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# *Studies on Phosphorylation. Part XII.* Selective Anionic Dealkylation of Neutral Esters of Phosphoric and Thiophosphoric Acids.*

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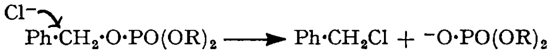
The method of anionic fission developed for monodebenzylation of neutral esters of the oxyacids of phosphorus (Part VII, *J.*, 1950, 2031) can be extended to the removal of alkyl groups. Selective monodealkylation of a number of esters of phosphoric and thiophosphoric acids is described, and the conditions governing its success are discussed.

In Part VII of this series (Clark and Todd, *J.*, 1950, 2031) it was shown that neutral esters of phosphorous and phosphoric acid containing one or more benzyl groups can be monodebenzylated by heating them with inorganic salts such as lithium chloride in ethoxyethanol solution. The mechanism postulated for this anionic fission involved an attack by the anion of the salt on the electrophilic $CH_2$ group in the benzyl residue :



$$\overset{Cl^{-}\curvearrowright}{Ph{\cdot}CH_2{\cdot}O{\cdot}PO(OR)_2} \longrightarrow Ph{\cdot}CH_2Cl + {}^{-}O{\cdot}PO(OR)_2$$

As was to be expected on the basis of this mechanism lithium chloride had no effect on triphenyl phosphate, but the fact that it brought about monodebenzylation of dibenzyl phosphoramidate (aminophosphonate) led to the suggestion (*loc. cit.*) that the method might, under appropriate conditions, be applicable to groups, such as alkyl, with considerably less electrophilic character than the benzyl group. The present paper records a number of experiments which indicate that this is indeed so.

For the investigation, a number of hitherto undescribed mixed triesters of phosphoric acid containing both aryl and alkyl groups were prepared, as well as some neutral thiol- and thiono-phosphates. Mixed esters containing phenyl as well as alkyl groups seemed of particular interest since it was expected that the phenyl groups would indirectly increase the electrophilic character of the α-carbon of the alkyl groups and so facilitate monodealkylation by the above mechanism. Each ester was treated with lithium chloride under standard conditions, *viz.*, in 2-ethoxyethanol solution at 100° for 3 hours. The results obtained are summarised in the Table.

*Monodealkylation of phosphates and thiophosphates with lithium chloride at* 100°.

| Ester | Yield (%) of monodealkylated product | Ester | Yield (%) of monodealkylated product |
|---|---|---|---|
| Diphenyl *n*-propyl phosphate ... | 85 | Diphenyl *n*-propyl thionophosphate ............................ | 27 |
| Phenyl di-*n*-propyl phosphate ... | 50 | Diethyl *S*-phenyl thiophosphate | 75 |
| Tri-*n*-propyl phosphate ......... | 25 | *S*-Ethyl diphenyl thiophosphate | No reaction |
| Diphenyl *iso*propyl phosphate ... | 85 | | |
| *cyclo*Hexyl diphenyl phosphate | 45 | | |

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In considering these results it should be remembered that the yields quoted are based on the weight of isolated diester (either as such or as an appropriate derivative) and are thus only very roughly quantitative; again, it cannot be assumed that the chosen reaction conditions are optimum in any case. Pyrolytic decomposition of phosphates at high temperatures causes dealkylation: for example, diphenyl *iso*propyl phosphate is converted almost quantitatively into diphenyl hydrogen phosphate at *ca.* 180°. This type of decomposition is certainly not the main cause of the dealkylation observed in our studies; at 100°, in the absence of lithium chloride, diphenyl *n*-propyl phosphate was unaffected and only minor decomposition occurred with diphenyl *iso*propyl phosphate ($\ngtr$16%), *cyclo*hexyl diphenyl phosphate ($\ngtr$12%), and diethyl *S*-phenyl thiophosphate ($\ngtr$10%).

From the Table it can be seen that, as expected, dealkylation is made easier by the presence of phenyl groups. It also appears that steric factors are important; it is hard to account otherwise for the comparatively low yield from *cyclo*hexyl diphenyl phosphate. Variation in yields when different salts are used has been reported for the monodebenzylation of neutral phosphates (Clark and Todd, *loc. cit.*); similar variations are observed in the removal of alkyl groups. Salts are more powerful debenzylating agents than tertiary bases. Thus, dibenzyl phosphoramidate resists the action of 4-methylmorpholine but is monodebenzylated by lithium chloride (Clark and Todd, *loc. cit.*); in the same way, diphenyl *n*-propyl phosphate is unaffected by refluxing 4-methylmorpholine (b. p. 115°) for 3 hr., although under the same conditions conversion of tribenzyl phosphate into dibenzyl phosphate is well-nigh quantitative. The addition of a small amount (5%) of water to the ethoxyethanol used in the dealkylation experiments caused little diminution in the yield of dealkylated product in the case of diphenyl *n*-propyl phosphate. Large amounts of water are, however, deleterious; thus, when the same ester is refluxed with calcium chloride in 98% ethanol, the yield of calcium diphenyl phosphate was 22%, and in 60% ethanol it fell to 3%.

It is known that many thiophosphates form complexes with silver nitrate, the metal presumably becoming co-ordinated to a sulphur atom; the sulphonium salt so formed can then break up under appropriate conditions of temperature with expulsion of an alkyl group (cf., for example, Emmett and Jones, *J.*, 1911, 715; Pistschimuka, *J. pr. Chem.*, 1911, **84**, 746). However, diphenyl *n*-propyl thionophosphonate gave only a trace of precipitate with silver nitrate, whereas *S*-ethyl diphenyl thiophosphate gave a copious precipitate of complex salt. Since the former ester is dealkylated under our standard conditions whereas the latter is not, it seems clear that lithium chloride dealkylation of thiophosphates is essentially analogous to that of the phosphates and differs from the silver nitrate reactions mentioned above. The failure of the attempted dealkylation of *S*-ethyl diphenyl thiophosphate with lithium chloride under the standard conditions is probably explained by the smaller electronegativity of sulphur compared with oxygen.

Pistschimuka (*J. Russ. Phys. Chem. Soc.*, 1912, **44**, 1406) reported the isolation of two distinct sodium salts of diphenyl hydrogen thiophosphate; an insoluble salt $(PhO)_2PO{\cdot}SNa$ he claimed to obtain by the action of sodium methoxide on triphenyl thionophosphate, and a soluble one $(PhO)_2PS{\cdot}ONa$ by treating diphenyl thionophosphorochloridate with sodium hydroxide. We have been unable to confirm these findings. Treatment of triphenyl thionophosphate with sodium methoxide or sodium hydroxide gave the same soluble sodium salt as lithium chloride dealkylation of diphenyl *n*-propyl thionophosphate. Our findings thus parallel those of Mastin, Norman, and Weilmuenster (*J. Amer. Chem. Soc.*, 1945, **67**, 1662) and of Foss (*Acta Chem. Scand.*, 1947, **1**, 8) on salts of dialkyl hydrogen thiophosphates, and it seems clear that the claim to separate existence of isomeric thiol- and thiono-acid salts cannot be upheld.

Because of its potential application in the nucleotide field, we are interested in the possibility of direct replacement of alkyl groups in neutral phosphates by hydrogen using anionic fission. This we were unable to effect using calcium hydride, while lithium aluminium hydride reacted vigorously with triphenyl phosphate yielding phosphine and phenol and a similar reaction occurred with diphenyl *n*-propyl and phenyl di-*n*-propyl phosphate. Karrer and Jucker (*Helv. Chim. Acta*, 1952, **35**, 1586) have independently observed a similar action of lithium aluminium hydride on cetyl dihydrogen phosphate. This reaction of

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lithium aluminium hydride is analogous to that of phenylmagnesium bromide which displaces the alkoxy-groups in alkyl phosphates (Gilman and Robinson, *Rec. Trav. chim.*, 1929, **48**, 328).

## EXPERIMENTAL

*Diphenyl* n-*Propyl Phosphate.*—Diphenyl phosphorochloridate (26·8 g.; Brigl and Müller, *Ber.*, 1939, **72**, 2121) in dry benzene (25 c.c.) was added slowly to an ice-cold stirred solution of *n*-propanol (6 g.) and dry pyridine (7·9 g.) in benzene (50 c.c.). The temperature rose slightly and pyridine hydrochloride began to separate during the addition. The mixture was set aside overnight, water was added, and the benzene layer separated, washed with aqueous sodium carbonate, then with water, and finally dried ($Na_2SO_4$). After evaporation, the residue (28 g.) was distilled under reduced pressure, care being taken to avoid overheating (which causes decomposition). *Diphenyl* n-*propyl phosphate* distilled as a colourless liquid at 148—150°/0·1 mm. and had $n^{15·5}$ 1·5242 (Found: C, 61·9; H, 6·2. $C_{15}H_{17}O_4P$ requires C, 61·6; H, 5·9%).

*Diphenyl* iso*Propyl Phosphate.*—Prepared as above from diphenyl phosphorochloridate (26·8 g.) and *iso*propanol (6 g.), the crude ester weighed 28 g. When distillation of the ester was attempted under a pressure of 0·1 mm. brisk decomposition began when the bath temp. reached 180°; after 15 min. at a bath temp. of 225° the material was completely converted into diphenyl hydrogen phosphate, m. p. and mixed m. p. 68—70°. *Diphenyl* iso*propyl phosphate* was therefore purified by short-path distillation at 98—100°/$10^{-4}$ mm., forming a colourless liquid, $n^{15·5}$ 1·5232 (Found: C, 61·1; H, 5·6. $C_{15}H_{17}O_4P$ requires C, 61·6; H, 5·9%).

cyclo*Hexyl Diphenyl Phosphate.*—Prepared as above, the crude ester (30·5 g. from 26·8 g. of diphenyl phosphorochloridate) crystallised slowly when kept at 0°. Recrystallised from light petroleum (b. p. 40—60°), it had m. p. 34—35° (Found: C, 65·2; H, 6·2. Calc. for $C_{18}H_{21}O_4P$: C, 65·1; H, 6·3%).

*Phenyl Di*-n-*propyl Phosphate.*—Phenyl phosphorodichloridate (21·1 g.; Brigl and Müller, *loc. cit.*) in dry benzene (25 c.c.) was added slowly with stirring to an ice-cold solution of *n*-propanol (12 g.) and dry pyridine (15·8 g.) in benzene (100 c.c.). The mixture was set aside overnight, then worked up as described for diphenyl *n*-propyl phosphate. The *product* distilled at 165° (bath-temp.)/0·1 mm. (Found: C, 56·5; H, 7·3. $C_{12}H_{19}O_4P$ requires C, 55·8; H, 7·4%).

*Diphenyl Thionophosphorochloridate.*—The following modification of the method of Autenrieth and Meyer (*Ber.*, 1925, **58**, 840) is recommended. Phenol (94 g.) in dry benzene was slowly added to a suspension of powdered sodium (23 g.) in benzene (*ca.* 500 c.c.). Then the mixture was stirred at room temperature until the reaction slackened, and reaction was completed by 5 hours' refluxing. The suspension of sodium phenoxide so obtained was cooled to −5° and a solution of thiophosphoryl chloride (84 g.) in dry benzene (100 c.c.) added slowly with stirring. When all had been added the mixture was allowed to come to room temperature and was then heated under reflux for 2 hr., cooled, and filtered. The filtrate was washed with water, dried ($Na_2SO_4$), and evaporated. The residual oil (126 g.) solidified; recrystallised from 98% ethanol or light petroleum, it had m. p. 67—68°.

*Diphenyl* n-*Propyl Thionophosphate.*—Diphenyl thionophosphorochloridate (33·2 g.) was added to a stirred solution of *n*-propanol (14 g.) and dry pyridine (9·2 g.) in benzene (100 c.c.). Precipitation of pyridine hydrochloride was very slow and the mixture was set aside for 2 weeks to ensure complete reaction. Water was then added and the benzene layer was washed successively with cold dilute hydrochloric acid, aqueous sodium carbonate, and water, before being dried ($Na_2SO_4$) and evaporated. The residue was distilled in a short-path still at 106°/2·17 × $10^{-3}$ mm., giving *diphenyl* n-*propyl thionophosphate* (25·3 g.) as a colourless liquid, $n^{16}$ 1·5578 (Found: C, 58·0; H, 5·4. $C_{15}H_{17}O_3SP$ requires C, 58·4; H, 5·5%). The ester was also prepared in rather similar yield by treating diphenyl thionophosphorochloridate with sodium *n*-propoxide (1 mol.) in dry ether or benzene; reaction in this case was complete after 24 hr. at room temperature.

*Diethyl* S-*Phenyl Thiophosphate.*—Thiophenol (21·5 g.) was added to powdered sodium (4·5 g.), suspended in benzene, and the reaction completed by 3 hours' heating under reflux. The suspension was then cooled and diethyl phosphorochloridate (33·7 g.; McCombie, Saunders, and Stacey, *J.*, 1945, 380) dissolved in benzene (50 c.c.) was added slowly with stirring. The mixture was set aside overnight, then filtered, and the filtrate was washed first with aqueous sodium hydroxide, then with water, dried ($Na_2SO_4$), and evaporated. The residual *diethyl* S-*phenyl thiophosphate* (43 g.) distilled at 108°/0·2 mm. as a colourless liquid, $n^{16}$ 1·5240 (Found: C, 49·1; H, 6·1. $C_{10}H_{15}O_3SP$ requires C, 48·9; H, 6·1%).

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S-*Ethyl Diphenyl Thiophosphate*.—Ethanethiol (36·9 g.) was added in one portion to a suspension of pulverised sodium (13·5 g.) in benzene, and the mixture stirred at room temperature till the main reaction was over. The suspension was heated to 70° for 1 hr. to complete reaction, then cooled to 0°, and diphenyl phosphorochloridate (143 g.) dissolved in dry benzene (200 c.c.) was added slowly with stirring. The mixture was stirred at room temperature for a further 3 hr., then filtered. The filtrate was thoroughly washed with aqueous ammonia (10%), hydrochloric acid, and water, then dried ($Na_2SO_4$) and evaporated. The residue distilled at 140°/0·02 mm., giving the colourless liquid *ester* (111 g.) (Found: C, 56·9; H, 4·8. $C_{14}H_{15}O_3SP$ requires C, 57·1; H, 5·1%).

*Monodealkylation of Triesters of Phosphoric and Thiophosphoric Acids with Lithium Chloride. Standard Procedure*.—The neutral ester (0·01 mole) was heated for 3 hr. at 100° with anhydrous lithium chloride (3 equivs.) in 2-ethoxyethanol (25 c.c.). Ethoxyethanol was removed under reduced pressure at $<100°$ and water was added to the cooled product. Unchanged triester was extracted with ether (2 × 20 c.c.). The aqueous layer was acidified with dilute sulphuric acid and then extracted with chloroform. The chloroform extract was dried ($Na_2SO_4$) and evaporated and the acidic ester identified as such or as an appropriate derivative. The following products were obtained from the several esters examined: Diphenyl hydrogen phosphate, identified as such (m. p. 68—70°) or as its cyclo*hexylammonium* salt which crystallised from ethanol as silky needles, m. p. 200—201° (Found: C, 62·2; H, 6·7; N, 4·2. $C_{18}H_{24}O_4NP$ requires C, 61·9; H, 6·9; N, 4·0%). In a dealkylation experiment with diphenyl *n*-propyl phosphate and calcium chloride, *calcium diphenyl phosphate* was obtained; it formed bunches of short colourless needles when recrystallised from ethanol [Found: C, 53·5; H, 3·8. $(C_{12}H_{10}O_4P)_2Ca$ requires C, 53·5; H, 3·7%].

Phenyl *n*-propyl hydrogen phosphate gave a cyclo*hexylammonium* salt, colourless needles (from ethanol), m. p. 124—125° (Found: C, 57·1; H, 8·3. $C_{15}H_{26}O_4NP$ requires C, 57·5; H, 8·6%). This acid ester was also obtained by alkaline hydrolysis of diphenyl *n*-propyl phosphate.

On dealkylation with lithium chloride, tri-*n*-propyl phosphate (Dutton and Noller, *J. Amer. Chem. Soc.*, 1953, **55**, 424) gave di-*n*-propyl hydrogen phosphate, identified as its lead salt, m. p. 149—151° (Cavalier and Prost, *Bull. Soc. chim.*, 1900, **23**, 678).

Diphenyl hydrogen thiophosphate, obtained as an oil by the action of lithium chloride on diphenyl *n*-propyl thionophosphate, was treated with *cyclo*hexylamine in ether. The cyclo*hexylammonium* salt recrystallised from water as colourless needles, m. p. 127—128°, containing both S and P (Found: C, 59·4; H, 6·7. $C_{18}H_{24}O_3NSP$ requires C, 59·2; H, 6·6%). The same salt (m. p. and mixed m. p. 127—128°) was obtained by hydrolysis of diphenyl thionophosphorochloridate with potassium hydroxide and treatment of the acid obtained with *cyclo*hexylamine.

Ethyl *S*-phenyl hydrogen thiophosphate, obtained from diethyl *S*-phenyl thiophosphate as an oil, yielded a cyclo*hexylammonium* salt crystallising from acetone as colourless needles, m. p. 128—129°; the salt contained both S and P (Found: C, 52·7; H, 7·2; N, 4·9. $C_{14}H_{24}O_3NSP$ requires C, 53·0; H, 7·6; N, 4·4%).

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