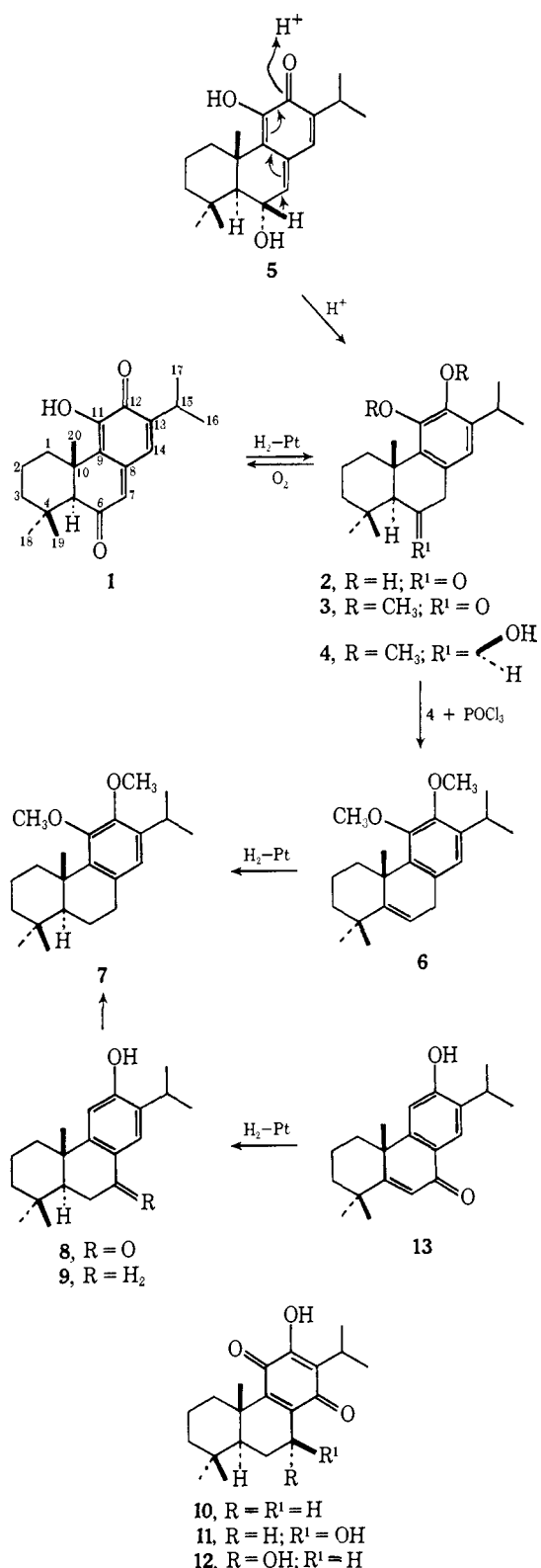


Scheme I



oxidation. Taxoquinone thus differs from horminone⁸ (12) only in the configuration of the hydroxy group. In the nmr spectrum of taxoquinone (11) the 7-proton signal is a triplet centered at τ 5.20 with a splitting of 7 cps, indicative of an α -axial proton, while the corresponding broad signal for horminone (τ 5.23, half-width 8 cps) indicates a β -equatorial 7-proton.¹⁰ The

(10) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, pp 77-83.

structure of Δ^5 -dehydrostugiol (13) [$\lambda_{\text{max}}^{\text{MeOH}}$ 246, 313 $m\mu$ (ϵ 22,000, 13,200); $\lambda_{\text{max}}^{\text{KBr}}$ 6.10, 6.19, 6.31, 6.39, 6.65 μ ; τ (pyridine-*d*₅) 1.55 (1 H, s, 7-*H*), 2.70 (1 H, s, 11-*H*), 3.32 (1 H, s, 6-*H*), 3.50 (1 H, br s, 12-OH), 6.33 (1 H, septet 15-*H*), 8.52, 8.65, 8.78, 8.82 (15 H, five CH₃)] was established by conversion to ferruginol (9) upon catalytic hydrogenation.

The observed growth-inhibitory activity of taxodione (1) and taxodone (5) confirms and extends an earlier report of antitumor activity of quinone methides.¹¹

Investigations are in progress to determine the significance of the reactive quinone methide and of other structural features in relation to the tumor-inhibitory activity of taxodione and taxodone.

(11) E. Schwenk, *Arzneimittel-Forsch.*, 12, 1143 (1962).

S. Morris Kupchan, Aziz Karim, Carol Marcks

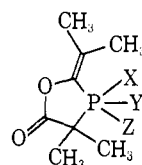
Department of Pharmaceutical Chemistry
University of Wisconsin, Madison, Wisconsin 53706

Received August 12, 1968

A New Phosphorane Obtained from Dimethylketene

Sir:

The synthesis and intermediacy of pentacovalent compounds of phosphorus (phosphoranes) have received considerable attention in the past few years.^{1,2} We report here a new series of cyclic phosphoranes, I,



Ia, X, Y, Z = OCH₃

Ie, X = N(CH₃)₂; Y, Z = -OCH₂CH₂O-

Ib, X, Y = OCH₃; Z = N(CH₃)₂ If, X = N(CH₃)₂; Y, Z = -OCH₂CH₂N(CH₃)-

Ic, X = OCH₃; Y, Z = -OCH₂- CH₂O- Ig, X = OCH₃; Y, Z = -(CH₃)-

Id, X = OCH₃; Y, Z = -OCH₂- CH₂N(CH₃)-

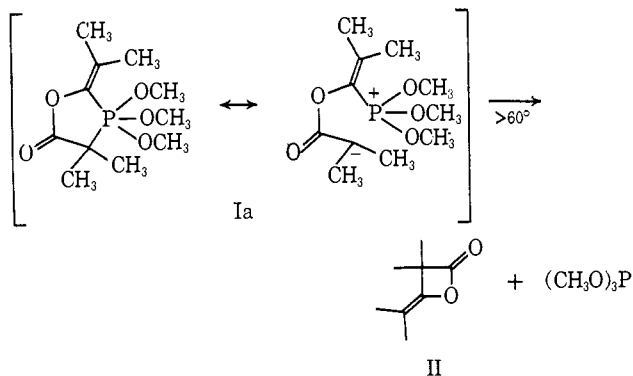
from the smooth reaction of dimethylketene with trivalent phosphorus derivatives.³ These 2:1 adducts contain the vinyl ester functionality as part of the ring system, a structural feature not accessible by other methods. In addition, these phosphoranes undergo a variety of clean and characteristic reactions. Preparation of the phosphorane Ia is achieved by addition of a solution of dimethylketene to trimethyl phosphite cooled to Dry Ice temperature followed by removal of volatile materials under vacuum yielding quantitative

(1) For reviews, see (a) F. Ramirez, *Accounts Chem. Res.*, 1, 168 (1968); (b) F. H. Westheimer, *ibid.*, 1, 70 (1968).

(2) For recent work, see: (a) D. B. Denney, D. Z. Denney, and L. A. Wilson, *Tetrahedron Letters*, 85 (1968); (b) W. Hawes and S. Trippett, *Chem. Commun.*, 295 (1968); (c) A. N. Hughes and S. Uaboonkul, *Tetrahedron*, 24, 3437 (1968); (d) B. Akermark, *Acta Chem. Scand.*, 21, 584 (1967); (e) J. Wulff and R. Huisgen, *Angew. Chem. Intern. Ed. Engl.*, 6, 457 (1967); (f) B. A. Arbuзов, N. A. Polezhaeva, and V. S. Vinogradova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2281 (1967); (g) F. Ramirez, M. Nagabhushanam, and C. P. Smith, *Tetrahedron*, 24, 1785 (1968).

(3) The reaction of diphenylketene with triethyl phosphite was reported⁴ to yield a 2:1 adduct for which the structure was not determined. It is possible that the structure of this adduct is analogous to that proposed for I.

(4) T. Mukaiyama, H. Nambu, and M. Okamoto, *J. Org. Chem.*, 27, 3651 (1962).

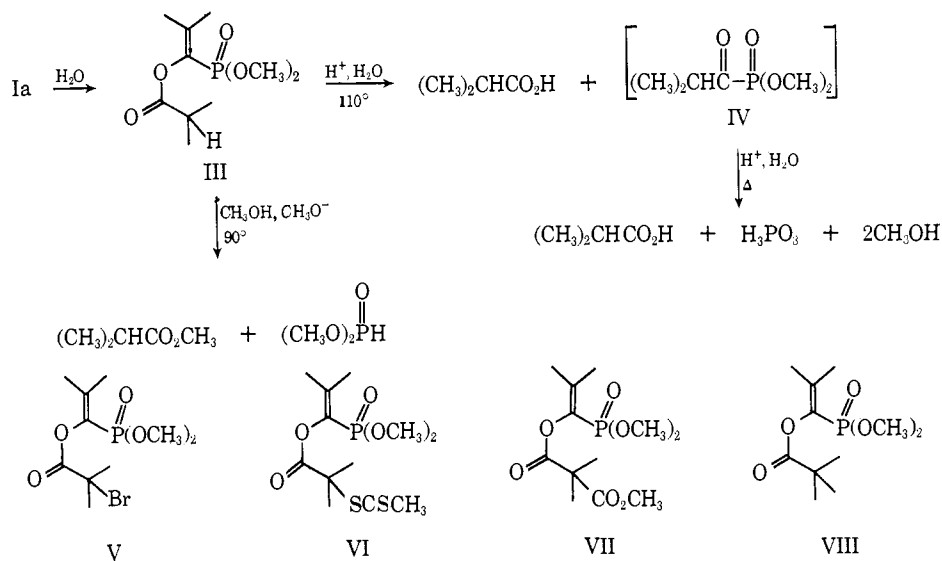


amounts of the 2:1 adduct Ia, a viscous and colorless liquid. Ia has important ir bands (neat film) at 1735 (s) and 1630 (w) cm^{-1} . Its pmr spectrum (neat) shows resonances of appropriate areas at 3.54 (doublet, $J_{\text{HP}} = 13.0$ Hz, CH_3O), 1.87 (doublet, $J_{\text{HP}} = 3.0$ Hz, vinyl methyl), 1.85 (doublet, $J_{\text{HP}} = 3.0$ Hz, vinyl methyl), and 1.58 ppm (singlet, *gem*-dimethyl group). P^{31} nmr shows absorption at +53.8 ppm relative to external H_3PO_4 , which is indicative of a pentacovalent species.^{1a}

The structure of Ia was further deduced as follows. At temperatures above 60° , Ia was converted quantitatively to the dimethylketene dimer II and trimethyl phosphite.⁵

Hydrolysis of Ia in different solvents at 0 – 30° gave III (Scheme I) the structure of which was shown by its pmr

Scheme I



spectrum (neat): 3.62 (doublet, $J_{\text{HP}} = 11.5$ Hz, CH_3O), 1.67 and 2.07 (doublets, $J_{\text{HP}} = 2.5$ and 3.0 Hz, vinyl methyl groups), 1.19 (doublet, $J_{\text{HH}} = 7.0$ Hz, isopropyl methyls), and 2.66 ppm (multiplet, methine hydrogen). The intensities of the pmr absorptions are appropriate for the structure assignment III. Important ir bands (neat film) occur at 1750 (s), 1650 (w), and 1265 (s) cm^{-1} . Acid hydrolysis of III gave 1.6 moles of iso-

(5) This explains the reported⁶ influence of small amounts of phosphites in catalyzing the dimerization of dimethylketene in a strongly exothermic reaction to II rather than to tetramethyl-1,3-cyclobutane-dione which is formed in the absence of phosphites. Other phosphoranes analogous to Ia which we have prepared from certain other phosphites and phosphoramidites exhibit greater thermal stability than I and are distillable, a property consistent with a pentacovalent structure.

(6) E. U. Elam, *J. Org. Chem.*, **32**, 215 (1967).

butyric acid and 1.8 moles of methanol/mole of III as observed by vpc.⁷ Likewise, reaction of III with methanol which contained a small amount of sodium yielded only methyl isobutyrate and dimethyl phosphite. With methanol, Ia afforded methyl isobutyrate and trimethyl phosphite as the only products detectable by vpc.

The reaction of Ia with bromine in carbon tetrachloride at 5° gave V, the pmr spectrum (CDCl_3) of which shows peaks of appropriate areas at 2.00 (singlet, α -bromo-*gem*-dimethyl group), 1.82 and 2.12 (doublets, $J_{\text{HP}} = 2.5$ and 3.0 Hz, vinyl methyl groups), and 3.73 ppm (doublet, $J_{\text{HP}} = 11.5$ Hz, CH_3O). The ir bands (film) of note occur at 1750 (s), 1650 (w), and 1270 (s) cm^{-1} .

In a very clean and rapid exothermic reaction, Ia and CS_2 combined to yield VI. The pmr spectrum of VI (benzene) exhibits absorptions at 1.82 (singlet, *gem*-dimethyl group), 1.62 and 2.00 (doublets, $J_{\text{HP}} = 2.5$ and 3.0 Hz, vinyl methyl groups), 2.35 (singlet, $\text{C}(\text{S})\text{CH}_3$), and 3.53 ppm (doublet, $J_{\text{HP}} = 11.5$ Hz, OCH_3) which have the appropriate areas. The ir bands (film) occur at 1750 (s), 1650 (w), and 1265 (s) cm^{-1} .

The phosphorane Ia underwent very facile carbonation at room temperature to yield a colorless crystalline (mp 37°) adduct (VII) for which the pmr spectrum (CDCl_3) shows absorptions of appropriate intensities at 1.50 (singlet, *gem*-dimethyl group), 1.73 and 2.12 (doublets,

$J_{\text{HP}} = 2.5$ and 3.0 Hz, vinyl methyls), 3.71 (doublet, $J_{\text{HP}} = 11.5$ Hz, phosphonate methoxyls), and 3.75 ppm (singlet, ester methoxyl). Important ir bands (film) occur at 1760 (s), 1740 (s), 1640 (w), and 1265 (s) cm^{-1} .

Excess methyl iodide and Ia reacted at room temperature in several days to give a near quantitative yield of VIII for which the pmr spectrum (benzene) shows peaks of appropriate intensities at 1.28 (singlet, *t*-butyl group), 1.51 and 2.07 (doublets, $J_{\text{HP}} = 2.5$ and 3.0 Hz, vinyl

(7) The hydrolysis of III would be expected to yield 1 mole each of isobutyric acid and the ketophosphonate IV. However, IV would not survive the hydrolysis conditions,⁸ but would react further with water to give isobutyric acid, methanol, and phosphorous acid.

(8) (a) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier Publishing Co., New York, N. Y., 1967, p 153; (b) K. D. Berlin and H. A. Taylor, *J. Am. Chem. Soc.*, **86**, 3862 (1964).

methyl groups), and 3.54 ppm (doublet, $J_{HP} = 11.5$ Hz, OCH_3). Noteworthy ir bands (film) occur at 1745 (s), 1640 (w), and 1265 (s) cm^{-1} .

Quantitative elemental analysis and mass spectral data are consistent with the structures of the reaction products.

These results are consistent with a compound (Ia) having a very reactive, polarized carbon-phosphorus bond as indicated by the inclusion of the polar canonical structure. In fact, the carbanion-like reactivity of Ia suggests that perhaps a small equilibrium amount of a dipolar intermediate may be present. The high positive chemical shift in the P^{31} nmr is that expected for a penta-covalent species rather than a dipolar structure, although the effects of the carbonyl and olefinic groups on the P^{31} chemical shifts are difficult to predict. The apparent lack of coupling between phosphorus and the geminal methyls has led us to consider other possible structures for the phosphorane in which the geminal methyls are not adjacent to phosphorus; however, the chemical evidence lends considerable support to the structure assignment Ia.

We have successfully applied this synthesis to a broad range of cyclic and acyclic phosphites and phosphoramidites to show its generality (Ib-g). These phosphoranes undergo reactions analogous to those reported for Ia. These results will be reported in a full paper.

Acknowledgment. This work was supported in part by National Institutes of Health Grant 1805FR07092-01 and a National Institutes of Health Predoctoral Fellowship (W. D. J.). We are indebted to Dr. Louis P. Lindeman and Dr. T. V. Liston of Chevron Research Co. and Mr. Frank Parker of the University of Michigan for P^{31} nmr data.

Wesley G. Bentrude, W. Delmar Johnson
Department of Chemistry, University of Utah
Salt Lake City, Utah
Received August 1, 1968

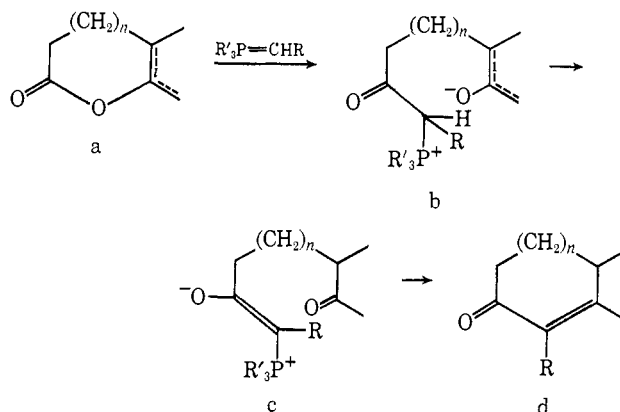
The Reaction of Phosphoranes and Phosphonate Anions with Enol Lactones. A New Method for the Preparation of Cyclic α,β -Unsaturated Ketones¹

Sir:

The synthetic methods utilized for the preparation of cyclic α,β -unsaturated ketones from acyclic precursors often suffer from the disadvantage that alternate condensation reactions frequently occur which lead to isomeric unsaturated ketones or other undesirable products.² In principle, the unidirectional cyclization process depicted by the transformations a-d constitutes a useful general method for the synthesis of α,β -unsaturated ketones. Thus, attack of a phosphonium ylide on the cyclic enol lactone (a) should yield the ketophosphorane (c) after proton reorganization within the

(1) Publication No. 347 from the Syntex Institute of Steroid Chemistry. Publication No. 346: S. Kaufmann, L. Tökes, J. Murphy, and P. Crabbé, submitted for publication.

(2) For examples see S. Julia, *Bull. Soc. Chim. Fr.*, 780 (1954); K. D. Zwahlen, W. J. Horton, and G. I. Fujimoto, *J. Amer. Chem. Soc.*, 79, 3131 (1957); W. S. Johnson, J. J. Korst, R. A. Clement, and J. Dutta, *ibid.*, 82, 614 (1960); L. Velluz, G. Nominé, and J. Mathieu, *Angew. Chem.*, 72, 725 (1960); L. J. Chinn and H. L. Dryden, *J. Org. Chem.*, 26, 3904 (1961); J. A. Marshall and D. J. Schaeffer, *ibid.*, 30, 3642 (1965); M. Ohashi, H. Kamachi, H. Kakisawa, and G. Stork, *J. Amer. Chem. Soc.*, 89, 5460 (1967).



initially formed phosphonium enolate salt (b). Cyclization could then proceed by an intramolecular Wittig reaction to yield the enone (d). This process would be expected to compete favorably with the intermolecular reaction which is known to be sluggish in the case of stabilized ylides.³ In this communication we wish to report that both alkylidetriphenylphosphoranes and dialkyl alkylphosphonate anions attack a variety of cyclic enol lactones according to the proposed scheme to yield in one step the desired cyclic α,β -unsaturated ketones.

Exposure of benzylidenephthalide (1) to 1.0 equiv of methylene-triphenylphosphorane (2) (prepared from methyltriphenylphosphonium bromide and butyllithium in tetrahydrofuran) for 24 hr at 23° afforded in 44% yield 3-benzylidenindan-1-one (3a)⁴ [mp 104–105°; $\nu_{max}^{CCl_4}$ 1720, 1595 cm^{-1} ; λ_{max}^{EtOH} 218, 235, 257, 263, 290, 301, 314 $m\mu$ (log ϵ 4.34, 4.20, 4.08, 4.07, 4.18, 4.20, 4.09); nmr 3.49 (d, $J = 2$ cps, 2-H), 7.18 (t, $J = 2$ cps, $C_6H_5CH=C<$), 7.1–7.9 ppm (m, aromatic H)]⁵ and 32% of starting material.

Similarly reaction of 1 with 1.1 equiv of *n*-butylene-triphenylphosphorane gave a 30% yield of 3-benzyl-2-*n*-propylindanone (4)⁶ [yellow oil, $\nu_{max}^{CCl_4}$ 1710, 1605 cm^{-1} ; λ_{max}^{EtOH} 236, 243, 315, 395 $m\mu$ (log ϵ 4.59, 4.62, 3.01, 2.76); nmr 0.92 (t, $J = 7$ cps, $CH_3CH_2CH_2-$), 1.50 (m, $CH_3CH_2CH_2-$), 2.33 (t, $J = 7$ cps, $CH_3CH_2CH_2-$), 3.93 (s, $C_6H_5CH_2-$), 6.7–7.5 ppm (m, aromatic H)] and 29% of 2-propyl-3-benzylidenindanone (3b) [mp 84–86°; ν_{max}^{film} 1715, 1610 cm^{-1} ; λ_{max}^{EtOH} 221, 239, 296, 305, 318 (sh) $m\mu$ (log ϵ 4.26, 4.24, 4.29, 4.30, 4.16); nmr 0.72 (t, $J = 7$ cps, $CH_3CH_2CH_2-$), 3.7 (m, 2-H), 7.2–8.0 ppm (m, olefinic and aromatic H)].

The tetra-cyclic enol lactone (\pm)-3-methoxy-15-methyl-16-oxaestra-1,3,5(10),6,8,14-hexaen-17-one (5)⁷ also reacts in tetrahydrofuran with 2 to give only the

(3) (a) A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, p 138; (b) see also E. E. Schweizer and J. G. Liehr, *J. Org. Chem.*, 33, 583 (1968); H. G. Lehmann and R. Wiechert, *Angew. Chem. Intern. Ed. Engl.*, 7, 300 (1968).

(4) 3-Benzylindanone, the initial product of this reaction, is isomerized to 3a via the enolate anion in turn generated by the ylide 2. When 1.8–2.0 equiv of ylide is used, 3a is obtained in greater than 90% yield.

(5) Satisfactory analyses were obtained for all fully characterized compounds. Nmr spectra were obtained on Varian A-60 and HA-100 spectrometers in deuteriochloroform solutions (10% w/v) containing tetramethylsilane as internal reference. Chemical shifts are reported as parts per million on the δ scale. We thank Miss J. Tremble for these determinations. In the presentation of data d = doublet, t = triplet, and m = multiplet.

(6) Compare the reaction of benzylidenephthalide with phenylmagnesium bromide which yields 2,3-diphenylindanone. See "Organic Syntheses," Coll. Vol. III, R. N. Adams, Ed., John Wiley & Sons, Inc., New York, N. Y., 1955, p 353.

(7) W. R. J. Simpson, D. Babbe, J. A. Edwards, and J. H. Fried, *Tetrahedron Lett.*, 3209 (1967).