Reactions of Phosphoranes with Peracids[1,2]

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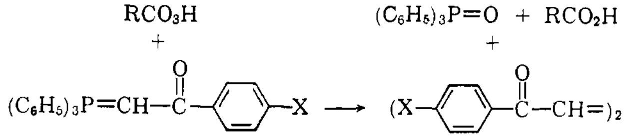
It has been found that addition of peracids to phosphoranes, $(C_6H_5)_3P{=}CH{-}COR$, R = aryl, alkyl, or alkoxyl, leads to formation of dimeric substances, $RCOCH{=}CHCOR$, in moderate to good yield. Substituted phosphoranes, $(C_6H_5)_3P{=}CR'COR$, give none or very little of the expected dimeric product when treated with peracid. More basic phosphoranes also do not undergo the reaction. These results are rationalized mechanistically.

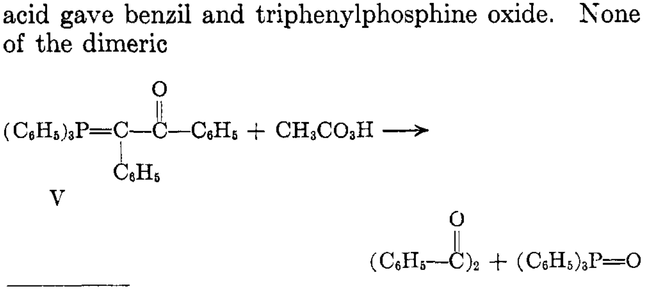
The use of phosphoranes in organic synthesis has been a major development in the last decade. A profusion of reactions has been developed.[5] It is the purpose of this report to present still another valuable synthetic reaction of some phosphoranes.

Addition of peracid, either 40% peracetic in acetic acid or percaprylic, to the phosphoranes, Ia–e, led to the formation of triphenylphosphine oxide and the appropriate 1,2-dibenzoylethylene. In the case of Ia, *trans*-1,2-dibenzoylethylene was the only stereoisomer found, *i.e.*, no *cis* could be detected. Similarly, with the other materials only one substance was isolated and this was assumed to be *trans*. The yields of the dibenzoylethylenes ranged from 40–70%. Addition of peracid to acetylmethylenetriphenylphosphorane (II) gave *trans*-diacetylethylene in 52% yield. Treatment of carbethoxymethylenetriphenylphosphorane (III) with peracetic acid in acetic acid gave diethyl fumarate, 41%, and ethyl acetate, *ca.* 25–30%. α-Carbethoxyethylidenetriphenylphosphorane (IV), the methyl analog of III, gave only a 7% yield of diethyl dimethylfumarate on treatment with peracid. Reaction of α-benzoylbenzylidenetriphenylphosphorane (V) with peracetic acid gave benzil and triphenylphosphine oxide. None of the dimeric product of the type isolated with the other phosphoranes could be found. Triphenylbenzylidenephosphorane (VI) did not give stilbene on treatment with peracid.



Ia. X = H
b. X = Br
c. X = NO₂
Id. X = NHCOCH₃
e. X = OCH₃

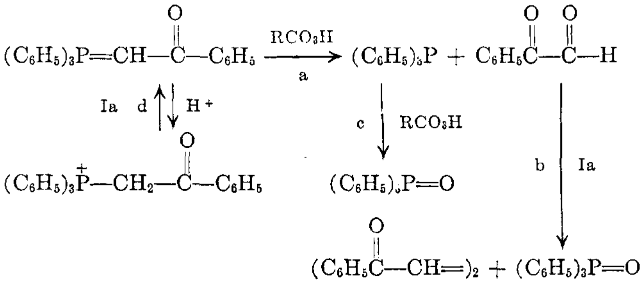
$$\underset{\text{III}}{(C_6H_5)_3P{=}CH{-}CO_2C_2H_5} + CH_3CO_3H \longrightarrow (C_2H_5O_2C{-}CH{=})_2 + (C_6H_5)_3P{=}O + CH_3CO_2H + CH_3CO_2C_2H_5$$



$$(C_6H_5)_3P{=}C(C_6H_5){-}\overset{O}{\overset{\|}{C}}{-}C_6H_5 + CH_3CO_3H \longrightarrow (C_6H_5{-}\overset{O}{\overset{\|}{C}})_2 + (C_6H_5)_3P{=}O$$

V

The results of these experiments show that the dimerization reaction can be used as a synthetic tool. It is clear, though, that the reaction is limited to a certain type of phosphorane. The limitations of the reaction are most adequately understood in terms of the following mechanism, wherein Ia is used as an example. It is postulated that initial oxidation of phosphorane yields triphenylphosphine and an aldehyde or ketone; in this case phenylglyoxal is the product. If this material can react rapidly in the Wittig reaction with the parent phosphorane, then dimerization occurs, step b. The triphenylphosphine formed in step a reacts rapidly with peracid to give triphenylphosphine oxide, step c. Several experiments serve to substantiate this mechanism. Addition of phenylglyoxal to Ia at room temperature led to an immediate reaction with the production of *trans*-1,2-dibenzoylethylene and triphenylphosphine oxide. Addition of Ia to excess peracid (2 moles), the inverse of the dimer-forming reaction, gave triphenylphosphine oxide but no *trans*-1,2-dibenzoylethylene was found. Evidently under these conditions, *i.e.*, where excess phosphorane was not present, the Wittig reaction did not occur. Since excess peracid was used, it was necessary to show that *trans*-1,2-dibenzoylethylene was stable under these conditions. This was found to be the case. It is clear therefore that using the inverse addition procedure, the dimerization reaction does not take place. This is in agreement with the proposed mechanism provided that step a in the presence of excess peracid and a minimum amount of Ia can exclude step b. This postulate is certainly not unreasonable. Further confirmation for the mechanism is provided by the reaction of V. With this substance the reaction was arrested at the carbonyl state. This is undoubtedly due to the reluctance of benzil and V to undergo the Wittig reaction. That this should be the case is reasonable since both steric and electronic factors operate to inhibit



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[2] Published in part as a Communication in *J. Am. Chem. Soc.*, **82**, 2396 (1960).

[3] National Science Foundation Coöperative Graduate Fellow, 1959–1960.

[4] Recipient of an American Cyanamid Junior Educational Award, 1961–1962.

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step b.[6] The low yield of dimer obtained from IV is also in agreement with this scheme. It is clear that the dimerization reaction will only be effective when the derived carbonyl compound and the phosphorane can react fairly rapidly.[7]

The other major limitation is that as the phosphoranes become more basic, salt formation, step d, becomes the predominant reaction. This is evidenced by the formation of ethyl acetate in the reaction of III. Hydrolysis of the salt probably occurred during processing of the reaction mixture which involved treatment with base. This reaction is well known.[8] Similarly, it can be understood why VI did not give stilbene. These results show that basic phosphoranes cannot be used; however, Bestmann[9] has shown that air oxidation of basic phosphoranes leads to the formation of olefins by a similar dimerization reaction. Thus the two methods complement each other and a wide variety of phosphoranes can be converted to dimeric products if the proper reaction conditions are chosen.

Experimental[10]

Phosphorane Syntheses and Properties.—The following phosphoranes were known compounds: benzoylmethylenetriphenylphosphorane (Ia), m.p. 182–184° (lit.,[11] 178–180°); acetylmethylenetriphenylphosphorane (II), m.p. 206–208° (lit.,[11] 205–206°); carbethoxymethylenetriphenylphosphorane (III), m.p. 127–129° (lit.,[12] 125–127.5°); α-carbethoxyethylidenetriphenylphosphorane (IV), m.p. 163–165° (lit.,[13] 156–157°); α-benzoylbenzylidenetriphenylphosphorane (V), m.p. 192–194° (lit.,[14] 191–192°). The equivalent weights of Ia, II, III and IV were determined by the method of Ross and Denney[15] and were in all cases within a few per cent of theory. Analysis of V by this method was not satisfactory, presumably because of the weak basicity of V.

p-Bromobenzoylmethylenetriphenylphosphorane (Ib).—To a hot stirred solution of 47.3 g. (0.18 mole) of triphenylphosphine in 100 ml. of benzene was added a solution of 50 g. (0.18 mole) of p-bromophenacyl bromide at *ca.* 33°. The mixture was stirred for 1 hr. and filtered. The collected solid was washed with benzene and then added to 300 ml. of water and 300 ml. of benzene. The stirred mixture was treated with 4 *N* aqueous sodium hydroxide solution until the pH reached and remained at 10. The precipitate was collected and dissolved in 300 ml. of chloroform which was washed with three 30-ml. portions of water and dried with magnesium sulfate. Concentration afforded 71 g. of crude Ib, which was crystallized from 95% ethanol to give 62.7 g. (76%) of phosphorane, m.p. 199–201°, equivalent weight[15]: calcd., 459; found, 461.

Anal. Calcd. for $C_{26}H_{20}BrOP$: C, 68.00; H, 4.36. Found: C, 67.75; H, 4.42.

p-Nitrobenzoylmethylenetriphenylphosphorane (Ic).—Following the procedure outlined above, p-nitrobenzoylmethylenetriphenylphosphonium bromide was prepared. The crude salt, 17.0 g. (0.033 mole), was added to a stirred mixture of 100 ml. of water and 150 ml. of 95% ethanol cooled to 0°. The mixture was treated with 5% aqueous sodium hydroxide until pH 10 was maintained. The product was isolated as described above in 78% yield after recrystallization from ethanol, m.p. 162–164°.

Anal. Calcd. for $C_{26}H_{20}NO_3P$: C, 73.40; H, 4.70. Found: C, 72.71; H, 4.75.

p-Acetamidobenzoylmethylenetriphenylphosphorane (Id).—This compound was prepared by a procedure similar to that used for Ic. The phosphorane was recrystallized from ethanol, m.p. 284–286°.

Anal. Calcd. for $C_{28}H_{24}NO_2P$: C, 77.00; H, 5.50. Found: C, 76.71; H, 5.60.

p-Methoxybenzoylmethylenetriphenylphosphorane (Ie).—The same general procedure was followed. The phosphorane was recrystallized from ethanol–ethyl acetate (1:9) to give material, m.p. 159–161°.

Anal. Calcd. for $C_{27}H_{23}O_2P$: C, 79.00; H, 5.61. Found: C, 78.64; H, 5.70.

Peracid–Phosphorane Reactions—Procedure A.—Ia, II, III, IV, and V were treated with 40% peracetic acid in acetic acid. A representative procedure follows: A solution of 5.4 g. (*ca.* 0.028 mole) of peracetic acid in acetic acid in 40 ml. of dry ether was added dropwise over a period of 20 min. to a stirred solution of 10.2 g. (0.0268 mole) of benzoylmethylenetriphenylphosphorane in 250 ml. of dry benzene. The reaction mixture was allowed to stand at room temperature for 15 hr. It was extracted with two 50-ml. portions of water and two 50-ml. portions of 10% aqueous sodium carbonate solution. The benzene solution was dried over magnesium sulfate and then distilled to give 9 8 g. of solid residue. This was extracted with several 75-ml. portions of boiling hexane. The insoluble residue, 6.4 g. (86%), had m.p. 156–158°. The infrared spectrum was identical to that of a known sample of triphenylphosphine oxide and there was no depression of melting point on admixture with a known sample.

Evaporation of the hexane extracts followed by crystallization of the residue from absolute ethanol gave 2.3 g. (73%) of *trans*-1,2-dibenzoylethylene, m.p. 110–112° (lit.,[16] 110°). The material was converted to 3,6-diphenylpyridazine, m.p. 220–222° (lit.,[16] 221–222°).

Similarly, acetylmethylenetriphenylphosphorane (II) gave triphenylphosphine oxide (91%), m.p. 157–159°, and *trans*-diacetylethylene (52%), m.p. 78–79° (lit.,[17] 75.5–76.5°). The *bis*-2,4-dinitrophenylhydrazone had m.p. 290–292° (lit.,[17] 291–292°).

Carbethoxymethylenetriphenylphosphorane (III) gave triphenylphosphine oxide (96%) and diethyl fumarate (41%), b.p. 100° (block) at 10 mm. The infrared spectrum was identical to that of a known sample. The material was further characterized by conversion to di-p-nitrobenzyl fumarate, m.p. 152–154° (lit.,[18] 151°). The benzene-ether distillate from the reaction mixture had carbonyl absorption in the infrared. The spectrum of the distillate was nearly identical to that of a known solution prepared from 10 ml. of benzene, 1 ml. of ether and 4 drops of ethyl acetate. Gas–liquid chromatography of the distillate on a 10-ft. silicone grease column at room temperature showed a component was present whose retention time was identical to that of ethyl acetate.

α-Carbethoxyethylidenetriphenylphosphorane (IV) gave triphenylphosphine oxide (89%) and diethyl dimethylfumarate (7%), b.p. 105° (9 mm.) (lit.,[19] 111–112°, 12 mm.). Saponification yielded dimethylfumaric acid, m.p. 247–248° (lit.,[20] 240°). The infrared spectra of all of these compounds were in accord with the assigned structures.

Treatment of V with peracetic acid yielded 75% of impure triphenylphosphine oxide and a yellow oil which had absorption at 5.85 μ in the infrared. Treatment of the yellow oil with semicarbazide afforded a semicarbazone, m.p. 242°. The disemicarbazone prepared from authentic benzil had m.p. 243–245°. The mixed melting point was 243–245°.

Reaction of Phenylmethylenetriphenylphosphorane with Peracetic Acid.—Triphenylbenzylphosphonium chloride, 8.95 g. (0.023 mole), was added to 50 ml. of ethanol containing 0.022 mole of sodium ethoxide. Peracetic acid (4.25 g., *ca.* 0.022 mole, *ca.* 40% in glacial acetic acid) in 15 ml. of absolute ethanol was added dropwise with stirring to the phosphorane solution. The yellow color of the solution was discharged after about one-third of the peracid solution had been added. The colorless ethanol solution which contained a white solid was poured into water and excess sodium carbonate was added. An oily layer having the odor of toluene was formed. Extraction with ether followed by evaporation gave 4.0 g. (66%) of material, m.p.

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[6] In general, ketones are considerably less reactive in the Wittig reaction than are aldehydes. See G. Fodor and I. Tomaskozi, *Tetrahedron Letters*, **16**, 579 (1961).

[7] In some cases this limitation could be overcome by using a very slow rate of addition of peracid to the phosphorane.

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153–155°. The infrared spectrum of this material was identical to that of triphenylphosphine oxide.

Procedure B.—This procedure was used for Ib–e. A typical example follows. To a stirred solution of 6.5 g. (0.015 mole) of *p*-nitrobenzoylmethylenetriphenylphosphorane in 75 ml. of methylene chloride at *ca.* −30° was added 2.56 g. (0.016 mole) of percaprylic acid in 26 ml. of methylene chloride. The solution was stirred for 1.5 hr. and then concentrated *in vacuo* until crystallization occurred. Filtration afforded 1.14 g. (46%) of *p,p'*-dinitrodibenzoylethylene, m.p. 203–209°, which was recrystallized from methylene chloride, m.p. 208–211°.

Anal. Calcd. for $C_{16}H_{10}N_2O_6$: C, 58.99; H, 3.65. Found: C, 58.85; H, 3.21.

Similarly, Ib gave 57% of *p,p'*-dibromodibenzoylethylene, m.p. 189–191° (lit.,[21] 188.5°). The infrared spectrum was consistent with the assigned structure.

p-Acetamidobenzoylmethylenetriphenylphosphorane gave 43% of *p-p'*-diacetamidodibenzoylethylene, m.p. 282–284°.

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.60; H, 5.14. Found: C, 68.37; H, 5.46.

p-Methoxybenzoylmethylenetriphenylphosphorane gave 57% of *p-p'*-dimethoxydibenzoylethylene, m.p. 165–167°.

Anal. Calcd. for $C_{18}H_{16}O_4$: C, 73.00; H, 5.42. Found: 73.53; H, 5.61.

Reaction of I and Phenylglyoxal.—To a stirred solution of 10.0 g. (0.0262 mole) of I in 200 ml. of dry benzene was added dropwise at room temperature 3.5 g. (0.0262 mole) of phenylglyoxal in 150 ml. of dry benzene. Immediately after the addition an aliquot was titrated.[15] It was found that 98% of I had reacted. Evaporation of a portion of the benzene afforded a solid whose infrared spectrum had all of the bands of *trans*-1,2-dibenzoylethylene. The bulk of the solution was evaporated to give a yellow solid which was recrystallized from absolute ethanol to give *trans*-1,2-dibenzoylethylene, m.p. 110–111°.

Addition of I to Peracetic Acid.—Several experiments were conducted in which I (1 mole) was added to peracetic acid (2 moles). All other conditions were maintained as close as possible to those used for the dimer-forming reaction. In all cases it was possible to isolate good yields of triphenylphosphine oxide. In no case was *trans*-1,2-dibenzoylethylene isolated. Small amounts of neutral oils were obtained.

To make sure that the excess peracid was not decomposing the *trans*-1,2-dibenzoylethylene, a control experiment was conducted. Treatment of 1.0 g. (0.00424 mole) of crude *trans*-1,2-dibenzoylethylene, m.p. 98–108°, which was obtained from a dimerization reaction, with 0.88 ml. (0.004 mole) of 40% peracetic acid for 17 hr. in 25 ml. of benzene gave, after extraction with base and water and evaporation of the solvent, 1.0 g. of *trans*-1,2-dibenzoylethylene, m.p. 98–108°. There was no depression on admixture with the starting material. The infrared spectra of the two compounds were identical.

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Conformational Analysis. XXXV. The Configurations and Conformations of Ring A in the 2-Fluoro-5α-Androstane-3,17-Diones[1,2]

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The dipole moments, rotatory dispersions, ultraviolet, infrared, and proton magnetic resonance spectra of 2α- and 2β-fluoroandrostane-3,17-dione have been determined and prove that the previously assigned configurations are correct. Ring A is in the chair conformation in both compounds.

Recent interest in compounds containing a fluorine atom on a carbon adjacent to a carbonyl group[4–7] prompted us to study further the 2-fluoro-3-keto steroids. The only compounds of this type so far reported for which both of the C-2 epimers are known are the 2-fluoroandrostane-3,17-diones[8] and related C-17 oxygenated compounds. There are a variety of physical methods which have been and may be used to establish the configuration of the halogen in such compounds, and these include infrared spectra,[7,9] ultraviolet spectra,[7,10] rotatory dispersion,[11] nuclear magnetic resonance spectra,[12] polarographic reduction potentials[13] and dipole moments.[7,14] Of these, the latter is one of the more definitive and has been used in the present work. The problem is more difficult than other similar cases which have been studied,[4–7] because the oxygen at C-17 introduces an extra unwanted dipole into the system. If the oxygen is as a hydroxyl or acetoxyl, conformational ambiguities exist, but this difficulty is alleviated by studying the 17-ketones which are also known compounds.

The two known epimers of 2-fluoro-5α-androstane-3,17-dione have had their configurations assigned previously on the basis of their methods of preparation and their spectral properties.[8] The aims of the present investigation were to confirm the configurational assignments, to examine the conformation of ring A in these compounds, and to develop general methods for dealing with molecules containing more than two dipoles.

Assuming initially an ordinary regular chair conformation for ring A, the moments expected for the 2α- and the 2β-fluoroandrostane-3,17-diones were calculated. The necessary data were obtained by projecting a Dreiding model of the molecule into a coördinate

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[2] This research was supported in part by the U. S. Army Research Office under grant number DA-20-018-ORD 22743, and in part by the National Science Foundation under grant number 19981.

[3] Predoctoral U. S. Public Health Service Fellow, General Division of Medical Sciences, 1960–1962.

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