617. *Studies on Phosphorylation. Part XVIII.* Base-inhibited Hydrogenolysis in the Selective Debenzylation of Phosphoric and Phosphoramidic Esters.*

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The hydrogenolytic debenzylation of the neutral esters of phosphoric, phosphoramidic, and certain *N*-substituted phosphoramidic acids is subject to inhibition by a variety of bases. From this a convenient method of selective debenzylation has been developed and is exemplified by the preparation of a number of *N*-substituted benzyl hydrogen phosphoramidates.

Investigation of the phosphorylation of alcohols under mild conditions led to the development of dibenzyl phosphorochloridate as a convenient reagent, the two benzyl groups of the initially formed triester being removed subsequently by hydrogenolysis.[1] These triesters can provide suitable starting materials for pyrophosphate synthesis by the selective removal of one of the benzyl groups by means of a tertiary amine [2] or a salt containing a polarisable anion,[3] and these methods have been applied in a variety of syntheses of pyro- and poly-phosphates.[4]

In the preliminary work on simple alcohols [1] it was noted that hydrogenolysis of dibenzyl *iso*pentyl phosphate with a palladised charcoal catalyst in the presence of *N*-*n*-butylpiperidine was slow, but gave the *mono*debenzylated product, isolated as a silver salt. Inhibition of hydrogenation has been observed in a number of systems. Thus, Naves [5] showed that the hydrogenolysis of esters of benzyl alcohol with Raney nickel was generally rapid and complete in ethanol but much slower in dioxan or in the presence of dimethylaniline, and Baltzly and his co-workers [6] have indicated that such hydrogenolyses are inhibited by alkali and by free amines of basic strength above a certain minimum. Maxted and Walker [7] and, more recently, Devereux, Payne, and Peeling [8] have demonstrated that hydrogenation of aromatic amines with a platinum oxide catalyst is inhibited by the amine itself and its reduction product, while Maxted and Biggs [9] have recorded the deactivating effect of dry ammonia upon platinum in the hydrogenation of *cyclo*hexene.

The effect of alkali on the activity of the catalyst varies in the different examples studied [10] and depends to a large extent on the degree of subdivision, a coarse-grained, relatively inactive catalyst often being far more sensitive to poisoning than a finely divided, highly active one.[11] Baltzly and Buck,[6] following the work of Hartung and Crossley,[12] confirmed the superiority of palladium catalysts for hydrogenolytic debenzylation and we now record a method for the selective debenzylation of esters of phosphoric and a number of *N*-substituted phosphoramidic acids using such catalysts in the presence of bases.[13]

In the presence of one molecular equivalent of 4-methylmorpholine, the rate of hydrogenation of tribenzyl phosphate in presence of 10% palladised charcoal at room

* Part XVII, *J.*, 1958, 2968.

[1] Atherton, Openshaw, and Todd, *J.*, 1945, 382; cf. Zervas, *Naturwiss.*, 1939, **27**, 317.
[2] Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815.
[3] Clark and Todd, *J.*, 1950, 2030; Cremlyn, Kenner, Mather, and Todd, *J.*, 1958, 528.
[4] Cf. Todd, *Proc. Roy. Soc.*, 1954, *A*, **226**, 70.
[5] Naves, *Helv. Chim. Acta*, 1944, **27**, 261.
[6] Baltzly and Buck, *J. Amer. Chem. Soc.*, 1943, **65**, 1984; Baltzly and Phillips, *ibid.*, 1946, **68**, 261.
[7] Maxted and Walker, *J.*, 1948, 1093.
[8] Devereux, Payne, and Peeling, *J.*, 1957, 2845.
[9] Maxted and Biggs, *J.*, 1957, 3844; cf. Bremner, *Research*, 1948, **1**, 281.
[10] Reasenberg, Lieber, and Smith, *J. Amer. Chem. Soc.*, 1939, **61**, 384.
[11] Maxted and Evans, *J.*, 1937, 603.
[12] Hartung and Crossley, *J. Amer. Chem. Soc.*, 1934, **56**, 158.
[13] Cf. Todd, *Angew. Chem.*, 1948, **60**, 69; Vollmar and Cramer, *ibid.*, 1957, **69**, 104.

temperature and atmospheric pressure was greatly reduced, but there was no point of inflexion in the curve of hydrogen uptake against time which might correspond to the selective removal of one benzyl group. On increasing the amount of amine present, progressive retardation after the removal of one benzyl group was observed. Thereafter, use of a variety of bases gave similar effects, as illustrated in Fig. 1; for example, in the presence of 5 mols. of sodium methoxide hydrogenation of tribenzyl phosphate gave a 72% yield of dibenzyl hydrogen phosphate.

With dibenzyl phosphoramidate, selective debenzylation was performed in similar fashion, base again having a marked effect on both the rate of uptake and the total hydrogen absorption (Fig. 2). By using two mols. of triethylamine as inhibitor, it was possible, after hydrogenation, to isolate benzyl hydrogen phosphoramidate in high yield and the method has been extended to the preparation of the corresponding *N*-benzyl, *N*-1-phenylethyl, *N-cyclo*hexyl, *N*-phenyl, *N-p*-hydroxyphenyl, and *N-p*-tolyl derivatives. Earlier preparations of the monobenzyl esters of various *N*-substituted phosphoramidic

FIG. 1. FIG. 2.

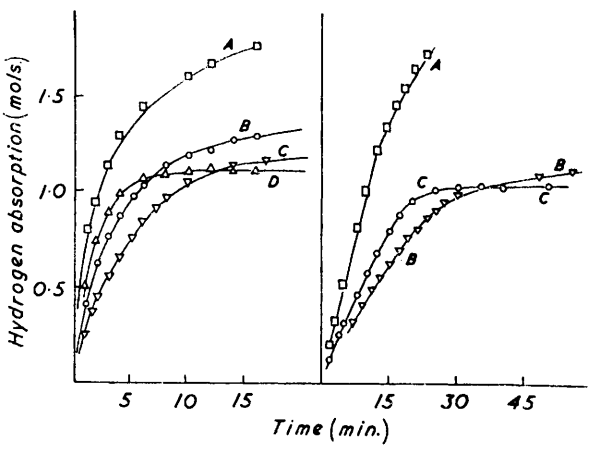

FIG. 1. *Hydrogenolysis of tribenzyl phosphate* (1·23 *g.*) *in ethanol* (110 *ml.*) *with* 10% Pd–C *catalyst* (200 *mg.*) *at* 12·5° *in the presence of various bases* (5 *mols. each of*; *A*, *morpholine*; *B*, cyclo*hexylamine*; *C*, 4-*methylmorpholine*; *D*, *sodium methoxide*).

FIG. 2. *Hydrogenolysis of dibenzyl phosphoramidate* (510 *mg.*) *in ethanol* (30 *ml.*) *with* 10% Pd–C *catalyst* (50 *mg.*) *at* 20° *in the presence of varying amounts of base* (*A*, *no base*; *B*, 1 *mol. of triethylamine*; *C*, 2 *mols. of triethylamine*).

acids for use in pyrophosphate synthesis [14] had been accomplished by anionic debenzylation of the corresponding dibenzyl ester, but the present method appears to be more convenient. Anionic debenzylation of phosphoramidic, as opposed to phosphoric, esters requires not only somewhat forcing conditions but usually that the product should be precipitated during the reaction, thereby displacing the equilibrium in the desired direction.[3] Such a separation of the product is by no means invariable; for example, after treatment with sodium iodide in ethyl methyl ketone under reflux for 1 hr. dibenzyl *N-cyclo*hexylphosphoramidate was recovered in 85% yield, no precipitation of product having occurred.

Of the palladium catalysts used, palladium black [15] was much less susceptible to inhibition than palladised charcoal, possibly owing to its greater subdivision. Dibenzyl phosphoramidate was rapidly and completely debenzylated by hydrogenation in presence of palladium black, and Zervas and Katsoyannis [16] have recorded analogous results in their preparation of *N*-phosphorylated amino-acids from the corresponding *P*-dibenzyl esters.

[14] Clark, Kirby, and Todd, *J.*, 1957, 1497.
[15] Wieland, *Ber.*, 1912, **45**, 484.
[16] Zervas and Katsoyannis, *J. Amer. Chem. Soc.*, 1955, **77**, 5351.

Hydrogenolysis of esters may be akin to protonolysis, the relative ease of removal, benzyl ⩾ *cyclo*hexyl > *sec.*-butyl > ethyl ⩾ methyl,[17] supporting this view. The reaction rate would then depend on the surface concentration of protons, and hydrogenolysis might be slowed down or stopped by introduction of a base. However, although the rate of hydrogen uptake is reduced on addition of base, the initial rate in the presence of 2 mols. of amine is greater than in the presence of 1 mol. (Fig. 2) and this has been our experience during several years. It seems therefore that base affects, not only the stationary work function of the catalyst surface,[18] but also the adsorption–desorption equilibrium at that surface, the monodebenzylated material being desorbed rapidly under the conditions used. Our work throws little light on the mechanism of the catalysis, though the conditions are readily reproducible; however, it provides a very satisfactory preparative method of partial debenzylation.

Experimental

Palladised Charcoal Catalyst.[19]—Charcoal (Karbak H.T. 20) was heated under reflux for 5 hr. with a 1 : 1 v/v mixture of concentrated hydrochloric acid and water to remove traces of metals and, after washing with distilled water until nickel-free, was dried at 110° for 12 hr. A solution of palladium chloride (2 g.) in N-hydrochloric acid (25 ml.) at 40° was cooled and diluted with water (250 ml.). The charcoal (20 g.) was added and the palladium reduced on to the support by shaking the whole in hydrogen for 1 hr. at room temperature and atmospheric pressure (uptake, 500 ml., theor. 270 ml.). The catalyst was filtered off, washed until free from chloride ion, and dried at 80° for 24 hr.

Effect of Various Bases on the Hydrogenation of Tribenzyl Phosphate.—Aliquot parts (100 ml.) of tribenzyl phosphate (12·3 g.) in dry ethanol (1 l.) were used for the various hydrogenations. A further small volume (10 ml.) of ethanol was used in each case for the introduction of the catalyst (200 mg.) and to enable a correction to be made for the volume of base added. Before each hydrogenation the catalyst was saturated with hydrogen at atmospheric pressure.

The results obtained by use of 5 mols. of *cyclo*hexylamine, morpholine, 4-methylmorpholine, or sodium methoxide are indicated in Fig. 1. To the solution from the hydrogenation in presence of alkoxide, 3N-hydrochloric acid (25 ml.) was added and the mixture extracted with chloroform (2 × 25 ml.). The extract was shaken with 10% aqueous sodium hydroxide (25 ml.) and the alkaline layer then acidified with dilute sulphuric acid and again extracted with chloroform (3 × 25 ml.). Evaporation gave an oil which crystallised on addition of ether. Recrystallisation from ether gave dibenzyl hydrogen phosphorate (670 mg., 72%), m. p. 78°, undepressed in admixture with an authentic specimen.[20]

Effect of Triethylamine on the Hydrogenation of Dibenzyl Phosphoramidate.—The rates of hydrogen uptake in the hydrogenation of dibenzyl phosphoramidate with 10% palladised charcoal in the absence of base and in the presence of 1 and 2 mols. of triethylamine are compared in Fig. 2. When palladium black [15] was used as catalyst, complete debenzylation occurred even in the presence of 2 mols. of triethylamine (cf. ref. 16).

Benzyl Hydrogen Phosphoramidate.—Dibenzyl phosphoramidate (3·0 g.) in ethanol (75 ml.) containing triethylamine (2·2 g., 2 mol.) was hydrogenated over 10% palladised charcoal (300 mg.) at room temperature and atmospheric pressure. After 45 min. the suspension was filtered and the filtrate treated with a solution from sodium (0·25 g., 1 mol.) in a little ethanol. The precipitated sodium salt (1·93 g.) was kept at 5° for 1 hr., collected, washed with ethanol and ether, and dried *in vacuo*. *Sodium benzyl phosphoramidate* crystallised from aqueous ethanol as colourless plates (Found, after drying over P_2O_5 at 20°/0·1 mm.: C, 40·0; H, 4·5; N, 6·7. $C_7H_9O_3NPNa$ requires C, 40·2; H, 4·3; N, 6·7%).

The crude sodium salt (0·50 g.) was dissolved in water (3 ml.), filtered and treated with ethanol (1 ml.) followed by 3N-hydrochloric acid (1 ml.). Benzyl hydrogen phosphoramidate separated immediately as plates, which, after 15 min. at 0°, were collected, washed with a little ice-cold water, and dried (P_2O_5) (yield 0·29 g., 50%). The infrared spectrum between 4000 and 650 cm.$^{-1}$ was identical with that of Clark and Todd's [3] specimen.

[17] Adkins and Folkers, *J. Amer. Chem. Soc.*, 1932, **54**, 1145.
[18] Dowden, *J.*, 1950, 242.
[19] Cf. *Org. Synth.*, Coll. Vol. III, 1955, p. 685.
[20] Lossen and Köhler, *Annalen*, 1891, **262**, 211.

Benzyl Hydrogen N-cyclo*Hexylphosphoramidate.*—Dibenzyl *N-cyclo*hexylphosphoramidate [21] (0·50 g.) in ethanol (20 ml.) containing triethylamine (0·28 g., 2 mol.) was hydrogenated over 10% palladised charcoal (50 mg.) at room temperature and atmospheric pressure, the hydrogen uptake being complete after 50 min. After evaporation of solvent, the residue was shaken with water (20 ml.) and 10% sodium hydroxide solution added until the product had dissolved. Catalyst was filtered off and the filtrate acidified with 3N-hydrochloric acid, benzyl hydrogen *N-cyclo*hexyl phosphoramidate being precipitated. After 1 hr. at 5° the product was collected, washed with water, and dried (P_2O_5). Recrystallisation from ethyl acetate gave needles (0·27 g., 72%), m. p. 96—100° undepressed on admixture with an authentic specimen.[14]

Benzyl Hydrogen N-*Benzylphosphoramidate.*—Dibenzyl *N*-benzylphosphoramidate [21] (0·66 g.) was monodebenzylated under the conditions described above for the *N-cyclo*hexyl derivative. The crude benzyl hydrogen *N*-benzylphosphoramidate (0·44 g.) was recrystallised from ethyl acetate, forming prisms (0·27 g., 54%), m. p. 98—100° (Found: C, 60·5; H, 6·0; N, 5·0. Calc. for $C_{14}H_{16}O_3NP$: C, 60·6; H, 5·8; N, 5·1%).

Benzyl Hydrogen N-1-*Phenylethylphosphoramidate.*—Dibenzyl *N*-1-phenylethylphosphoramidate [21] (0·685 g.) was debenzylated as in the preceding example. The aqueous alkaline extract of the reaction product, acidified with 3N-hydrochloric acid, gave *benzyl hydrogen* N-1-*phenylethylphosphoramidate* as needles which, after 1 hr. at 5°, were collected, washed with water, and dried *in vacuo* (P_2O_5) (yield 0·46 g., 88%) (Found: C, 61·8; H, 6·2; N, 4·9. $C_{15}H_{18}O_3NP$ requires C, 61·9; H, 6·2; N, 4·8%). Recrystallised from ethyl acetate, these had m. p. 88—92°.

Benzyl Hydrogen N-*Phenylphosphoramidate.*—Dibenzyl *N*-phenylphosphoramidate [21] (0·65 g.) was hydrogenated in the presence of triethylamine (0·37 g., 2 mols.). After 40 min. hydrogenation was discontinued, the suspension filtered, and the filtrate treated with sodium (0·042 g., 1 mol.) dissolved in ethanol (10 ml.). Evaporation yielded crude *sodium benzyl* N-*phenylphosphoramidate* (0·50 g.). Recrystallised from ethanol–ether, the salt * formed needles (0·38 g., 68%) (Found: C, 51·5; H, 4·8; N, 5·0. $C_{13}H_{13}O_3NPNa,H_2O$ requires C, 51·5; H, 4·9; N, 4·6%). Treatment of the salt (100 mg.) in water (5 ml.) with excess of 3N-hydrochloric acid at 5° precipitated *benzyl hydrogen* N-*phenylphosphoramidate* (80 mg.) (Found: C, 59·1; H, 5·6; N, 5·55. $C_{13}H_{14}O_3NP$ requires C, 59·3; H, 5·3; N, 5·3%). Recrystallisation from aqueous ethanol was accompanied by decomposition; the acid then formed colourless plates, m. p. 120—122° (Found: C, 58·7; H, 5·7; N, 5·5%).

Benzyl Hydrogen N-p-*Tolylphosphoramidate.*—As in the previous example, *sodium benzyl* N-p-*tolylphosphoramidate* (0·49 g.) was obtained from the dibenzyl ester [21] (0·66 g.). Recrystallised from ethanol–ether, the salt formed needles (0·37 g., 69%) (Found: C, 54·1; H, 4·9; N, 4·8. $C_{14}H_{15}O_3NPNa,\frac{1}{2}H_2O$ requires C, 54·6; H, 5·2; N, 4·5%). Treatment of the salt (100 mg.) with 3N-hydrochloric acid gave the free *acid* (65 mg.) as needles, m. p. 113—116° (Found: C, 60·3; H, 5·9; N, 5·2. $C_{14}H_{16}O_3NP$ requires C, 60·6; H, 5·8; N, 5·1%).

Dibenzyl N-p-*Hydroxyphenylphosphoramidate.*—*p*-Aminophenol (1·1 g.) and triethylamine (2 ml.) in dry acetone (50 ml.) were mixed with dibenzyl phosphonate (2·6 g.) in carbon tetrachloride [21] (10 ml.) and left at room temperature for 20 hr. Precipitated triethylammonium chloride was removed and the filtrate evaporated, the residue being taken up in chloroform (20 ml.). The solution was washed with 3N-hydrochloric acid (20 ml.) and water (2 × 20 ml.); during each washing a crystalline product separated at the interface. This was collected and the washed chloroform layer kept at 5° until no more material separated (total yield, 1·60 g.). After drying (Na_2SO_4), the chloroform solution was concentrated (to 10 ml.) and light petroleum added. A second crop of product (0·40 g.) separated. Recrystallisation from chloroform–light petroleum gave *dibenzyl* N-p-*hydroxyphenylphosphoramidate* as plates (1·75 g., 47%), m. p. 118—120° (Found: C, 64·9; H, 5·65; N, 4·0. $C_{20}H_{20}O_4NP$ requires C, 65·0; H, 5·4; N, 3·8%).

Acetylation of the dibenzyl ester with acetic anhydride–pyridine gave the O-*acetate*, which, recrystallised from aqueous ethanol, had m. p. 86—87°, $\nu_{max.}$ 1760 cm.$^{-1}$ (Nujol mull) (Found: C, 64·0; H, 5·6. $C_{22}H_{22}O_5NP$ requires C, 64·2; H, 5·4%).

Benzyl Hydrogen N-p-*Hydroxyphenylphosphoramidate.*—The dibenzyl ester (300 mg.) in ethanol (20 ml.) was hydrogenated in the presence of triethylamine (250 mg., 3 mols.)

* Also prepared by Dr. D. H. Marrian (personal communication) using thiocyanate ion (cf. ref. 3).

[21] Atherton, Openshaw, and Todd, *J.*, 1945, 660.

and 10% palladised charcoal (20 mg.). After 25 min. the hydrogenation was interrupted and the solution filtered. Evaporation of the filtrate left a gum which was dissolved in water (5 ml.). Treatment with excess of N-hydrochloric acid precipitated *benzyl hydrogen* N-p-*hydroxyphenylphosphoramidate*, which was washed sparingly with water, dissolved in a minimum of 0·1N-sodium carbonate, and reprecipitated with N-hydrochloric acid as plates (121 mg., 52%). After further washing, the product was dried at room temperature *in vacuo* (P_2O_5), then having m. p. 126—128° (Found: C, 54·9; H, 5·4; N, 5·1. $C_{13}H_{14}O_4NP,\frac{1}{2}H_2O$ requires C, 54·2; H, 5·2; N, 4·9%).

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