The infrared spectrum in CH_2Cl_2 had bands at (μ) 2.92 (OH), 5.85 (CO), 7.40, 8.35, and 8.70.

Reaction of the Phospholane VI with an Excess of Water. Water (8 ml, 462 mmoles) was added to a solution of the phospholane VI (15 g, 58 mmoles) in benzene (50 ml). The mixture was kept 4 hr at reflux. The water layer was extracted with benzene. The combined benzene extracts and original solution were fractionated as before. Diacetylmethylcarbinol (XVIII) was isolated in 75% yield.

Reaction of the Phospholane VI with 1 Molar Equiv of Water. a. In $CDCl_3$ Solution. Water (1 molar equiv) was added to a solution of the phospholane VI in $CDCl_3$ at 20°. After the vigorous exothermic reaction had subsided, the solution was analyzed by P^{31} nmr spectrometry at 40.5 Mc/sec. Only the signals due to trimethyl phosphate and to diacetylmethylcarbinol dimethyl phosphate (XI) were observed. The experiment was repeated using D_2O and a 6 *M* solution of the phospholane VI in $CDCl_3$; the H^1 nmr after 5 min had the signals due to trimethyl phosphate, the deuteriodiacetylmethylcarbinol (XVIII), the open phosphotriester XI, and deuteriomethanol.

b. In Benzene Solutions. Water (1 molar equiv) was added to a 2 *M* solution of phospholane VI in benzene at 0°. The solvent was removed after *ca.* 1 min at 0° (3 min). The residue was dissolved in $CDCl_3$. The P^{31} and H^1 nmr spectra showed the signals of the species mentioned above plus those of some unreacted phospholane VI. There was no evidence for the formation of the cyclic phosphate ester XXV.

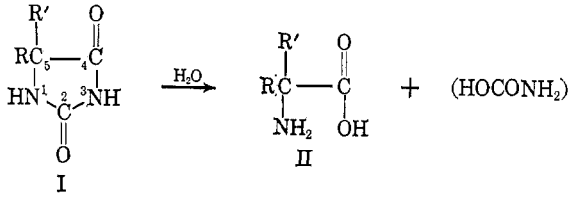
A New Synthesis of 5-Acylhydantoins, Precursors of β-Keto-α-amino Acids

Fausto Ramirez,[1] S. B. Bhatia, and C. P. Smith

Contribution from the Department of Chemistry of the State University of New York at Stony Brook, Stony Brook, New York 11790.
Received February 21, 1967

Abstract: A new reaction leading to 5-acylhydantoins, the precursors of β-keto-α-amino acids, is described. In this reaction, a trialkyl phosphite induces the condensation of one molecule of an α-diketone with two molecules of an aryl isocyanate with formation of the 5-acylhydantoin and a trialkyl phosphate. Three steps are involved, and the intermediates can, but need not, be isolated. The intermediates are organic compounds with pentacovalent phosphorus as shown by P^{31} nmr spectroscopy.

The hydantoins I are one of the classical synthetic precursors of the α-amino acids[2] II.

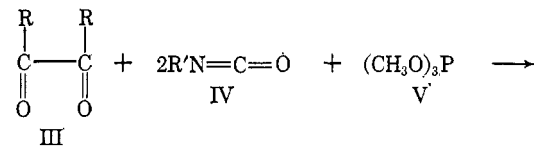


I

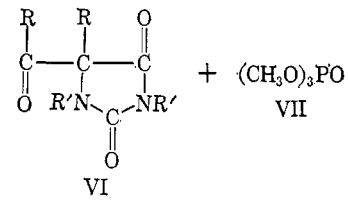
II

This type of heterocycle is associated with powerful anticonvulsant action; for example, 5,5-diphenylhydantoin (Dilantin) is widely used in the control of epilepsy.[2] Consequently, many alkyl- and arylhydantoins have been prepared.[2] On the other hand, the 5-acylhydantoins, which are the precursors of β-keto-α-amino acids, have not received much attention.[2c] Modifications of the carbonyl function of the 5-acylhydantoins prior to hydrolysis would make available a variety of β-substituted α-amino acids.

This paper describes a new approach to 5-acylhydantoins VI based on the condensation of an α-dicarbonyl compound III with an isocyanate[3] IV under the influence of a trialkyl phosphite[4,5] V.



III IV V



VI VII

Results

The 2,2,2-trialkoxy-1,3,2-dioxaphospholene[6] (VIII), prepared from biacetyl and trimethyl phosphite, reacted with phenyl isocyanate (IX) at 30°. The course of the reaction was followed by means of infrared and H^1 and P^{31} nmr spectroscopy. Two distinct steps were observed. The first step was the nucleophilic addition of a carbon atom of the phospholene VIII to the carbonyl carbon of the isocyanate. The product was 2,2,2-trimethoxy-4-phenylimino-5-acetyl-5-methyl-1,3,2-dioxaphospholane (X).

(1) This investigation was supported by Public Health Service Grant No. CA-04769-08 from the National Cancer Institute, and by the National Science Foundation, Grant CP-6690-Y.

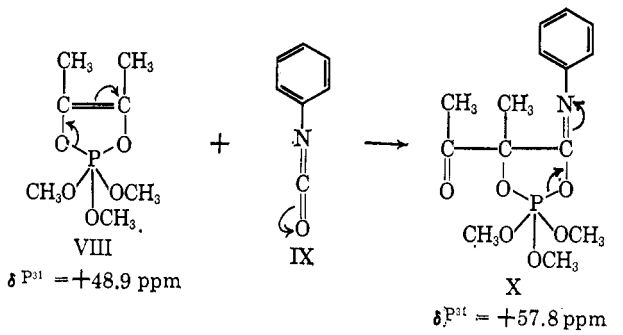
(2) For reviews of hydantoin chemistry see: (a) E. Ware, *Chem. Rev.*, **46**, 403 (1950); (b) E. S. Schipper and A. R. Day in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957; (c) H. Finkbeiner, *J. Org. Chem.*, **30**, 3414 (1965).

(3) For reviews on isocyanates see: (a) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *Chem. Rev.*, **57**, 47 (1957); (b) C. V. Wilson, *Org. Chem. Bull.*, **35**, 1 (1963); (c) P. A. S. Smith, "The Chemistry of Open-Chain Organic Nitrogen Compounds," W. A. Benjamin, Inc., New York, N. Y., 1965, Chapter 6.

(4) The deoxygenation of alkyl isocyanates by trialkyl phosphites at elevated temperatures (180–190°) has been reported: *cf.* T. Mukaiyama, H. Nambu, and M. Okamoto, *J. Org. Chem.*, **27**, 3651 (1962).

(5) The formation of certain 2-iminooxazolidines and 2-imidazolidones from the reaction of aryl isocyanates with ethyl bis(β-aminoethyl)-phosphite has been described: *cf.* O. Mitsunobo, T. Ohashi, and T. Mukaiyama, *Bull. Chem. Soc. Japan*, **39**, 708 (1966).

(6) The literature has been reviewed by F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964).

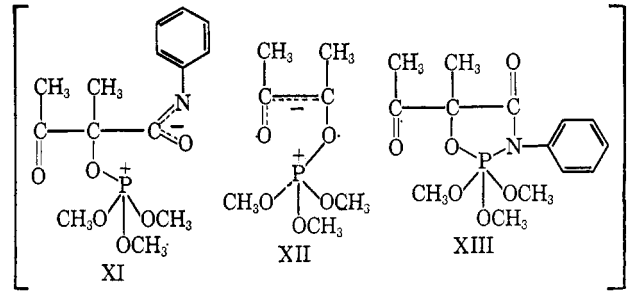


$\delta P^{31} = +48.9$ ppm

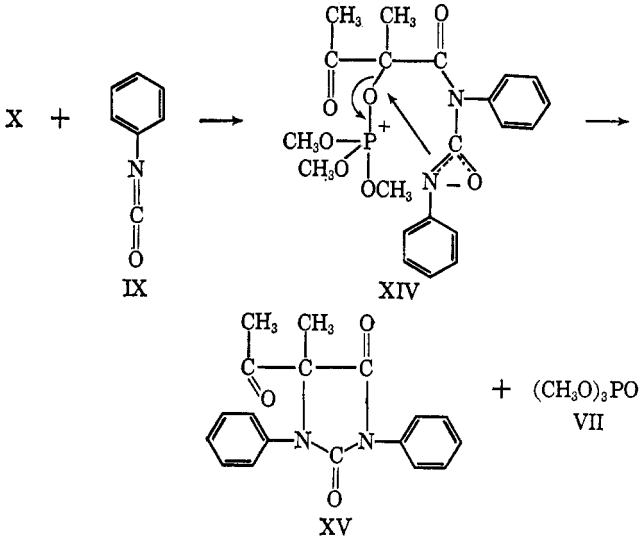
$\delta P^{31} = +57.8$ ppm

The phospholane X may arise in one concerted step which requires little or no charge separation.[7] There was no experimental indication of the presence of open dipolar structures[8] such as XI and XII.

Furthermore, a structural isomer of the pentaoxyphosphorane X, namely, the aminotetraoxyphosphorane XIII, could not be detected. This is consistent with our previous observations on the relative stabilities of these ring systems.[8,9]



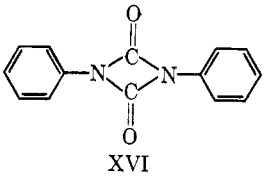
The phospholane X reacted with a second molecule of phenyl isocyanate. The products were trimethyl phosphate (VII) and 1,3-diphenyl-5-acetyl-5-methylhydantoin (XV).



No intermediate could be detected in this reaction, but we assume that the nitrogen of the phospholane X first performed a nucleophilic addition to the carbon of the isocyanate to form a dipolar intermediate XIV. The latter then cyclized to a five-membered hydantoin ring with ejection of phosphate ester, instead of forming a seven-membered cyclic phosphorane.

A structural isomer of the hydantoin, which would be derived from an attack by oxygen on carbon in the intermediate XIV, could not be isolated.

It was shown that the isocyanate dimer XVI, prepared by addition of traces of tri-*n*-butylphosphine to the isocyanate,[10] did not react with the phospholene VIII.



XVI

The rates of the reactions of phenyl isocyanate with the phospho*lene* VIII and with the phospho*lane* X were very similar. Therefore, the best procedure to make phospholane X involved a slow addition of isocyanate to an excess of phospholene VIII.

The preparation of hydantoin XV was very simple. Isocyanate (2 moles) and phospholene VIII (1 mole) were allowed to react in boiling methylene chloride solution. Compound XV was isolated in 75% yield. Small amounts of a second substance, not investigated further, were found in the residues.

It was possible to condense biacetyl with 2 moles of phenyl isocyanate and 1 mole of trimethyl phosphite *in situ*, without isolation of intermediates, as shown in the scheme III + IV + V → VI + VII.

The following data established the structure of the phospholane X. (1) The P^{31} nmr shift, $\delta P^{31} = +57.8$ ppm *vs.* H_3PO_4, showed that five oxygen atoms were bound to the phosphorus.[6,9,11] The shift of the aminotetraoxyphosphorane XIII should fall in the range 30–40 ppm.[8]

(2) The H^1 nmr spectrum of X had a 3 H^1 singlet at τ 7.71 and another at τ 8.36, which correspond to the acetyl and the methyl groups, respectively.[6,9] The 9 H^1 of the three methoxy groups gave rise to one doublet, $J_{HP} = 13$ cps, at τ 6.41. As was the case with a number of related compounds, the three methoxy groups were magnetically indistinguishable at 20°, probably due to rapid positional exchange in the trigonal bipyramid.[6,9]

(3) The infrared spectrum of X had strong bands at 5.98 and 5.78 μ, which are attributed to the C=N and the C=O groups, respectively.

The hydantoin XV had infrared bands at 5.62 and 5.83 μ attributed to the carbonyl groups at the 4 and 2 positions, respectively.[12] The band due to the acetyl carbonyl was at 5.78 μ. The H^1 nmr spectrum of XV had the expected 10 H^1 aromatic multiplet and the 3 H^1 singlets at τ 7.68 and 8.28 due to the acetyl and the methyl groups, respectively.

p-Cyanophenyl isocyanate (XVII) reacted faster than the unsubstituted isocyanate IX with the phospholene VIII. The N-(*p*-cyanophenyl)hydantoin (XVIII) was isolated in 75% yield.

(7) (a) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, 30, 2575 (1965); (b) *ibid.*, 31, 474 (1966); (c) *ibid.*, 31, 3159 (1966).

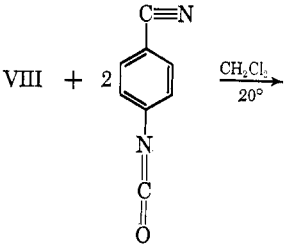
(8) (a) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Am. Chem. Soc.*, 87, 4973 (1965); (b) F. Ramirez, A. V. Patwardhan, H. J. Kugler, and C. P. Smith, *Tetrahedron Letters*, 3053 (1966).

(9) F. Ramirez, *Bull. Soc. Chim. France*, 2443 (1966).

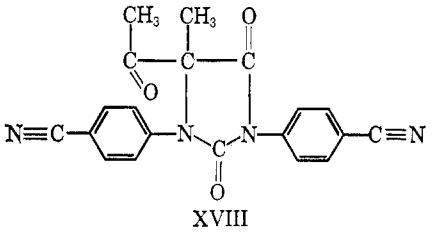
(10) R. B. Buckles and L. A. McGrew, *J. Am. Chem. Soc.*, 88, 3582 (1966).

(11) W. C. Hamilton, S. J. LaPlaca, and F. Ramirez, *ibid.*, 87, 127 (1965).

(12) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p 221.



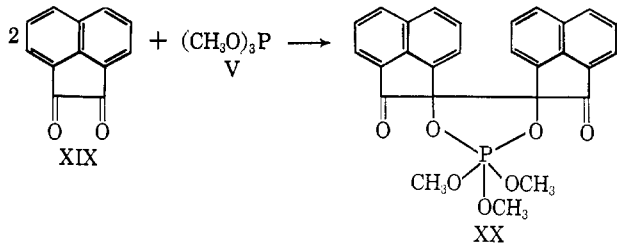
XVII



XVIII

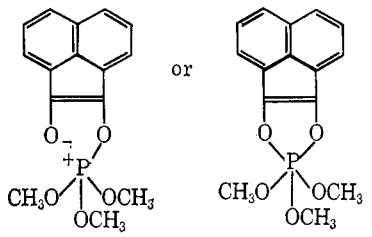
Discussion

The formation of a 2,2,2-trialkoxy-1,3,2-dioxaphospholane (XX) from the reaction of the α-dicarbonyl compound XIX with the trialkyl phosphite V was first reported in 1961.[13] The exact nature of the precursor, XXI or XXII, of the phospholane XX could not be established, since this precursor reacted very rapidly with a second molecule of the carbonyl compound.



XIX, XX

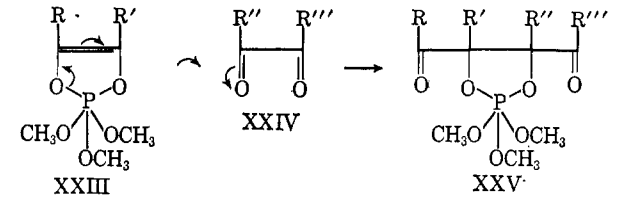
$\delta^{P^{31}} = +48.0$ ppm



XXI, XXII

not isolated

Shortly thereafter, it was demonstrated that isolable 2,2,2-trialkoxy-1,3,2-dioxaphospholenes (XXIII) underwent nucleophilic additions to carbonyl functions XXIV with formation of analogous phospholanes[14] XXV.



XXIII, XXIV, XXV

$\delta^{P^{31}} = +48.9$ ppm

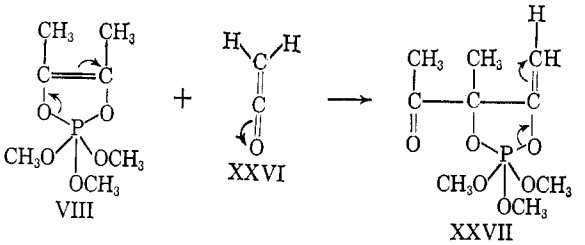
$\delta^{P^{31}} = +54.8$ ppm

(13) F. Ramirez and N. Ramanathan, *J. Org. Chem.*, **26**, 3041 (1961).

(14) F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Am. Chem. Soc.*, **84**, 1317 (1962).

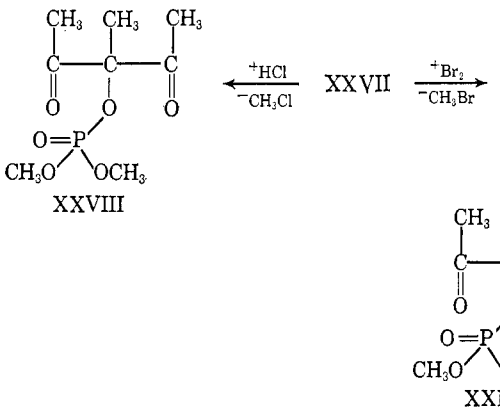
Subsequently, the mechanism and the synthetic scope of this new reaction were investigated in detail.[6,7,9]

More recently, it was found that the phospholene VIII condensed very readily with ketene XXVI to give 4-methylene-2,2,2-trialkoxy-1,3,2-dioxaphospholane[15] (XXVII).



VIII, XXVI, XXVII

The *exo*-methylenephospholane XXVII proved to be a valuable reaction intermediate. It was readily converted into the phosphate esters of α-hydroxy-β-diketones and of γ-bromo-α-hydroxy-β-diketones[15] XXVIII and XXIX.



XXVIII, XXIX

The present paper emphasizes the generality of this new method of making carbon–carbon single bonds by means of triply and quintuply connected phosphorus compounds.[16] Evidently, the method seems adaptable to the syntheses of α-amino acids and of carbohydrates. These studies are now in progress.

Experimental Section

The analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The instrumentation was described previously.[6,7] All P^{31} nmr shifts are given in parts per million from 85% H_3PO_4 as zero; they were measured at 40.5 Mc/sec.

Reaction of 2,2,2-Trimethoxy-4,5-dimethyl-1,3,2-dioxaphospholene (VIII) with 1 Molar Equiv of Phenyl Isocyanate. The phospholene[6,7] VIII (11.8 g, 56 mmoles) and the isocyanate IX (5.9 g, 50 mmoles) were mixed at 20° in the absence of solvent and with protection against moisture. There was no visible reaction, but the infrared and H^1 nmr spectra showed evidence of reaction within 1 hr. After 20 hr at 20° under stirring, all the isocyanate had been consumed and there were new infrared bands at 5.62, 5.78, 5.82, and 5.93 μ. The H^1 nmr spectrum in $CDCl_3$ showed some unreacted dioxaphospholene VIII, some trimethyl phosphate (doublet at τ 6.32, J_{PH} = 11 cps), the dioxaphospholane X, and the hydantoin XV. Better resolution was achieved in CH_2Cl_2. The P^{31} nmr spectrum in CH_2Cl_2 confirmed the presence of the phospholene (δP^{31} = +48.9 ppm), the phospholane (δP^{31} = +57.8 ppm), and trimethyl phosphate (δP^{31} = −2.2 ppm).

(15) F. Ramirez, S. B. Bhatia, and C. P. Smith, *ibid.*, **89**, 3026 (1967).

(16) While this work was in progress, A. J. Kirby [*Tetrahedron*, **22**, 3001 (1966)] described the reaction of the dioxaphospholene VIII with carbon disulfide. Our studies of the reaction of VIII with a number of systems having cumulated double bonds will be published soon.

The mixture was freed from the phospholene VIII and trimethyl phosphate by short-path distillation at 0.3 mm. The residue was dissolved in ether (40 ml) and kept at −20° to effect crystallization of the hydantoin XV. The latter (2.0 g, 28% yield) was collected and was recrystallized from benzene–hexane. 1,3-Diphenyl-5-acetyl-5-methylhydantoin (XV) had mp 134–135°.

Anal. Calcd for $C_{18}H_{16}O_3N_2$: C, 70.1; H, 5.2; N, 9.1; mol wt, 308. Found: C, 70.2; H, 5.3; N, 9.3; mol wt, 300 (cryoscopic in benzene).

The H^1 nmr spectrum (τ values in parts per million from TMS = 10, in $CDCl_3$) had signals at 2.58 (four aromatic protons), 2.71 (six aromatic protons), 7.68 (three acetyl protons), and 8.28 (three methyl protons). The infrared spectrum (in CH_2Cl_2) had bands at 5.62 (m), 5.78 (s), 5.82 (s), 6.23 (w), 6.67 (m), 7.13 (ms), 7.42 (m) and 8.45 (m) μ.

The ether filtrate was evaporated. The residue was shown to contain more hydantoin and small amounts of trimethyl phosphate; the main component was the dioxaphospholane X. The latter is best prepared as described below.

Reaction of the Dioxaphospholene VIII with 2 Molar Equiv of Phenyl Isocyanate. Optimum Conditions for the Synthesis of Hydantoin XV. The phospholene VIII (9.8 g, 46.7 mmoles) and the phenyl isocyanate (11.1 g, 93.5 mmoles) were dissolved in 25 ml of methylene chloride. The solution was kept 24 hr at reflux temperature, and then the solvent was removed at 20° (20 mm). The residue was kept several hours at −20° under ether, and the first crop (8 g) of nearly pure hydantoin XV was filtered. The filtrate was evaporated to remove first ether and then trimethyl phosphate (0.1 mm, bath at 80°). The residue was kept several hours at 20° under ethanol giving a second crop (2.1 g) of hydantoin XV; combined yield 70%. The material balance consisted of more hydantoin (estimated 10–15%) and a second substance whose structure was not investigated further.

Direct Synthesis of 5-Acyl-5-alkylhydantoin (XV) from α-Diketone, Isocyanate, and Phosphite without Isolation of Intermediates. Biacetyl (8.6 g, 100 mmoles) and phenyl isocyanate (24 g, 200 mmoles) were dissolved in 20 ml of methylene chloride. The solution was cooled to 0° and was treated with trimethyl phosphite (12.5 g, 100 mmoles). The solution was stirred 1 hr at 0° and 0.5 hr at 20°. It was then kept at reflux for 7 hr; the infrared spectrum showed little unreacted isocyanate. The reaction mixture was worked up as described above, after an additional 8–10-hr reflux period. The hydantoin was isolated in 70% yield.

Isolation of 2,2,2-Trimethoxy-4-phenylimino-5-acetyl-5-methyl-1,3,2-dioxaphospholane (X). Phenyl isocyanate (9.7 g, 82 mmoles) was introduced into the stirred dioxaphospholene VIII (34.3 g, 164 mmoles) over a 12-hr period, at 20°. The mixture was stirred for an additional 12-hr period. The excess of phospholene and a small amount of trimethyl phosphate were removed at 0.1 mm and a bath temperature of 80°. The residue (22 g) was the viscous, noncrystalline dioxaphospholane X. The latter had the following spectral characteristics: δP^{31} = +57.8 ppm (CH_2Cl_2); τ ($CDCl_3$) 6.48 (doublet), J_{HP} = 13 cps, 7.72 (singlet), 8.35 (singlet); τ (CH_2Cl_2) 6.50, J_{HP} = 13 cps, 7.75 and 8.40; τ (benzene) 6.60, J_{HP} = 13 cps, 7.80 and 8.40; infrared bands (CH_2Cl_2) at 5.78 (s), 5.93 (s), 6.27 (ml), 6.70 (ms), 6.92 (m), 7.20 (ms), 7.40 (m), 8.50 (m), 8.70 (m), 9.30–9.40 (vs and broad), 9.86 (m), 11.72 (ms), and 12.15 (ms) μ.

Reaction of the Trimethyl Biacetyl(phenyl isocyanate)phosphite Adduct X with Phenyl Isocyanate. The phospholane X obtained above was converted into the hydantoin XV by 1 molar equiv of phenyl isocyanate in methylene chloride at reflux temperature.

Effect of Temperature and of Solvent on the Yield of Hydantoin XV. (a) In 1,2-Dichloroethane. The phospholene VIII and 2 molar equiv of phenyl isocyanate were dissolved in 1,2-dichloroethane, and the solution was kept at various temperatures for various periods of time. The hydantoin XV was isolated in the following yields: 65% after 10 hr at 55°, 59% after 8 hr at 65°, 63% after 17 hr at 65°. A second substance was also isolated from these experiments in about 10% yield.

(b) In Ether. Significant amounts of phenyl isocyanate remained after 24 hr at reflux temperature.

(c) In the Absence of Solvent. The hydantoin XV was isolated in *ca.* 40% yield after 24 hr at 20°. At higher temperatures the reaction was erratic and, at times, violent. In one case, 48% of hydantoin was isolated after 4 hr at 60°.

Reaction of 5-Acylhydantoin XV with 2,4-Dinitrophenylhydrazine. The hydantoin XV (800 mg) in ethanol (30 ml) was treated with a solution made from 2,4-dinitrophenylhydrazine (1.2 g), H_2SO_4 (1.5 ml, concentrated), and methanol (30 ml), The red solution was kept 2 hr at reflux, cooled, and filtered yielding the yellow 2,4-dinitrophenylhydrazone, mp 195–196° (benzene).

Anal. Calcd for $C_{24}H_{20}O_6N_6$: N, 17.2. Found: N, 17.1.

The infrared spectrum (CH_2Cl_2) had bands at 3.15 (w), 5.62 (m), 5.80 (s), 6.18 (s), 6.27 (s), 6.67 (s), 7.15 (s), 7.46 (s), and 7.62 (m) μ, among others.

Reaction of the Dioxaphospholene VIII with 2 Molar Equiv of *p*-Cyanophenyl Isocyanate (XVII). The phospholene VIII (9.1 g, 43.1 mmoles) was added to a suspension of *p*-cyanophenyl isocyanate (12.5 g, 86.4 mmoles) in 1,2-dichloroethane at 20°. The mixture was stirred at 20° for 12 hr. The first crop of the cyanohydantoin XVIII (8.8 g) was filtered. The filtrate was evaporated, and the residue was kept several hours at 20° under ether to give a second crop of hydantoin (1.1 g), combined yield 70%. The analytical sample of 1,3-di-(*p*-cyanophenyl)-5-acetyl-5-methylhydantoin (XVIII) had mp 234–235° (from $CH_2Cl \cdot CH_2Cl$).

Anal. Calcd for $C_{20}H_{14}O_3N_4$: C, 67.1; H, 3.9; N, 15.6. Found: C, 67.2; H, 4.1; N, 15.7.

The H^1 nmr in $AsCl_3$ had the following signals (in τ): aromatic multiplet at 2.1–2.6, acetyl protons at 7.53, and methyl protons at 8.09. The infrared spectrum (in CH_2Cl_2) had bands at 4.50 (m) (CN), 5.62 (ms) (CO). 5.78 (s) (CO), 5.82 (s) (CO), 6.23 (ms), 6.65 (ms), 7.20 (s), and 7.48 (ms) μ.

Attempted Reaction of the Dioxaphospholene VIII with the Phenyl Isocyanate Dimer[10] XIV. The phenyl isocyanate dimer XIV was formed immediately when a few drops of tri-*n*-butylphosphine was added to the isocyanate.[10] The dimer was filtered, washed with ethanol, and recrystallized from boiling toluene; it had mp 174–175° and showed infrared bands at 5.60 (s), 6.23 (w), 6.67 (s), and 7.23 (s) μ in CH_2Cl_2 in which it was slightly soluble.

The dimer failed to react with the dioxaphospholene VIII, with or without solvents, at 20° for several days.