) ^b	65
4-MeO ₂ C	5-MeO ₂ C (50%) ^g 6-MeO ₂ C (50%) ^g	33

^a All analyses by n.m.r. at 60 MHz except for the products from 4-methylphthalic anhydride. ^b Relative amounts estimated by n.m.r.; confirmed by g.l.c. (140 °C; 10 ft, SE-30). ^c N.m.r. analysis at 220 MHz. ^d As in *b* but 180 °C; 7 ft, Carbowax 20M. ^e Major product isolated by fractional crystallisation; m.p. 126—127° [lit., 127° (C. A. Buehler, T. A. Powers, and J. G. Michels, *J. Amer. Chem. Soc.*, 1944, **66**, 417)]. ^f Mixed m.p. with authentic² dimethylaminophthalide. ^g As in *b* but 215 °C.

DISCUSSION

4-Substituted Phthalic Anhydrides.—In these cases, steric effects of the 4-substituents on attack at the anhydride function should be negligible. The product distribution should therefore reflect any influence of electronic effects on the selectivity of reduction. Indeed, the Table indicates that, when the 4-substituent is electron-donating [(2), (3), and (4)], a preference for reduction at the *meta*-carbonyl group is observed. As expected on the basis of substituent constants,^{7,8} protection of the *para*-carbonyl group from nucleophilic

⁵ T. Watanabe, F. Hamaguchi and S. Ohki, *Chem. and Pharm. Bull. (Japan)*, 1972, **20**, 2123.

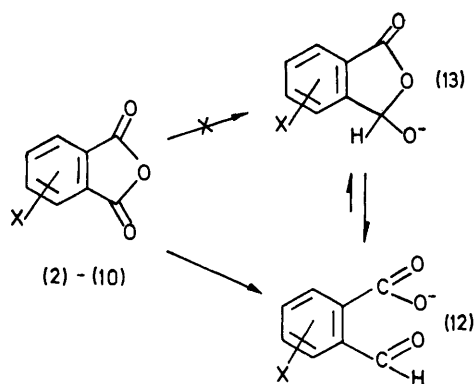
⁶ J. F. Bunnett and C. F. Hauser, *J. Amer. Chem. Soc.*, 1965, **87**, 2214.

⁷ H. H. Jaffe, *Chem. Rev.*, 1953, **53**, 191.

⁸ L. H. Altschul, *J. Amer. Chem. Soc.*, 1952, **74**, 410.

attack is most marked for the dimethylamino-substituent. However, with the electron-withdrawing substituents, no selectivity was observed, although some preference for reduction *para* to the methoxycarbonyl group would be expected.

It has been suggested³ that aldehydes and ketones do not react with sodium borohydride in dry nonhydroxylic media, reduction only taking place on addition of a hydroxylic solvent during work-up. In the present investigation, it seems likely that reduction of the anhydrides occurred before work-up, as evidenced by the loss of the yellow colour due to (4) and (8), presumably the least reactive members of this series, following their addition to the sodium borohydride suspension. These reductions probably involve anhydride ring opening to give the formyl carboxylate (12). Further reduction of



SCHEME Possible intermediates formed by hydride attack on substituted phthalic anhydrides

the aldehyde function and lactonisation may occur only on work-up.

3-Substituted Phthalic Anhydrides.—In order to account for the product distributions in the Table, a major contribution from steric effects must be invoked. In all cases examined, reduction takes place preferentially at

the carbonyl group *ortho* to the substituent, suggesting that nucleophilic attack at this site is accompanied by relief of steric compression between the reacting carbonyl group and the 3-substituent. Formation of an intermediate (13) with an sp^3 -hybridised carbon atom could account for this. However, in the light of the above discussion of the difference in reactivity between aldehydes and ketones on the one hand and cyclic anhydrides on the other, we favour a mechanism involving direct ring opening (Scheme). In this mechanism, the reacting carbonyl group, upon attack by hydride, rotates out of the plane of the aromatic ring, while the incipient carboxylate departs essentially in the plane. For reduction at the other carbonyl group the bond-breaking process would lead to an increase in steric compression between the departing carboxylate and the 3-substituent with no concomitant strain release from rotation of the incipient aldehyde carbonyl group.

EXPERIMENTAL

General experimental details and the syntheses of substituted phthalic anhydrides and phthalides are described elsewhere.²

Reductions of the Phthalic Anhydrides with Sodium Borohydride.—A solution of the anhydride (1.0 g) in dry tetrahydrofuran (4-dimethylaminophthalic anhydride was added as a suspension in dry tetrahydrofuran) was added dropwise over 5–10 min to a stirred, ice-cold suspension of an equimolar amount of sodium borohydride in the same solvent. The resulting mixture was stirred for a further 2 h at 20 °C. Work-up involved careful acidification with dilute hydrochloric acid and extraction into ether (in the case of 3- and 4-dimethylaminophthalic anhydrides, an excess of aqueous sodium hydrogen carbonate was added before extraction). The extract was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. Product yields and distributions of the phthalide isomers are recorded in the Table.

[7/262 Received, 14th February, 1977]