77. *The Solvolysis of Dibenzyl* trans-2-*Hydroxycyclohexyl Phosphate.*

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Dibenzyl *trans*-2-hydroxycyclohexyl phosphate is decomposed by base in three ways: by competitive attack of the neighbouring hydroxyl group (*a*) on phosphorus with cyclic phosphate formation and (*b*) on carbon with formation of cyclohexene oxide and dibenzyl phosphate (hydroxide and t-butoxide); and by attack on phosphorus with expulsion of cyclohexane-1,2-diol (by methoxide). Qualitatively similar behaviour is shown by dibenzyl 2-hydroxyethyl phosphate.

Dibenzyl *trans*-2-hydroxycyclohexyl phosphate (I) is hydrolysed rapidly by aqueous alkali and from chromatographic evidence it was deduced[1] that benzyl 2-hydroxycyclohexyl hydrogen phosphate (IV) was the sole product, in accord with observations on other phosphate triesters having a vicinal hydroxyl group.[2] During a further study of the ester (I) it was noted that appreciable amounts of cyclohexene oxide were formed. The hydrolysis was therefore re-investigated and the results are here recorded. The effects of methoxide and t-butoxide on the ester (I) are also described.

When the phosphate (I) was heated with 2N-alkali at 100° cyclohexene oxide (0·30—0·32 mol.) was produced. These values are minimal, since the method of determination is not completely stoicheiometric. Acidification of the hydrolysed solution yielded crystalline dibenzyl hydrogen phosphate (0·27—0·29 mol.). Paper chromatography showed that, in addition to these two products, benzyl 2-hydroxycyclohexyl hydrogen phosphate (IV) and

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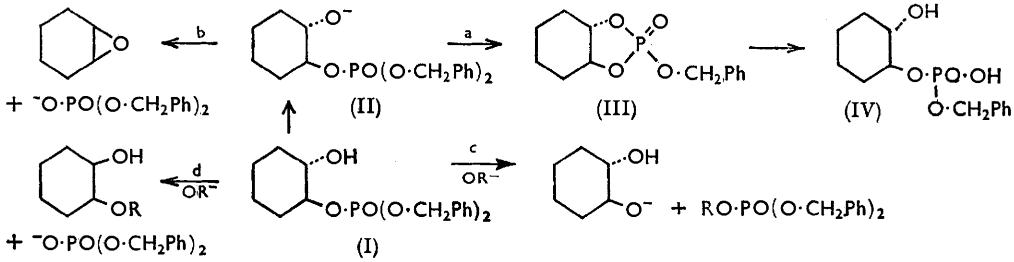
[1] Brown and Higson, *J.*, 1957, 2034.

[2] Brown, Magrath, and Todd, *J.*, 1952, 2708.

2-hydroxycyclohexyl dihydrogen phosphate were the only other phosphorus-containing materials present. Dibenzyl 2-hydroxyethyl phosphate under the same conditions gave only 0·01—0·02 mol. of ethylene oxide and dibenzyl hydrogen phosphate, the major product being benzyl 2-hydroxyethyl hydrogen phosphate.

Esters related to the phosphate (I) normally break down by route (a) (see chart).[2] Evidently the phosphate (I) can also undergo base-catalysed fission by route (b) through displacement of the dibenzyl phosphate anion by rear-side attack by the hydroxyl group on carbon. Displacements of this type have been observed to take place with 2-amino-[3] and 2-mercapto-groups,[4] but not, heretofore, with a 2-hydroxyl group. It may be noted that vigorous hydrolysis of benzyl *trans*-2-hydroxycyclohexyl hydrogen phosphate (IV) gave only 2-hydroxycyclohexyl dihydrogen phosphate. However, the monoethyl[5] and the monobenzyl[6] ester of glycerol 1-phosphate under those conditions afforded 0·06—0·08 mol. of methyl and benzyl dihydrogen phosphate respectively, in addition to glycerol phosphate: in these cases, then, it may be that a small proportion of the reaction involved epoxide formation.



There are two ways additional to (a) and (b) by which esters of type (I) could be solvolysed. These, represented by (c) and (d), are of course not specific for esters carrying a vicinal hydroxyl group. There is evidence that (d) does not occur in aqueous solution, and in other cases evidence is available to show that it must be very much slower than reaction (c).

Since route (b) is the only one which allows the generation of epoxide, the amount of the latter is a direct measure of the fraction of ester (I) breaking down in this way. Since the amount of dibenzyl hydrogen phosphate formed is almost equivalent to that of the epoxide on a molar basis it follows that little or none of the former could have been formed by reaction (c). In any event, reaction by path (c) could not explain the unusual lability of these esters to alkali.

Treatment of the phosphate (I) with potassium t-butoxide in t-butyl alcohol likewise afforded cyclohexene oxide (0·31—0·34 mol.) and dibenzyl hydrogen phosphate (0·26—0·29 mol.). In view of the experimental errors inherent in the methods of estimation these values are in remarkably close agreement with those obtained in the hydrolytic experiments. They suggest that the relative amounts of the anion (II) breaking down by routes (a) and (b) depend essentially on the stereochemistry of the vicinal alkoxide group and only to a small extent on the solvent. There is, however, a possible complicating factor, namely, that the cyclic phosphate (III) might be opened by t-butoxide attack, although this would be surprising on general chemical grounds. Our failure to obtain crystalline dibenzyl hydrogen phosphate after reaction suggests that traces of another water-insoluble phosphate were present. The rather higher yields of epoxide, too, might argue in favour of the reversibility of reaction (a), so that a greater proportion of the reaction could then proceed by path (b). Paper chromatography, however, gave no indication of the presence of t-butyl esters.

[3] Brown and Osborne, *J.*, 1957, 2590.

[4] Heath, *J.*, 1958, 1643.

[5] Fleury, Lecocq, and Le Dizet, *Bull. Soc. chim. France*, 1956, 1193.

[6] Dr. G. E. Hall, personal communication.

With sodium methoxide in dry methanol the ester (I) gave no detectable cyclohexene oxide and only very small amounts of dibenzyl hydrogen phosphate (0·01—0·03 mol.). However cyclohexane-1,2-diol was formed, corresponding to 0·85—0·88 mol. Dibenzyl 2-hydroxyethyl phosphate, too, afforded 0·76—0·79 mol. of glycol. In the case of the phosphate (I), which was more thoroughly studied, the amount of diol formed was independent of the time allowed for reaction, in so far as the yield was the same after 0·5 hr. at room temperature or 12 hr. under reflux. The nature of the phosphate esters formed was, in contrast, markedly dependent on the time of reaction. Under the former conditions the major proportion of the phosphorus was present as ether-soluble tertiary phosphates which were not further studied. When the latter conditions were employed, over 90% of the phosphorus was present as water-soluble diesters, of which dimethyl hydrogen phosphate (60—70%) and benzyl methyl hydrogen phosphate (30%) accounted for almost all of the material, as indicated by chromatography.

Since no epoxide and little dibenzyl hydrogen phosphate were produced, at most 15% of the products were formed by paths (a) and (b). The evidence points to reaction (c) as the fastest and shows that the diol is expelled preferentially to benzyl alcohol. This is to be expected in view of our earlier studies [7] and because diols appear to be considerably more acidic than monohydric alcohols [8] (*i.e.*, their anions are more stable). Transesterification of the initially formed triester, presumably dibenzyl methyl phosphate, and then the gradual dealkylation by methoxide of all triesters with alkyl-oxygen fission,[9] would then account for the formation of dimethyl and benzyl methyl hydrogen phosphate as the stable end products, but these processes must be much slower than reaction (c). The absence of epoxide in the reaction mixture might be accounted for by its subsequent reaction with methoxide, but no evidence for 2-methoxycyclohexanol could be found, treatment of ethereal extracts with 3,5-dinitrobenzoyl chloride affording only the corresponding derivative of benzyl alcohol.

It is, at first sight, surprising that there should be a change in solvolytic mechanism on changing from hydroxide to methoxide. It appears that this could result from a greater nucleophilic power of methoxide than of hydroxide with respect to attack at the phosphoryl group, coupled with the weaker basic strength of the former.[8] Taken together, these factors must diminish the importance of the neighbouring group displacements [reactions (a) and (b)] in the methoxide solvolysis. These observations, too, are in accord with analogous cases in the carboxylic ester series where it is found that, although methoxide ion is a weaker base than hydroxide ion, it is a more active nucleophile.[9] The experiments of Orloff *et al.*[10] with dimethyl phenyl phosphate indicate a corresponding difference in reactivity between methoxide and hydroxide ions in phenoxide displacement.

EXPERIMENTAL

Paper chromatography was carried out with Whatman No. 1 paper and propan-2-ol–water–ammonia (*d* 0·880) (7 : 2 : 1). Standard substances were invariably run for purposes of identification.

Dibenzyl trans-*2-Hydroxycyclohexyl Phosphate.*—Dibenzyl hydrogen phosphate (1 mol.), cyclohexene oxide (1·05 mol.), and dry ether (5 ml. per g. of phosphate) were mixed and kept at 30° until no free acid remained (*ca.* 5 hr.). Light petroleum (2 vol.; b. p. 60—80°) was added and the product crystallised (m. p. 77°) and then recrystallised from the same solvent, giving needles (78%), m. p. 79—80° (lit.,[11] 78—80°).

Reaction of Ester with Sodium Hydroxide.—A weighed quantity of the above phosphate ester (0·5—1·5 mmoles) was added to 2N-sodium hydroxide (10 ml.) and steam-distilled until 50 ml. of distillate had collected. Cyclohexene oxide was estimated in the distillate by Ross's

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[7] Brown, Hall, and Higson, *J.*, 1958, 1360.

[8] Hine and Hine, *J. Amer. Chem. Soc.*, 1952, **74**, 5266.

[9] Bender and Glasson, *ibid.*, 1959, **81**, 1590.

[10] *Inter al.*, Orloff, Calvin, Worrel, and Markley, *ibid.*, 1958, **80**, 724.

[11] Baddiley, Clark, Michalski, and Todd, *J.*, 1949, 815.

method,[12] in which reaction of the oxide with thiosulphate is followed acidimetrically. For reproducible results the solution was kept at 60° for 0·5 hr. as the oxide reacted slowly, and even under the best conditions the reaction was only approximately stoicheiometric.

The distillation residue (15—20 ml.) was neutralised, extracted with ether (2 × 20 ml.), boiled to remove ether, and acidified to pH 1 with dilute sulphuric acid. Dibenzyl hydrogen phosphate, m. p. and mixed m. p. 78°, separated in needles during a few hours. In one experiment with 215 mg. of ester there were formed 45 mg. of dibenzyl hydrogen phosphate (0·28 mol.) and cyclohexene oxide (0·31 mol.).

In another experiment the epoxide was steam-distilled into ethanol (10 ml.) and 2N-sulphuric acid (10 ml.), and after neutralisation with sodium hydrogen carbonate the cyclohexanediol produced was estimated by periodate titration (Found: 0·31 mol.).

Paper chromatography indicated the production of diesters of phosphoric acid and 2-hydroxycyclohexyl phosphate.

Reaction of Ester with Sodium Methoxide.—A weighed quantity of the ester (1—2 mmoles) was treated with 2N-sodium methoxide in dry methanol for (*a*) 30 min. at room temperature, (*b*) 12 hr. at room temperature, and (*c*) 12 hr. under reflux.

Cyclohexanediol was estimated by neutralising the mixture with glacial acetic acid and removing most of the methanol *in vacuo*. Water (30 ml.) was added, the solution extracted with ether (2 × 20 ml.), and solid sodium hydrogen carbonate added to the aqueous phase, to saturation. Periodate titration showed the presence of 0·85—0·88 mol., independently of reaction time.

In separate experiments cyclohexene oxide was sought as above; none was found. For the estimation of dibenzyl hydrogen phosphate produced, the reaction mixture was evaporated *in vacuo*, the residual solid dissolved in water (20 ml.), and the solution extracted with ether (2 × 20 ml.); on acidification, the aqueous layer deposited crystals of dibenzyl hydrogen phosphate (0·01—0·03 mol.).

The distribution between neutral and acidic phosphate esters was investigated by the following procedures. The reaction mixture was neutralised with glacial acetic acid, methanol was removed under reduced pressure, and the residue dissolved in water (20 ml.). Neutral esters were extracted into ether (2 × 20 ml.). In reaction (*a*), only small amounts of water-soluble products were formed, characterised as dibenzyl hydrogen phosphate and, probably, benzyl *trans*-2-hydroxycyclohexyl hydrogen phosphate by chromatography. The main products were ether-soluble neutral esters which were nor further studied.

In reaction (*c*), at least 90% of the products were water-soluble, consisting of dimethyl hydrogen phosphate (60—70%), benzyl methyl hydrogen phosphate, and traces of dibenzyl hydrogen phosphate and benzyl 2-hydroxycyclohexyl hydrogen phosphate, characterised on paper chromatograms.

The ethereal solution contained only traces of esters which on alkaline hydrolysis gave benzyl methyl and dimethyl hydrogen phosphate.

Reaction of Ester with Potassium t-Butoxide.—In a solution of potassium t-butoxide in dry t-butyl alcohol (20 ml. containing 1·5 g. of potassium) was dissolved the phosphate ester (1—2 mmoles), and the mixture was kept at 35° for 0·5 hr. Glacial acetic acid (2·5 ml.) was added, followed by water (30 ml.) and then sodium hydroxide solution to pH 8·4. The solution was steam-distilled and after 100 ml. of distillate had been collected an epoxide estimation was performed, as before (Found: 0·31—0·34 mol. of cyclohexene oxide). The steam-distillation residue was acidified; dibenzyl hydrogen phosphate separated but did not crystallise; it was estimated as orthophosphate in a separate experiment by adding water to the reaction mixture, steam-distilling it, and hydrogenating the residual solution over palladium–charcoal (Found: inorganic : total P, 0·29).

Chromatography of the solution before hydrogenation indicated the presence of fast-running diesters of phosphoric acid, which were converted on hydrogenation into 2-hydroxycyclohexyl dihydrogen phosphate and inorganic phosphate.

Dibenzyl 2-Hydroxyethyl Phosphate.—Dibenzyl hydrogen phosphate (3·0 g.; dried at 0·1 mm./50° over P_2O_5) was dissolved in dry carbon tetrachloride, cooled to 0°, treated with ethylene oxide (5 ml.), and kept at 0° for 15 min., then at 30° for 3 hr. A test showed the presence of a little free acid. The solution was washed with cold sodium hydrogen carbonate solution and water, and then dried (Na_2SO_4). Solvent was removed at 0° and the residual oil dried for

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[12] Ross, *J.*, 1950, 2297.

12 hr. at 0·1 mm. over phosphoric oxide at 0°. *Dibenzyl 2-hydroxyethyl phosphate* (2·97 g.) was obtained as a colourless oil, *n* 1·5364 (Found: C, 59·4; H, 6·3. $C_{16}H_{19}O_5P$ requires C, 59·6; H, 5·9%).

The reactions with sodium hydroxide and methoxide were carried out as described for the corresponding *trans*-2-hydroxycyclohexyl ester.

Cyclohexylammonium Benzyl 2-Hydroxyethyl Phosphate.—The above ester (0·8 g.) and cyclohexylamine (2 ml.) were boiled in 50% (v/v) aqueous methanol (20 ml.) under reflux for 6 hr. with exclusion of carbon dioxide. The solution was evaporated below 50° under reduced pressure to a pale yellow oil, which was dissolved in dry acetone. On cooling, the *product* separated in needles (0·72 g.), m. p. 153—154° (Found: C, 54·0; H, 8·0; N, 4·5. $C_{15}H_{26}O_5NP$ requires C, 54·4; H, 7·9; N, 4·5%).

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