[Contribution from the Chemical Laboratory of Harvard University.]

A NEW TYPE OF ADDITION REACTION.

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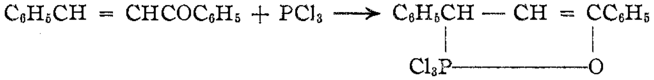
I. Introduction.

It was shown in a preliminary paper[1] that a keto-phosphonic acid was formed by the interaction of phosphorus trichloride, an α,β-unsaturated ketone and glacial acetic acid. By substituting acetic anhydride for the acid it has been possible to prove that the first step in the reaction consists of the 1,4-addition of phosphorus trichloride to the unsaturated ketone:



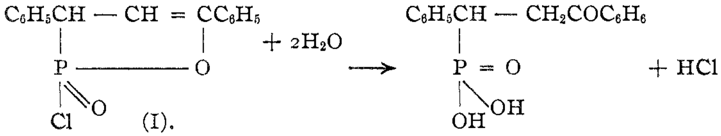
$$C_6H_5CH = CHCOC_6H_5 + PCl_3 \longrightarrow \begin{array}{l} C_6H_5CH - CH = CC_6H_5 \\ \quad | \qquad\qquad\quad | \\ Cl_3P\text{———————}O \end{array}$$

Such an addition is novel in that it involves adding only a single atom instead of the usual 2 atoms or groups. This single atom by increasing its valence unites with the ends of the conjugated system.

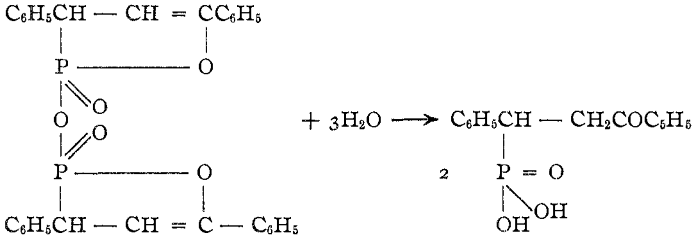
The mechanism of this reaction was difficult to establish because the reaction is reversible, the product is as sensitive as phosphorus pentachloride, and most reagents not only attack the chlorine atoms, but also open the ring. However, with acetic anhydride it was possible to obtain products in which the ring was still intact and to prove definitely their structure.

The Intermediate Products Formed with Acetic Anhydride.

Phosphorus trichloride, benzal-acetophenone, and acetic anhydride react rapidly at room temperature giving acetyl chloride and a material which readily reacts with water, producing the keto-phosphonic acid. This intermediate product was obtained as a thick oil. It is a mixture of 2 substances—an acid chloride (I), and an acid anhydride (II). With water these compounds immediately form the keto-phosphonic acid described in the earlier paper:



(I).



(II).

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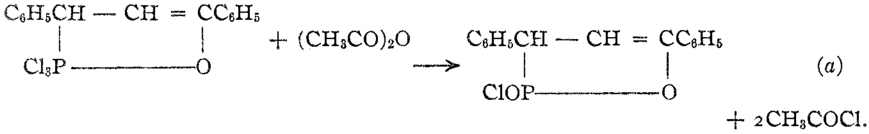
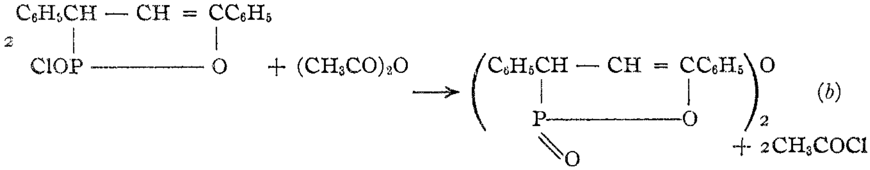
[1] This Journal, 39, 2679 (1917).

The hydrogen chloride produced in this reaction is a measure of the relative amounts of acid chloride and acid anhydride. If one molecule of acetic anhydride is employed in the initial reaction, the product is the acid chloride (I); if an excess is used various amounts of the anhydride (II) will also be formed (Equation *b*):

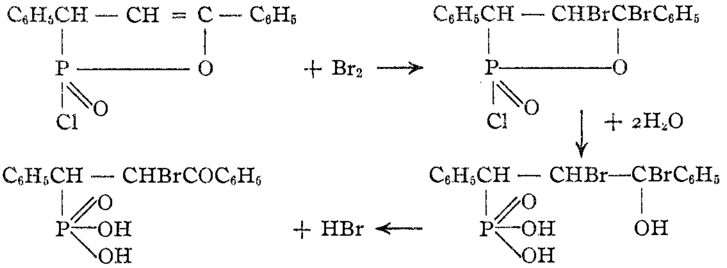


(*a*)



(*b*)

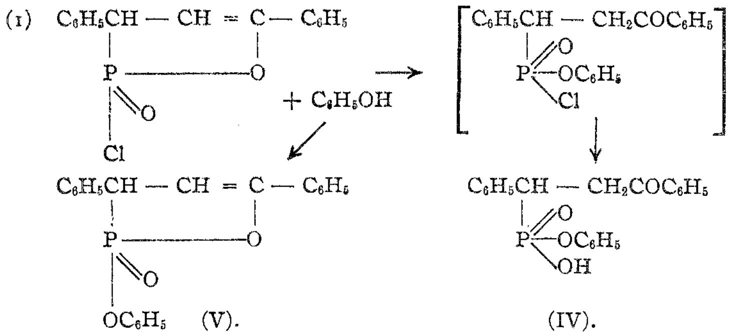
The acid chloride and the acid anhydride are both unsaturated compounds. This follows from the fact that they combine with one molecule of bromine without the evolution of hydrobromic acid. The position of the double linkage was established by treating the resulting dibromide with water; a β-bromoketo-phosphonic acid (III) and hydrogen bromide were formed. The equation for the reaction of the acid chloride is as follows (with the anhydride the reaction is, of course, essentially the same):



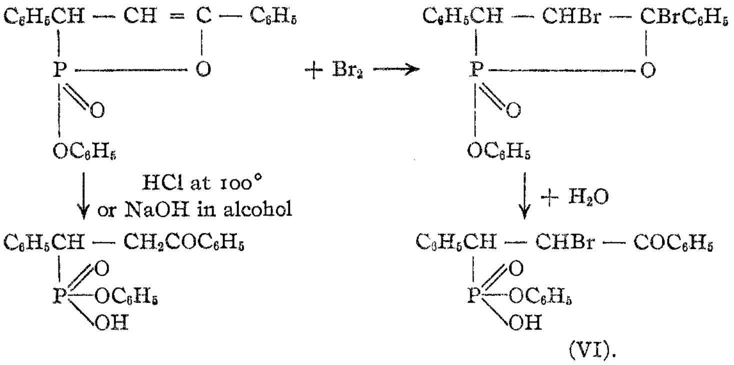
(III). Unstable intermediate product.

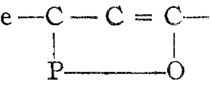
Phenol reacts with the acid chloride forming 2 substances—a monophenyl ester of the keto-phosphonic acid (IV) and a phenyl ester of an unsaturated cyclic acid (V). In the first case the ring is opened (probably by the hydrogen chloride), but in the second the acid chloride is simply transformed into the corresponding phenyl ester.

The constitution of the ester represented by Formula V was established in exactly the same way as that of the acid chloride (II). The substance is an unsaturated cyclic compound because it combines with bromine and because it can be transformed by acids or bases into the monophenyl ester of the keto-phosphonic acid. The ring is more stable in this ester



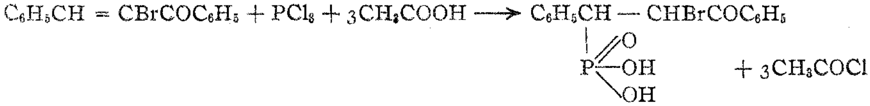
than in the acid chloride. The position of the unsaturation was shown by transforming the bromine addition product into a monophenyl ester of the β-bromoketo-phosphonic acid (VI). These transformations are summarized below:



The nature of the intermediate product formed when acetic anhydride is used, is thus definitely established. The reactions with water, bromine and phenol conclusively prove that the material is a mixture of 2 unsaturated cyclic compounds—one an acid chloride, the other the corresponding anhydride. Both of these compounds contain the linkage  $\begin{array}{l}—\mathrm{C} — \mathrm{C} = \mathrm{C}— \\ \quad\mathrm{P}——\mathrm{O}\end{array}$ since they are still unsaturated although formed by an addition reaction and since they combine with water forming the keto-phosphonic acid.

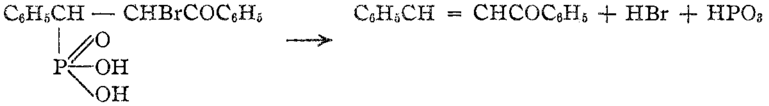
Structure of the Bromine Compounds.

The structure of the β-bromoketo-phosphonic acid (III) and its monophenyl ester (VI) is of importance since the position of the double bond in the intermediate compounds was established by reference to these substances. The position of the bromine atom was shown by synthesizing these substances from α-bromobenzal-acetophenone, phosphorus trichloride and glacial acetic acid:



$$C_6H_5CH = CBrCOC_6H_5 + PCl_3 + 3CH_3COOH \longrightarrow C_6H_5CH-CHBrCOC_6H_5 \ (P(O)(OH)_2) + 3CH_3COCl$$

The β-bromo acid (which can also be prepared by bromination of the keto-phosphonic acid) is unstable in aqueous solution. It decomposes slowly into benzal-acetophenone, hydrogen bromide, and metaphosphoric acid:



$$C_6H_5CH-CHBrCOC_6H_5 \ (P(O)(OH)_2) \longrightarrow C_6H_5CH = CHCOC_6H_5 + HBr + HPO_3$$

This decomposition is instantaneous in alkaline solution. It is similar to the loss of hydrobromic acid and carbon dioxide from such β-bromo acids as β-bromo-hydrocinnamic acid. Fortunately the phenyl esters of the acid are much more stable and the monophenyl ester can be dissolved in sodium carbonate without decomposition. These esters are readily formed from the acid by the action of thionyl chloride and phenol.

Because of its sensitiveness, the β-bromo acid could not be isolated from the product of the reaction of phosphorus trichloride on the bromobenzal-acetophenone. The crude material was, however, treated with thionyl chloride and phenol and thus converted into the more stable monophenyl ester (VI) which could be obtained in a pure condition. This ester was identical with that obtained from the transformations of the cyclic ester (V); it was also identical with the ester prepared from the β-bromoketo-phosphonic acid. This acid, in turn, was shown to be the same whether prepared by bromination of the keto-phosphonic acid or from the dibromide of the cyclic acid chloride. The structure of all the bromine compounds involved in this work was thus established.

The Mechanism of the Reaction.

The structure of the compounds formed with acetic anhydride (I and II) proves conclusively that the fundamental process in the reaction is the addition of the phosphorus atom to the ends of the conjugated system. This addition involves the increase of valence of the phosphorus atom from 3 to 5. It is the type of adddition reaction illustrated by the combination of phosphorus trichloride and chlorine or ammonia and hydrogen chloride. Such addition reactions, involving the increase of valence of one atom, are rare in organic chemistry; they have not hitherto been noted with conjugated systems, although it is possible that some reactions of tervalent nitrogen compounds and quadrivalent sulfur atoms may take place in the same manner.

The first step in the reaction in question is the formation of a 1,4-addition compound. In this compound the chlorine atoms are more reactive than in phosphorus trichloride and it behaves more like phosphorus pentachloride. With acetic acid the compound forms at once the phosphonic acid and acetyl chloride just as phosphorus pentachloride gives phosphoric acid and acetyl chloride. With acetic anhydride, the acid chloride II is produced. In glacial acetic acid this same intermediate compound is probably first formed and then the phosphorus oxygen ring is opened by the acetic acid or some hydrogen chloride which is always produced in small amounts.

Like many primary addition compounds, this addition compound is unstable and easily reverts to its factors. If the unsaturated ketone and phosphorus trichloride are mixed together and then treated with water, only a trace of the keto-phosphonic acid is produced. With a reagent like acetic acid or anhydride, however, the addition compound can react faster than the phosphorus trichloride, and *under these conditions* the reaction goes to completion. It will be shown in a subsequent paper that in the case of saturated aldehydes and ketones a 1,2-addition compound is formed, but in this case the intermediate product is more stable and larger yields of the phosphonic acid can be obtained by the direct treatment with water.

II. Experimental.

Reaction in Glacial Acetic Acid.

The keto-phosphonic acids described in the preliminary paper[1] were prepared by allowing the reaction to proceed in glacial acetic acid and then pouring into water. In this way very good yields of phosphonic acids were obtained from benzal-acetophenone, anisal-acetophenone, and dibenzal-acetone. It has now been possible to show that the phosphonic acid and acetyl chloride are formed before the treatment with water. The phosphonic acid may be thrown out of the acetic acid solution by dilution with an inert solvent like benzene.

Five grams of anisal-acetophenone was dissolved in 5 g. of acetic acid, 10 cc. of benzene and 4 g. of phosphorus trichloride. After standing 4 hours the clear solution was diluted with 50 cc. of benzene and seeded with the phosphonic acid. Crystallization immediately started and at the end of 48 hours, 4 g. of phosphonic acid was obtained (60% of the calculated amount).

Acetyl chloride was identified as the other product of the reaction by carrying out a similar experiment omitting the benzene. A simple distillation yielded acetyl chloride which was identified by redistillation and its reactions with water and aniline.

Reaction in Acetic Anhydride.

Acetic anhydride and phosphorus trichloride do not react at room temperature. When an unsaturated ketone is added, however, a reaction takes place with the evolution of considerable heat and is complete in about

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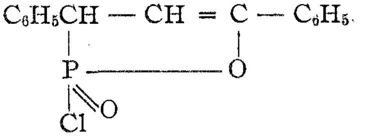
[1] *Loc. cit.*

30 minutes. On pouring into water the phosphonic acid is obtained. If the reaction mixture is evaporated under diminished pressure, an oil is obtained which is a mixture of the acid chloride and the acid anhydride described in the introduction. These substances are very sensitive to moisture, and very dry reagents must be used throughout the work, and precautions must be taken to prevent the entrance of moist air. The compounds also must not be heated to too high a temperature and the evaporation *in vacuo* must, therefore, be carried out below 80°. If one molecule of acetic anhydride is used for every molecule of phosphorus trichloride, the oil obtained is almost wholly the acid chloride. A typical experiment is as follows.

Ten grams (0.05 g. mol.) of benzal-acetophenone (dried over phosphorus pentoxide) was introduced into a mixture of 7 g. (0.05 g. mol.) of phosphorus trichloride and 5 g. of acetic anhydride (0.05 g. mol.). (The anhydride was purified by heating with phosphorus pentachloride and pentoxide and then carefully fractionating.) The reaction mixture was agitated from time to time and the temperature kept below 35°. At the end of one hour the volatile material was evaporated under diminished pressure in a stream of dry air. The material was heated in a water bath kept at about 70°. After 2 hours a thick, light colored oil was left behind. This was the crude acid chloride,  $\begin{array}{l}C_6H_5CH - CH = C - C_6H_5\\ \quad\;\; | \qquad\qquad\quad\;\; | \\ \quad\;\; P - - - - - O \\ \quad\;\; |\diagdown O \\ \quad\; Cl\end{array}$ It was dissolved in dry chloroform and the solution made up with more chloroform to a known volume. A one-cc. portion was then shaken with 50 cc. of water and the chloride ion in the aqueous layer was determined by the Volhard method. The total active chlorine in the entire material could then be calculated.

Calc. for acid chloride: 0.050 equivalents of chlorine. Found: 0.049.

The acidity of the aqueous layer was also determined. It was somewhat greater than the theoretical because of the slight solubility of the phosphonic acid.

Calc. for 1 HCl: 0.050 equivalents. Found: 0.057.

By using larger amounts of acetic anhydride and proceeding in exactly the same way, products could be obtained which contained much less of the acid chloride and more of the acid anhydride as shown by the amount of active chlorine. Ten grams of ketone, 7 g. of phosphorus trichloride and 15 g. of acetic anhydride (3 mol.) were treated as in the former experiment. The oil was dissolved in chloroform and a sample of the solution shaken with water and the aqueous layer analyzed.

Calc. for acid chloride: 0.050 equivalents of chlorine. Found: 0.012.

The mixture thus contains only about 25% of the acid chloride. Such results are, of course, only approximate as small amounts of acetyl chloride and phosphorus trichloride which might be held by the oil would tend to vitiate them.

Reactions of the Acid Chloride and Acid Anhydride.

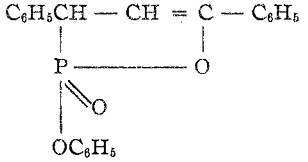
(*a*) **With Water.**—The oil obtained as just described was soluble in chloroform, carbon tetrachloride and benzene, but could not be made to crystallize, nor could it be distilled. Both the oil and its solutions energetically combine with water forming the phosphonic acid.

For example, 10 g. of benzal-acetophenone, 7 g. of phosphorus trichloride and 5 g. of acetic anhydride (equivalent quantities) were allowed to react and the product treated as described. The oil was dissolved in 25 cc. of dry carbon tetrachloride and 0.9 cc. of water (one mol.) was added. The drops of water soon disappeared completely and the temperature of the solution rose from 20° to 35°; a little hydrogen chloride was evolved. The solution was now shaken with 50 cc. of water and the carbon tetrachloride layer separated. Before the separation was finished, the phosphonic acid began to separate and was filtered off. The carbon tetrachloride was evaporated to dryness and the entire crude phosphonic acid was recrystallized from dilute alcohol solution; 11.5 g. of acid was thus obtained which was 78% of the theoretical amount.

In another parallel experiment in which 3 mols. of acetic anhydride was employed, a yield of 83% of phosphonic acid was obtained.

(*b*) **With Bromine.**—The oil obtained from 10 g. of benzal-acetophenone 7 g. of phosphorus trichloride, and 5 g. of acetic anhydride (one mol.) was dissolved in dry carbon tetrachloride. A solution of bromine in the same solvent was slowly added. The bromine immediately disappeared and some heat was produced but no hydrogen bromide was evolved. When $^3/_4$ equivalent of bromine had been added, a slight red color was apparent for a few minutes, but quickly faded. A permanent red color was produced only when a little less than one molecule of bromine had been added. In previous experiments attempts to isolate a solid dibromide had failed, so that the transformation with water was studied. A few drops of water when added to the solution quickly disappeared and the temperature rose 10°. The solution was then shaken with 50 cc. of water and the layers separated. Thirteen grams of the monobromo-phosphonic acid described below (m. p. 197–198°) was obtained from the carbon tetrachloride layer. (80% of the theoretical amount.) The aqueous layer was analyzed for bromide ion by titrating with standard chlorine water and 0.046 equivalent was found; 0.050 equivalents would have been present if exactly one molecule of hydrogen bromide had been liberated in the process. The identity of the monobromo-phosphonic acid was shown by mixed melting-point determinations.

(*c*) **With Phenol.**—The oil obtained from 10 g. of benzal-acetophenone, 7 g. of phosphorus trichloride and 5 g. of acetic anhydride was dissolved in chloroform and 4.5 g. of phenol (1 mol.) was added. The solution was evaporated under diminished pressure and then heated for 20 min. at 125°; some hydrogen chloride was evolved. The material was dissolved in ether and extracted with sodium hydrogen carbonate solution. On acidification this yielded 7 g. of the monophenyl ester, m. p. 146°. The ethereal solution was dried and evaporated to dryness; it yielded 7 g. of an oil which was shown to be principally the compound,



This substance is insoluble in cold sodium carbonate solution and aqueous sodium hydroxide. It is soluble in alcoholic sodium hydroxide and on acidification the monophenyl ester is obtained. Some of the compound was heated to 125° for 10 minutes and hydrogen chloride bubbled through it. On treatment with water the monophenyl ester, m. p. 146°, was obtained. The phosphorus-oxygen ring is thus evidently opened by cold alcoholic sodium hydroxide and also by hydrogen chloride at a higher temperature.

The reaction with bromine definitely establishes the nature of the compound. Two grams of it was dissolved in chloroform and treated with bromine. A little less than one molecule was taken up by the solution before a permanent red color resulted; no hydrogen bromide was evolved. The solution was then shaken with water and from the chloroform layer there was obtained 1 g. of β-bromo-monophenyl ester, m. p. 176° (described below).

It is thus evident that the acid chloride and acid anhydride in question react with phenol at 125° and produce 2 substances: (1) the monophenyl ester acid, m. p. 146°, the ring probably having been opened by some hydrogen chloride; and (2) the phenyl ester of the cyclic acid. The intermediate compound used for this reaction was made with only one equivalent of acetic anhydride. It was thus almost wholly the acid chloride and it is very probable that this substance alone was involved in the reaction with phenol.

α-Phenyl-β-bromo-β-benzoylethyl-phosphonic acid, $C_6H_5CH(PO_3H_2)$-$CHBrCOC_6H_5$.—The unsubstituted keto-phosphonic acid was prepared from benzal-acetophenone as described in an earlier paper.[1] 4.5 g. of this acid was dried at 130° and the resulting oil dissolved in chloroform. 2.3 g. of bromine in chloroform solution was added little by little. The reaction

[1] *Loc. cit.*

was started by heating for a few minutes on the steam bath. Hydrogen bromide was evolved and the bromine color rapidly disappeared until the equivalent amount of bromine had been added. The chloroform was removed by distillation under diminished pressure and the residual solid recrystallized from chloroform and petroleum ether. 3.5 g. of a white crystalline solid was thus obtained which melted at 196°. It could be recrystallized from a mixture of chloroform and petroleum ether or an alcohol-acetone solution.

The monobromo acid was very slightly soluble in water. The aqueous solution slowly became milky on standing and rapidly on heating. When treated with sodium hydrogen carbonate, sodium carbonate, or hydroxide, the monobromo acid was immediately transformed into benzal-acetophenone (an insoluble precipitate), sodium bromide and sodium phosphate. The reaction was almost quantitative. The phosphorus was to some extent eliminated from the molecule as a metaphosphate, as the solution gave the characteristic tests for this ion as well as for the orthophosphate ion.

Monophenyl ester of α-Phenyl-β-bromo-β-benzoylethyl-phosphonic acid, $C_6H_5COCHBrCH(C_6H_5)PO(OH)(OC_6H_5)$.—This compound can be prepared from the bromo acid by first forming the acid chloride. Three grams of the bromo-phosphonic acid was dissolved in chloroform, 1 g. of thionyl chloride added and the mixture heated to 100° for half an hour; hydrogen chloride and sulfur dioxide were evolved. 0.8 g. of phenol was then added, the chloroform boiled off, and the heating continued for another half hour. The mixture was taken up in ether and 2.5 g. of the bromo ester acid slowly crystallized from the solution. The melting point was 179°. Titration with a standard base showed the substance to be a monobasic acid.

Calc. for $C_{21}H_{18}O_7PBr$: Br, 17.9. Found: 17.8.

The constitution of this substance follows from its formation from α-bromo-benzal-acetophenone. This latter compound was prepared in the usual way from benzalacetophenone dibromide.[1] Three grams of the α-bromo-benzal-acetophenone and 2.5 g. of phosphorus trichloride were dissolved in 10 cc. of glacial acetic acid. The mixture was allowed to stand overnight and then the volatile materials were removed by distillation under reduced pressure. The residue, taken up in chloroform, was heated for an hour at 100° with 1 g. of thionyl chloride; 0.9 g. of phenol was then added in chloroform solution and the heating continued for 30 minutes, the solvent being allowed to distil off at the same time. The resulting oil was treated with sodium hydrogen carbonate solution, a small amount of insoluble oil was removed, and the solution acidified. The material thus obtained was contaminated by a small amount of oil which was removed by again dissolving in sodium hydrogen carbonate and extracting

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[1] *Am. Chem. J.*, **33**, 38 (1905); **44**, 323 (1910).

with ether. On precipitating with acid a material was obtained which could be crystallized from ether. Half a gram of the solid bromo-phenyl ester, m. p. 179°, was thus obtained and the identity of it and the product previously prepared was shown by making a mixed melting-point determination.

This bromo-monophenyl ester can be recrystallized from alcohol, since it is fairly soluble in the latter solvent. It dissolves in sodium hydrogen carbonate and carbonate solutions and the sodium salt may be prepared by cautious treatment with cold dil. sodium hydroxide solution. When warmed with sodium hydroxide or sodium carbonate solution it is decomposed in the same manner as the bromo-acid and produces benzal-acetophenone.

Monophenyl ester of α-Phenyl-β-benzoylethyl-phosphonic acid, $C_6H_5COCH_2CH(C_6H_5)PO(OH)(OC_6H_5)$.—The bromo-monophenyl ester just described can be prepared by bromination of the unsubstituted monophenyl ester in chloroform solution. This latter substance can be prepared from the phosphonic acid by using only one mol. of thionyl chloride and heating the product with phenol. 10 g. of the keto-phosphonic acid was dehydrated by heating to 125°. The resulting oil was dissolved in chloroform and 5 g. of thionyl chloride was added. The chloroform was evaporated off and the oil heated to 140° in an oil bath. 3.5 g. of phenol was then added in chloroform solution and after evaporation of the chloroform, the mixture was heated to 135° for 20 minutes. The material was then dissolved in chloroform and extracted with sodium carbonate solution. Acidification yielded a solid which was recrystallized from alcohol. Yield, 7.5 g. of a crystalline substance melting at 146°. The chloroform solution contained a small amount of the diphenyl ester.

Calc. for $C_{21}H_{19}O_4P$: C, 68.8; H, 5.2. Found: C, 68.9; H, 5.8.

Titration with standard sodium hydroxide solution using phenolphthalein as the indicator, showed the compound was a monobasic acid.

The most convenient method of preparing the bromo-monophenyl ester is from this ester; 3.5 g. of the ester was brominated in chloroform solution at the boiling point of the solvent. The chloroform was evaporated and the solid residue recrystallized from alcohol. Three grams was thus obtained melting at 179°.

Diphenyl Ester of α-Phenyl-β-benzoylethyl-phosphonic acid, $C_6H_5COCH_2CHC_6H_5PO(OC_6H_5)_2$.—This ester is obtained in small amounts when the monophenyl ester is prepared by the procedure just mentioned. It can be prepared in better yields by using 2 molecules of the thionyl chloride and then heating with 2 molecules of phenol. Thirty grams of the anhydrous phosphonic acid was dissolved in chloroform and heated with 10 g. of thionyl chloride for one hour at 100°; 36 g. of phenol was added in chloroform solution, the chloroform was distilled off and the mixture heated for 2 hours at 150°. The oily product was dissolved in ether and washed with sodium carbonate solution, and then with 5% sodium hydroxide solution to remove any phenol. On evaporating the ethereal solution a crystalline solid was obtained which was recrystallized from alcohol. Fourteen grams was thus obtained, which melted at 125°. Some monophenyl ester was obtained from the sodium carbonate solution.

Calc. for $C_{27}H_{23}O_7P$: C, 73.3; H, 5.2. Found: C, 73.9; H, 5.3.

This diphenyl ester can be readily hydrolyzed to the monophenyl ester in the following way. Six grams was dissolved in a solution of sodium alcoholate made from 0.3 g. of metallic sodium and 15 cc. of alcohol. After standing a few minutes the solution was poured into aqueous acid and the solid precipitate filtered off. This was purified by dissolving in sodium carbonate solution reprecipitating with acid and finally crystallizing from alcohol. Four grams of the monophenyl ester was thus obtained, melting at 146°.

Both the diphenyl ester and the monophenyl ester are hydrolyzed to the free phosphonic acid by warming with aqueous sodium hydroxide.

Summary.

1. α,β-Unsaturated ketones react with phosphorus trichloride in glacial acetic acid producing a keto-phosphonic acid and acetyl chloride.

2. In acetic anhydride solution the product is a mixture of an unsaturated acid chloride and acid anhydride which have a phosphorus-oxygen ring. These substances readily react with water forming the keto-phosphonic acid.

3. The structure of the acid chloride and anhydride follows from the fact that they combine with one equivalent of bromine and the product with water gives a β-bromoketo-phosphonic acid. This β-bromo acid was synthesized by a method which proves its structure.

4. Additional evidence of the structure of the acid chloride and anhydride is afforded by a study of the products formed by heating it with phenol.

5. The structure of the compounds formed in acetic anhydride solution shows that the first step in the reaction is the addition of the phosphorus atom of the phosphorus trichloride to the ends of the conjugated system. Such an addition reaction involving the increase of valence of one atom is a new type of 1,4 addition.

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