Fully Esterified Phosphates with Dissimilar Organic Groups Attached to the Phosphate Group[1]

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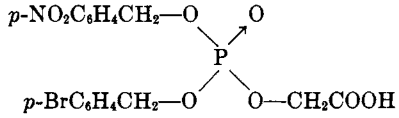
All efforts to synthesize phosphate esters of the type $R_1R_2R_3PO_4$ have given intractable compounds. Only three such stable crystalline esters have been isolated, but we were unable to resolve them. An unexpected product, tri-*p*-bromobenzyl phosphate, is obtained from the reaction of silver *n*-amyl *p*-nitrobenzyl phosphate with *p*-bromobenzyl iodide.

In connection with a study of the stereochemical problem of the phosphate esters, we have been interested in fully esterified phosphates in which all the constituent groups are dissimilar. Although there has been much interest in recent years in the synthesis of asymmetrical phosphate esters, only a few cases of neutral asymmetrical esters have been reported, to the best of our knowledge.[2]

Long duration attempts to synthesize esters of the type $R_1R_2R_3PO_4$ by various methods resulted in only three such crystalline compounds. The triester, *p*-nitrobenzyl *p*-bromobenzyl phosphoglycolic acid (I), was obtained by using the sodium iodide method of monodebenzylation[3] on the corresponding triesters as will be described in the Experimental section. The synthesis of the triester, phenyl *p*-cresyl phosphocholine sulfate (II), was achieved by application of Baer's method for phosphorylation of choline[4] with phenyl *p*-cresyl phosphorochloridate, while the synthesis of the triester, phenyl *p*-cresyl N,N-dimethylaminoethyl phosphate tetraphenylborate (III), was achieved by interaction of phenyl *p*-cresyl phosphorochloridate and N,N-dimethylaminoethanol in ethyl ether and by treatment of the crude chloride salt with a solution of sodium tetraphenylborate.[5]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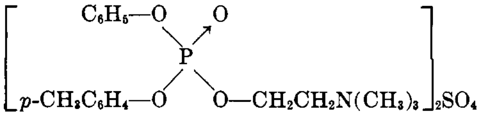
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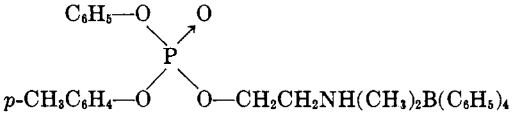
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The three substances I, II, and III are the first asymmetrical triesters to be reported which have been obtained in high purity and in crystalline state. These model triesters contain a phosphorus atom as the only asymmetric center of the molecule and moreover are characterized by their stability and the presence of an acidic or basic functional group which, in our opinion, would give the possibility of their optical resolution by chemical methods. Attempts in this direction, however, were unsuccessful though we have isolated in high purity the crystalline phenyl *p*-cresyl phosphocholine hydrogen D-dibezoyltartate (see Experimental).

During our synthetical studies of asymmetrical neutral phosphate esters, it was observed that all methods which have been applied suffer from greater difficulties than expected. The most serious difficulty in all experiments was the isolation of the product triester from the reaction mixtures. This was attributed, finally, to the high instability of the asymmetrical neutral esters. Numerous qualitative observations indicated that a widely varying reactivity characterizes asymmetrical triesters even with simple alkyl or aryl groups. There is evidence that stability of asymmetrical phosphate triesters could be expected only if such compounds were isolated in high purity and in crystalline (and not sirupy or liquid) state, because of the inability of a noncrystalline triester to get rid of the last traces of impurities, which accelerate molecular transformations and interchange of the different constituent groups.

It is of interest to note here that unusual chemical behavior has been observed while applying the different procedures for the preparation of various asymmetrical triesters. Interaction, for example, of silver *n*-amyl *p*-nitrobenzyl phosphate with *p*-bromobenzyl iodide resulted not in the expected triester but, besides other by-products, in an unexpected crystalline

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(1) This paper is based in part on the Habilitation Thesis of I. Dilaris, University of Athens, 1957, and on the Doctoral Dissertation of G. Eliopoulos, University of Athens, 1964.

(2) A. Morel, *Compt. rend.*, **128**, 507 (1899); E. C. Britton and C. L. Moyle (to the Dow Chemical Co.), U. S. Patent 2,275,041 (March 3, 1942); E. Baer and N. Kates, *Science*, **109**, 91 (1949); *J. Am. Chem. Soc.*, **72**, 942 (1950); E. Baer, J. Maurukas, and M. Russel, *ibid.*, **74**, 152 (1952); E. Baer and J. Maurukas, *ibid.*, **74**, 158 (1952); H. R. Gamrath and R. E. Hatton (to Monsanto Chemical Co.), U. S. Patent 2,678,329 (May 11, 1954); L. Acker, *Ber.*, **88**, 376 (1955); Monsanto Chemical Co., British Patent 727,213 (March 30, 1955); M. Fieser, L. Fieser, E. Toromanoff, Y. Hirata, H. Heymann, M. Tefft, and S. Bhattacharya, *J. Am. Chem. Soc.*, **78**, 2825 (1956); E. Baer and V. Mahadevan, *ibid.*, **81**, 2494 (1959); J. Cheymol, P. Chabrier, N. Selin, and P. Leduc, *Compt. rend.*, **249**, 2573 (1959); D. M. Brown and P. R. Hammond, *J. Chem. Soc.*, 4232 (1960); A. Boehringer, E. Boehringer, I. Liebrecht, J. Liebrecht, and W. Mayer-List (trading as C. H. Boehringer Sohn), British Patent 830,744 (March 23, 1960); E. Baer and S. K. Pavanaram, *J. Biol. Chem.*, **236**, 1269 (1961); J. Navech, *Compt. rend.*, **252**, 2250 (1961); A. N. Pudovik, G. P. Medvedera, and V. I. Kochetkova, *Zh. Obshch. Khim.*, **31**, 2650 (1961); E. Baer and A. Zschocke, *J. Biol. Chem.*, **236**, 1273 (1961); J. Maurukas and C. V. Holland, *J. Org. Chem.*, **26**, 608 (1961); F. L. Maklaev, M. I. Druzin, and I. V. Palagina, *Zh. Obshch. Khim.*, **31**, 1312 (1961); J. Maurukas, S. Kairys, and C. V. Holland, *Biochemistry*, **2**, 397 (1963); E. Baer and J. Blackwell, *J. Biol. Chem.*, **238**, 3591 (1963); N. Z. Stancey and E. Baer, *ibid.*, **239**, 410 (1964); D. Theodoropoulos and I. Souchleris, *Biochemistry*, **3**, 145 (1964).

(3) I. Papadimitriou-Dilaris, Doctoral Dissertation, University of Athens, 1948; L. Zervas and I. Dilaris, *J. Am. Chem. Soc.*, **77**, 5354 (1955); *Ber.*, **89**, 925 (1956).

(4) E. Baer, *J. Am. Chem. Soc.*, **69**, 1253 (1947).

(5) Use of phenyl *p*-nitrophenyl phosphorochloridate (see Experimental) gave unsatisfactory results only because the triester was contaminated with traces of impurities of hydroxyl-containing compounds and it was difficult to purify without decomposition of the triester.

compound, tri-*p*-bromobenzyl phosphate (see Experimental). We thought that a closer examination of various reactions of this sort should prove interesting and, therefore, we have their study under consideration.

Experimental

All reagents and starting materials were of the highest purity grade. Evaporations were carried out *in vacuo* at 35–40°. Melting points[6] were taken at a heating rate of *ca.* 3°/min.

Analysis.[7]—Total phosphorus and halogens were determined by Schoeniger's method[8]; labile chlorine (P–Cl), by hydrolysis in aqueous dioxane as described by Orloff, *et al.*[9]; neutralization equivalents, in aqueous ethanol solution with phenolphthalein as indicator. Except as otherwise stated, samples were dried at 56° under high vacuum over phosphorus pentoxide prior to analysis.

Paper chromatography[10] was performed on Whatman No. 1 paper using the ascending technique with the solvent system: ethylene glycol monomethyl ether–pyridine–glacial acetic acid–water (8:4:1:1, v./v.).

Infrared Spectra.[11]—Only maxima of significance in interpretation are reported.

***p*-Bromobenzyl Phosphoglycolic Acid Ethyl Ester (Sodium Salt, Ia).**—A suspension of 8.2 g. (0.015 mole) of silver di-*p*-bromobenzylphosphate[3] (dried at 90° for 1 hr. and finely powdered) in 60 ml. of benzene was treated with 3.2 g. (0.015 mole) of ethyl iodoacetate (freshly distilled), and the reaction mixture was shaken thoroughly and heated under reflux in an oil bath at 100–105° for 12–13 hr., during which time a yellow precipitate of silver iodide formed. The silver salts, while hot, were removed by filtration and washed repeatedly with warm benzene. After storage at room temperature overnight, traces of silver salts were filtered off and the solution was decolorized with Norit and concentrated to dryness; the unchanged ethyl iodoacetate was removed from the residual sirup by washing several times with a little petroleum ether. The dried sirup was crystallizable at ice temperatures but melted at room temperature, and was found unchanged after standing in a refrigerator for several days; yield 6.5 g. (83%, if it is assumed that the sirupy material is exclusively the triester, di-*p*-bromobenzyl phosphoglycolic acid ethyl ester).

Monode-*p*-bromobenzylation.—To a solution of 5.2 g. of crude di-*p*-bromobenzyl phosphoglycolic acid ethyl ester in 35 ml. of methyl ethyl ketone was added 1.65 g. (0.011 mole) of sodium iodide. The reaction mixture was refluxed for 2 hr. and then allowed to stand under refrigeration for 2–3 days with periodic scratching, during which time the sodium salt of hydrogen *p*-bromobenzyl phosphoglycolic acid ethyl ester (Ia) separated out in the form of a white voluminous mass. Ia was collected by filtration on a sintered funnel and washed three times with a little cold methyl ethyl ketone. The pale yellow product was left overnight in the dark, and the air-dried solid was then triturated with a little warm methyl ethyl ketone. A white solid was recovered by filtration; yield 3 g. (78%). A sample of the crude salt Ia was recrystallized from methyl ethyl ketone for analysis (m.p. 128–130°).

Anal. Calcd. for $C_{11}H_{13}O_6BrNaP$: C, 35.21; H, 3.47; Br, 21.31; P, 8.27. Found: C, 34.95; H, 3.69; Br, 21.27; P, 8.15.

The mother liquors from the above reaction were kept in a refrigerator for 1 week, during which time an additional small amount of Ia precipitated. This was filtered off and the filtrate was concentrated to dryness. Crystalline *p*-bromobenzyl iodide was obtained by treatment of the solid residue with water; 90%, m.p. 74–75° after recrystallization from ethanol.

Conversion of Ia to the Silver Salt (Ib).—To a clear solution of 3.75 g. (0.010 mole) of Ia in 15 ml. of distilled water, a solution of 1.8 g. (0.011 mole) of silver nitrate in 10 ml. of distilled water was added dropwise with vigorous stirring. A white precipitate appeared almost immediately. Upon termination of the addition, stirring was continued for an additional 15 min., and then the reaction mixture was kept overnight at room temperature in the dark. After cooling, the white silver salt was filtered and washed with a little cold water. The silver salt of hydrogen *p*-bromobenzyl phosphoglycolic acid ethyl ester (Ib) was kept in the dark; yield 3.6 g. (78%), m.p. 132–137°.

Anal. Calcd. for $C_{11}H_{13}O_6AgBrP$: Ag, 23.45; P, 6.73. Found: Ag, 23.15; P, 6.51.

***p*-Nitrobenzyl *p*-Bromobenzyl Phosphoglycolic Acid (I).**[12]—To a suspension of 4.6 g. (0.010 mole) of Ib (dried at 70° for 30 min.) in 20 ml. of benzene was added 2.6 g. (0.010 mole) of *p*-nitrobenzyl iodide.[3] The reaction mixture was shaken at room temperature for 10 min. and then refluxed for 2.5 hr. The silver salts were filtered off and washed with benzene. The combined filtrate was treated with Norit and evaporated to dryness. The sirupy residue was washed twice with cyclohexane to remove the traces of unchanged *p*-nitrobenzyl iodide, and was dried at room temperature over phosphorus pentoxide *in vacuo;* yield 4.6 g. (90%, if it is assumed that the sirupy material was exclusively *p*-nitrobenzyl *p*-bromobenzyl phosphoglycolic acid ethyl ester).

Partial Saponification.—To a suspension of 2.4 g. (0.005 mole) of the sirupy *p*-nitrobenzyl *p*-bromobenzyl phosphoglycolic acid ethyl ester in 40 ml. of water, 5 ml. of 1 *N* NaOH was added in five equal portions over a period of 2 hr. with vigorous shaking. The slightly alkaline reaction mixture was allowed to stand in a refrigerator for several hours. The clear filtrate was then cooled to −5° and acidified with hydrochloric acid (pH 1). An oil separated out which was crystallized by scratching and cooling; yield 1.7 g. (73%), m.p. 125–128°. Recrystallization was achieved from ethanol–water; m.p. 127–128°. Chemically pure samples of *p*-nitrobenzyl *p*-bromobenzyl phosphoglycolic acid (I) are stable and do not exhibit any change of their physical constants upon storage in a refrigerator for more than a year.

Anal. Calcd. for $C_{16}H_{15}BrNO_8P$: C, 41.76; H, 3.29; Br, 17.39; N, 3.04; P, 6.73; neut. equiv., 1 H^+/mole. Found: C, 42.21; H, 3.09; Br, 17.24; N, 3.29; P, 6.54; neut. equiv., 0.98 H^+/mole.

The infrared absorption spectrum shows an absorption in the bonded-OH region at 3.45, in the carbonyl region at 5.75, in the $P \rightarrow O$ region at 7.97, and in the $P-OCH_2$ region at 9.95 μ.

Silver Salt of I.—To a suspension of 2.3 g. (0.005 mole) of I in 20 ml. of distilled water was added 1 *N* NaOH dropwise until the greater part of I was dissolved. To the clear filtrate 0.9 g. (0.006 mole) of silver nitrate in 10 ml. of distilled water was added with vigorous stirring. After storage at room temperature overnight and cooling, the precipitate was filtered and washed with cold water; yield 2.4 g. (80%).

Anal. Calcd. for $C_{16}H_{14}AgBrNO_8P$: Ag, 19.04; P, 5.46. Found: Ag, 18.85; P, 5.32.

***n*-Amyl *p*-Nitrobenzyl Hydrogen Phosphate.**—To a suspension of 5.3 g. (0.011 mole) of the silver salt of di-*p*-nitrobenzyl hydrogen phosphate[3] (dried at 90° for 1 hr. and finely powdered) in 50 ml. of benzene was added 4 g. (0.02 mole) of *n*-amyl iodide. The reaction mixture was refluxed for 1 hr. and then the clear benzene filtrate was evaporated to dryness. The sirupy residual material was washed with petroleum ether and dried *in vacuo* at room temperature; yield 3.8 g. (80%, if it is assumed that the sirupy residue is exclusively *n*-amyl di-*p*-nitrobenzyl phosphate).

Monode-*p*-nitrobenzylation.—To a solution of 2.2 g. (0.005 mole) of crude *n*-amyl di-*p*-nitrobenzyl phosphate in 20 ml. of methyl ethyl ketone was added 0.8 g. (0.0055 mole) of sodium iodide. The reaction mixture was refluxed for 30 min. and then evaporated to dryness. The residual material was taken up with water and ethyl ether in a separatory funnel. The aqueous layer was washed twice with ethyl ether and decolorized with sodium sulfite; the clear solution was acidified with hydrochloric acid (pH 1). The hydrogen *n*-amyl *p*-nitrobenzyl phosphate was precipitated as a sirup which was crystallized on scratching and standing overnight in a refrigerator; yield 60%; m.p., after recrystallization from ethanol–water, 62–64°; R_f 0.90; infrared spectrum shows an absorption in $-CH_2-$ region at 3.45, in the NO_2

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[6] It was found that the melting points depend on variation in rates of heating. Higher melting points are associated with higher rates of heating.

[7] C, H, and N microanalyses were by Dr. A. Schoeller, Micro-Labor, Kronach, West Germany.

[8] K. D. Fleischer, B. C. Southworth, J. H. Hodecker, and M. H. Tuckermann, *Anal. Chem.*, **30**, 152 (1958).

[9] H. D. Orloff, C. J. Worrel, and F. X. Markley, *J. Am. Chem. Soc.*, **80**, 734 (1958).

[10] V. C. Runeckles and G. Krotov, *Arch. Biochem. Biophys.*, **70**, 445 (1957).

[11] Infrared spectra were kindly recorded by Dr. H. Mantzos, Analytical Laboratory of The Royal Hellenic Research Foundation, in potassium disks, on a Perkin-Elmer spectrophotometer, Model 137.

[12] I was also obtained by using as a starting material silver di-*p*-nitrobenzyl phosphate.[3] Use of the same procedure (toluene, bath 120–125°) permitted the preparation of crystalline di-*p*-nitrobenzyl phosphoglycolic acid ethyl ester (65% yield; m.p., after recrystallization from ethanol, 83–85°). The monodebenzylation led to sodium and silver *p*-nitrobenzyl phosphoglycolic acid ethyl ester, but the over-all yield in the triester I was very poor.

region at 6.57 and 7.48, in the P–OH region at 3.9 (w, br), and in the P→O region (H-bonded) at 8.7 μ.

Anal. Calcd. for $C_{12}H_{18}NO_6P$: C, 47.43; H, 5.93; N, 4.62; P, 10.23; neut. equiv., $1H^+$/mole. Found: C, 47.14; H, 5.52; N, 5.0; P, 9.97; neut. equiv., 0.97 H^+/mole.

Conversion to the Silver Salt.—The silver salt of hydrogen *n*-amyl *p*-nitrobenzyl phosphate was obtained as described for the silver salt of I. An additional amount of silver salt of hydrogen *n*-amyl *p*-nitrobenzyl phosphate was isolated by concentration of the mother liquors to a small bulk; total yield, 50%.

Anal. Calcd. for $C_{12}H_{11}AgNO_6P$: Ag, 26.34; P, 7.5. Found: Ag, 25.65; P, 7.35.

Isolation of Tri-*p*-bromobenzyl Phosphate.[3]—To a suspension of 2.0 g. (0.005 mole) of the silver salt of hydrogen *n*-amyl *p*-nitrobenzyl phosphate (dried *in vacuo* at room temperature) in 15 ml. of benzene was added 1.6 g. (0.005 mole) of *p*-bromobenzyl iodide. The reaction mixture was shaken at room temperature for 8 hr. (or refluxed for 3 hr.) and the filtrate was treated as usual. The resulting sirup was triturated with a little ethanol, and immediately a crystalline material appeared. The crude product, 0.5 g., was recrystallized from ethanol; m.p. 130–132°, while a mixture melting point with an authentic sample of tri-*p*-bromobenzyl phosphate was undepressed. The infrared spectrum of the isolated product was identical with the above authentic sample of the triester.

Phenyl *p*-Cresyl Phosphorochloridate (IIa)[13].—A mixture of 21 g. (0.1 mole) of phenyl phosphorodichloride,[14] 10.8 g. (0.1 mole) of *p*-cresol, and 0.5 g. of dry potassium chloride was heated in a bath at a temperature which was raised slowly to 180°. After the reaction was completed (9 hr.), the volatile products were evaporated under reduced pressure (18 mm.) at a temperature which was raised slowly to 190°. The residual material was then distilled and the fraction boiling at 186° (2 mm.) was collected; yield, 19.5 g. (70%) of phenyl *p*-cresylphosphorochloridate (IIa).

Anal. Calcd. for $C_{13}H_{12}ClO_3P$: P, 10.97; labile Cl, 2 H^+/mole. Found: P, 10.75; labile Cl, 1.95 H^+/mole.

Phenyl *p*-Cresyl Phosphocholine Sulfate (II).—To a solution of 7.6 g. (0.027 mole) of chloride IIa in 38 ml. of pyridine, 3.5 g. (0.025 mole) of choline chloride (dried under high vacuum over phosphorus pentoxide at 56° for 4 hr.) and 30 g. of small glass balls were added. The reaction mixture was stirred (magnetic stirrer) for 48 hr. During this time the reaction mixture turned to a clear solution and later to a clouded one. After washing out the reaction mixture with 40 ml. of water, the aqueous soution was evaporated to a sirup. Attempted crystallizations were unsuccessful. The material (9.7 g.) was used in the following experiment as unpurified phenyl *p*-cresyl phosphocholine chloride.

Phenyl *p*-Cresyl Phosphocholine Reineckate.—A clear solution of 9.7 g. of the above sirup in aqueous 8% anhydrous sodium carbonate (120 ml.) was added dropwise, with vigorous stirring, to a solution of 11.7 g. (0.03 mole) of ammonium reineckate in 500 ml. of water (clear and freshly prepared). A rose-colored solid was precipitated which, after being kept in the refrigerator overnight, was filtered off and washed with cold water and then with cold methanol and ethyl ether. The air-dried material was dissolved in 250 ml. of acetone and, to the clear filtrate, 750 ml. of water was added dropwise, with vigorous stirring. The rose-colored crystalline phenyl *p*-cresyl phosphocholine reineckate was filtered off and dried at room temperature in the dark; yield 75% (if it is assumed that the chloride salt is pure), m.p. 138–140° (170° dec.).

Anal. Calcd. for $C_{22}H_{31}CrN_7O_4PS_4$: C, 39.52; H, 4.69; N, 14.67; P, 4.64. Found: C, 38.95; H, 5.34; N, 14.40; P, 4.66.

Conversion of the Reineckate Salt to the Sulfate Salt (II).—To a clear solution of 5.35 g. (0.008 mole) of phenyl *p*-cresyl phosphocholine reineckate in 130 ml. of acetone, a solution of 1.25 g. (0.004 mole) of silver sulfate in 170 ml. of water at 50° was added dropwise, with vigorous stirring. The silver reineckate separated out immediately and was removed by filtration after the reaction mixture had been kept at room temperature for 3 hr. After the precipitate had been washed with water, the combined clear filtrate was evaporated to a small bulk (15 ml.); then any traces of silver or reineckate ions had to be removed from the solution. The resulting pure solution was concentrated to a sirup which was triturated with a little absolute acetone. After the mixture had been cooled overnight, crystals of phenyl *p*-cresyl phosphocholine sulfate (II) were deposited which were recovered by filtration and dried in a desiccator at room temperature under reduced pressure (18 mm.) and over calcium chloride; yield 70%. For a further purification, the crude II was dissolved in a few milliliters of a mixture of acetone–methanol (94:4) and the clear filtrate was evaporated to a sirup which then was triturated with acetone as described above. The infrared spectrum shows an absorption in the P→O (free) region at 7.8 and in the SO_4^{2-} region at 8.8–9.2 μ. The sulfate salt II loses its water of crystallization on standing under high vacuum over phosphorus pentoxide.

Anal. Calcd. for $C_{36}H_{50}N_2O_{12}P_2S \cdot 2H_2O$: C, 51.92; H, 6.47; N, 3.36; P, 7.45. Found: C, 51.76; H, 6.49; N, 3.50; P, 7.23.

Phenyl *p*-Cresyl Phosphocholine Hydrogen D-Dibenzoyltartrate.—After a column of Amberlite IRA (OH^-) (20 × 1 cm.) had been rinsed with aqueous ethanol (90%), a solution of 1.7 g. (0.002 mole) of the sulfate II in 10 ml. of aqueous ethanol was slowly run onto the column, followed by the solvent alone. The first the eluate was rejected until an alkaline eluate appeared which was allowed to drop in a solution of 1.13 g. (0.003 mole) of anhydrous D-dibenzoyltartaric acid[15] with shaking. The resulting solution (pH 3) was evaporated to a sirup which was extracted twice with ethyl acetate. The combined extract was kept undisturbed overnight, during which time crystals of phenyl *p*-cresyl phosphocholine hydrogen D-dibenzoyltartrate were deposited, which were filtered and dried at room temperature; yield 25%, m.p. 128–130°, $[\alpha]^{18}\text{D}$ −61.20° (*c* 0.8, ethanol), R_f 0.82. The infrared spectrum shows an absorption in the C═O region at 5.76, in the COO^- region at 6.25, and in the P→O region at 7.8 μ.

Anal. Calcd. for $C_{36}H_{38}NO_{12}P$: C, 61.10; H, 5.37; N, 1.98; P, 4.38; neut. equiv., 1 H^+/mole. Found: C, 61.08; H, 5.42; N, 2.13; P, 4.26; neut. equiv., 0.99 H^+/mole.

Phenyl, *p*-Cresyl N,N-Dimethylaminoethyl Phosphate Tetraphenylborate (III).—To a precooled solution of 2.3 g. (0.026 mole) of N,N-dimethylaminoethanol in 30 ml. of ethyl ether was added 3.6 g. (0.013 mole) of phenyl *p*-cresyl phosphorochloridate with vigorous stirring over a period of 30 min. The reaction mixture was stored at room temperature for 20 hr., during which time a crystalline material precipitated. The N,N-dimethylaminoethanol chloride was filtered off and washed with ether. The clear ether filtrate and washings were evaporated to a sirup which was treated with 20 ml. of ethyl ether saturated by hydrogen chloride. The crystals of phenyl *p*-cresyl N,N-dimethylaminoethyl phosphate chloride were collected by filtration and found to be sufficiently pure for the next experiment; yield 2.3 g.

Conversion of the Chloride Salt to the Tetraphenylborate Salt (III).—To a solution of 0.6 g. of the crude chloride salt in 100 ml. of water which had been acidified with hydrochloric acid (pH 2), 10 ml. of a 3% aqueous solution of sodium tetraphenylborate[16] was added dropwise with vigorous stirring. Upon addition of a few drops a turbidity developed and the first crystals appeared within a few minutes. After termination of the addition of the solution, the reaction mixture was stirred for an additional 20 min. The crystalline phenyl *p*-cresyl N,N-dimethylaminoethyl phosphate tetraphenylborate (III) was filtered off and washed twice with water. The crude, air-dried III was recrystallized from acetone–water or from ethanol. The recrystallization was carried out carefully, by the addition of water dropwise and slowly to a solution of the salt III in acetone, while the mixture was kept undisturbed at room temperature for 1 hr. and then in the refrigerator. The tetraphenylborate salt was deposited as beautiful needles; yield 65%, m.p. 117–118°, R_f 0.85. The infrared spectrum shows an absorption in the P→O (free) region at 7.81, in the $B–C_6H_5$ region at 7.03, and at 5.2–6.1 μ (w, several bands).

Anal. Calcd. for $C_{41}H_{43}BNO_4P$: C, 75.11; H, 6.55; N, 2.13; P, 4.73. Found: C, 75.25; H, 6.23; N, 2.15; P, 4.45.

Phenyl *p*-Nitrophenyl Phosphorochloridate.—A mixture of 28 g. (0.11 mole) of *p*-nitrophenyl phosphorodichloride,[14] 9.5 g. (0.1 mole) of phenol, and 0.5 g. of dry sodium chloride was

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(13) B. D. Wilkinson Luff and F. S. Kipping, *J. Chem. Soc.*, **95**, 2000 (1909).

(14) V. V. Katyshkina and M. Ya. Kraft, *Zh. Obshch. Khim.*, **26**, 3060 (1956).

(15) C. L. Butler and L. H. Cretcher, *J. Am. Chem. Soc.*, **55**, 2605 (1933).

(16) Sodium tetraphenylborate (3 g., Kalignost, Merck) was dissolved in 70 ml. of distilled water. The solution was then acidified with 2 drops of 1 *N* nitric acid and shaken with a small amount of alumina for 2–3 min. and then repeatedly passed through a folded filter when necessary. The clear solution was diluted to 100 ml. with water.

heated in a bath at a temperature which was raised slowly to 170°. After the reaction was completed (6 hr.) the volatile products were evaporated (18 mm.) at a temperature which was raised slowly to 200°. The fraction boiling at 203–209° (1 mm.) was collected and phenyl *p*-nitrophenyl phosphorochloridate was crystallized by cooling and scratching; yield 65%, m.p. 78–80°, fine needles. The infrared spectrum shows an absorption in the P→O (free) region at 7.65 μ. Chemically pure samples of the chloride are stable in refrigeration for more than 6 months.

Anal. Calcd. for $C_{12}H_9ClNO_5P$: C, 45.93; H, 2.87; N, 4.46; P, 9.88; labile Cl,[17] 2 H^+/mole. Found: C, 45.68; H, 2.58; N, 4.34; P, 9.57; labile Cl, 2.05 H^+/mole.

Phenyl, *p*-Nitrophenyl Hydrogen Phosphate.—To a solution of 4.25 g. (0.031 mole) of anhydrous potassium carbonate in 15 ml. of water, 9.4 g. (0.03 mole) of the above chloride was added in ten to fifteen portions, with vigorous stirring at a temperature not exceeding 75° (bath). An evolution of carbon dioxide gas was observed after a period of 30 min. The reaction mixture was cooled, acidified with sulfuric acid (1:2, pH 1), and then an oil precipitated which was extracted by ethyl ether. The ether layer was dried over potassium bromide and evaporated to a sirup. By treatment with hydrochloric acid a crystalline solid was obtained; yield 68%; m.p., after recrystallization from benzene, 101–102°.

Anal. Calcd. for $C_{12}H_{10}NO_6P$: N, 4.73; P, 10.5; neut. equiv. 1H^+/mole. Found: N, 4.92; P, 10.25; neut. equiv., 0.97 H^+/mole.

Phenyl *p*-Nitrophenyl Phosphamide.—3.1 g. (0.01 mole) of the chloride was treated with 5 ml. of ammonium hydroxide. A semisolid mass was precipitated which was crystallized by scratching; yield 70%; m.p., after recrystallization from ethanol, 167–168°.

Anal. Calcd. for $C_{12}H_{11}N_2O_5P$: N, 9.52; P, 10.51. Found: N, 9.63; P, 10.15.

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[17] For the titration precooled aqueous dioxane hydrolysate was used.

Thermal Decomposition of Dialkyl Oxalates

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Whereas dialkyl oxalates of tertiary alcohols thermally decomposed at about 140–160° to give good yields (80–100%) of olefins, those of primary and secondary alcohols resisted decomposition at least up to 325°. Dicyclohexyl, dibornyl, and diisobornyl oxalates, as well as oxalates of some cyclic tertiary alcohols, decomposed at higher temperatures, 200–300°, with decrease in olefin yield. Formate esters accompanied olefin formation whenever the decomposition temperature exceeded about 210°. With the exception of dibornyl and diisobornyl oxalates all other oxalates examined decomposed without skeletal rearrangements. The composition of the olefins obtained from the pyrolysis of dialkyl oxalates resembles those from acid and dimethyl sulfoxide dehydration of alcohols (Saytzeff-type elimination) rather than those from ester and xanthate pyrolysis (Hofmann-type elimination). An ion-pair mechanism is suggested for the reaction.

A wide variety of elimination reactions, whose mechanisms are fairly well understood, has been used for the preparation of olefins. The thermal decomposition of various esters, xanthates, amine oxides, halides, and related compounds involves cyclic concerted eliminations,[2] although in some cases of xanthate decomposition an ion-pair mechanism accommodates the results better.[3] The thermal decomposition of borate esters[4] and the dehydration of certain alcohols by dimethyl sulfoxide[5] have been interpreted in terms of ion-pair mechanisms.

We shall present the thermal decomposition of dialkyl oxalates as a convenient method for the dehydration of certain alcohols and briefly discuss the mechanism of the reaction.[6]

Results

Table I summarizes the results of the thermal decomposition of 22 dialkyl oxalates at atmospheric pressure. Olefin analysis was done by gas chromatography, n.m.r., and hydrogenation to saturated hydrocarbons. The n.m.r. analysis was facilitated by the differences in the chemical shifts of olefinic protons: terminal olefins (CH_2=) at τ *ca.* 5.4, nonterminal at 4.8–4.9, and endocyclic at 4.65 (cyclohexenes), 4.75 (cyclopentenes), and 4.38 (cyclobutenes). The gas chromatography and n.m.r. methods gave consistent results. At decomposition temperatures below about 160° the products are olefins and oxalic acid, whereas at higher temperatures the oxalic acid decomposes to water, carbon dioxide, and carbon monoxide.

Table II summarizes the results of the decomposition of dialkyl oxalates in quinoline solutions. In these reactions the oxalyl chloride was added to a solution of alcohol in quinoline and the oxalates were decomposed without prior isolation. The results are practically the same as those obtained from the decomposition of the pure oxalates.

In Table III the olefin composition is compared with those obtained from other elimination reactions. Table IV summarizes the *exo/endo* olefin ratios as functions of ring and alkyl group.

Dialkyl oxalates of primary and secondary acyclic alcohols, *e.g.*, neopentyl alcohol, 1-pentanol, 1-heptanol, 2-pentanol, and 3-pentanol, resisted decomposition up to 325°. Those of cyclohexanol, borneol, and isoborneol decomposed at higher temperatures than those of tertiary alcohols. Whenever the decomposition temperature exceeded 210° the olefins were accompanied by the formation of formates (eq. 1), whose identification was based on infrared (carbonyl stretch at 5.80 μ) and n.m.r. (formyl proton at τ 2.0) spectra. The

$$\mathrm{ROCOCOOR} \longrightarrow \mathrm{ROCHO} \qquad (1)$$

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[1] Fellow of the Alfred P. Sloan Foundation.

[2] For a review, see C. H. DePuy and R. W. King, *Chem. Rev.*, **60**, 431 (1960).

[3] (a) F. G. Bordwell and P. S. Landis, *J. Am. Chem. Soc.*, **80**, 6379 (1958); (b) D. G. Botteron and G. Shulman, *J. Org. Chem.*, **27**, 2007 (1962).

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[5] V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *ibid.*, **27**, 2377 (1962).

[6] This project originated in the laboratories of Professor P. D. Bartlett whom we thank for his encouragement.