aqueous solution containing the dibasic phospho monoesters (XIII and XIV) was submitted to ^{31}P and ^1H nmr spectrometry at several time intervals. *After 20 min*, two phosphorus nuclei were found: a singlet at +4.1 ppm (phosphate α to carbonyl as in XIII and a doublet at +1.5 ppm (phosphate β to carbonyl as in XIV, signal split by the methine proton).

The ^1H nmr spectrum of the same solution showed singlets at τ 8.35 (CH_3C) and 7.65 (CH_3CO) due to the α-phospho monoester (XIII) and singlets at τ 8.50 (CH_3C) and 7.70 (CH_3CO) due to the β-phospho monoester (XIV). The structural isomers were present in about equal proportions.

After 2 hr, the ^{31}P nmr signal of α-phospho monoester XIII (+4.1 ppm) had disappeared almost completely. The doublet due to β-phospho monoester XIV (+1.5 ppm) had doubled its intensity. The ^1H nmr signals of the α-phospho monoesters (τ 8.35 and 7.65) had decreased to about 10% of their original intensities, while the signals due to the β-phospho monoester (τ 8.50 and 7.70) had increased by about 90%.

Hydrolyses of the 5-Cyclic Phospho Triesters (Two Diastereomers at Phosphorus, Xa and Xb) with 1 Mol Equiv of Water.—Water (1 mol equiv) was added to a solution of the cyclic triesters, Xa and Xb (3.1 g, 12 mmol), in 12 ml of $CHCl_3$ at 20°. The solvent was removed at 20° and 20 mm, leaving a light brown, oily residue. The ^{31}P nmr spectrum of this liquid had two signals of about equal intensities. One of them at −0.5 ppm was due to the β-open phospho triester (XII). The other at −14.0 was due to the 5-cyclic phospho diester, XVa or XVb.

The ^1H nmr signal of the original $CHCl_3$ solution confirmed these assignments and showed the absence of methanol; *i.e.*, the methanol produced in the hydrolysis reacted with the cyclic triester, X, to give the open triester, XII.

Hydrolyses of the 5-Cyclic Phospho Triesters (Two Diastereomers at Phosphorus, Xa and Xb) with an Excess of Water.—The 5-cyclic triesters, Xa and Xb, were mixed with an equal volume of water in an nmr sample tube. After the exothermic reaction had subsided, the solution was analyzed by ^{31}P and ^1H nmr spectrometry at various time intervals. The signals due to the α monoester, XIII (+4.1, τ 8.35 and 7.65), which were observed after 30 min, had vanished completely after 2.5 hr. The corresponding signals due to the β-phospho monoester, XIV, had increased in intensity. When the solution was heated 3 min at 100°, it turned dark brown and was not investigated further.

Behavior of the Open-Chain β-Phospho Triester toward Hydrolysis. A.—The open-chain β-phospho triester, XII, was mixed with an equal volume of water at 20°. The ^1H nmr spectrum taken at 30-min intervals over a period of 8 hr revealed no significant change.

B.—Addition of 1 drop of phosphoric acid to the aqueous solution caused hydrolysis to the β-phospho monoester (XIV). After 10 min, the extent of the hydrolysis was roughly 5-10%; after 5 hr, approximately 5% of the original signal due to the $POCH_3$ group was present. These results were confirmed by ^{31}P nmr analysis.

Registry No.—VII, 15353-05-6; Xa, 15353-06-7; Xb, 15353-07-8; XII, 15353-08-9; disodium salt of XIV, 15353-09-0.

New Syntheses of β-Keto-α-hydroxy Acid Chlorides, of α-Hydroxy β-Diketones, and of Their Phosphate Esters

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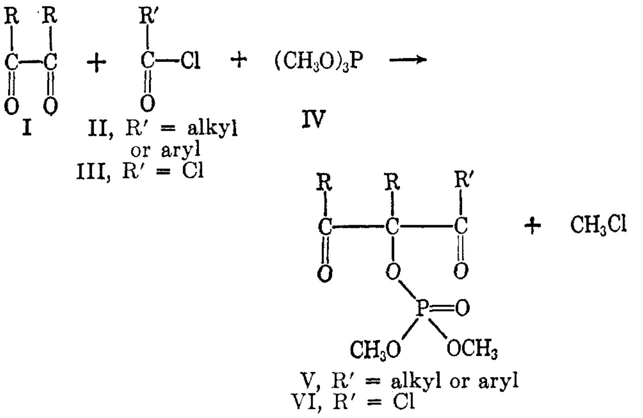
Received September 28, 1967

The 1:1 adduct made from biacetyl, $CH_3COCOCH_3$, and trimethyl phosphite, $(CH_3O)_3P$, namely, 2,2,2-trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene, performed a nucleophilic substitution at the carbonyl carbon of carboxylic acid chlorides, R′COCl, and of phosgene, ClCOCl. This new reaction provided a direct synthesis of phosphate esters derived from α-hydroxy β-diketones, R′COC(OH)(R)(COR), and from β-keto-α-hydroxy acid chlorides, ClCOC(OH)(R)(COR). The α-hydroxy β-diketone phosphates underwent an extraordinarily facile hydrolysis to the diketo alcohols.

This paper describes two related new reactions. In one of them, a trialkyl phosphite, IV, was used as the reagent to effect the carbon–carbon condensation of an α-diketone, I, with a carboxylic acid chloride, II, to form the phosphate ester, V, of an α-hydroxy β-diketone. In the second reaction, the trialkyl phosphite, IV, effected the condensation of an α-diketone, I, with phosgene, III, to form the phosphate ester, VI, of a β-keto α-hydroxy acid chloride.


I

II, R′ = alkyl or aryl

III, R′ = Cl

IV

V, R′ = alkyl or aryl

VI, R′ = Cl

These reactions were carried out in two steps. First, the α-diketone and the phosphite ester were combined in the form of a 2,2,2-trialkoxy-2,2-dihydro-1,3,2-dioxaphospholene,[2,3] VII. Then the phospholene VII was mixed with the acid chloride II or III to give methyl chloride and the corresponding phosphate ester V or VI. It was assumed[4] that a tetra-

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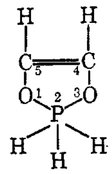
[1] This investigation was supported by Public Health Service Grant No. CA-04769-08 from the National Cancer Institute, and by the National Science Foundation Grant CP-6690-Y.

[2] The parent ring system can be named 2,2-dihydro-1,3,2-dioxaphospholene. This name implies the pentacovalency of the phosphorus.



[3] The literature on 2,2-dihydro-1,3,2-dioxaphospholenes has been reviewed: (a) F. Ramirez, *Pure Appl. Chem.*, **9**, 337 (1964); (b) W. C. Hamilton, S. J. LaPlaca, F. Ramirez, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 2268 (1967).

[4] (a) F. Ramirez, S. B. Bhatia, and C. P. Smith, *ibid.*, **89**, 3026 (1967); (b) F. Ramirez and N. B. Desai, *ibid.*, **82**, 2652 (1960).

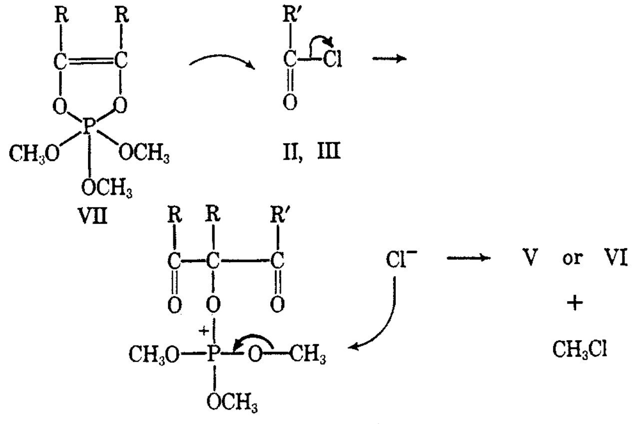
TABLE I

α-HYDROXY β-DIKETONE–DIMETHYL PHOSPHATES FROM THE REACTION OF THE BIACETYL–TRIMETHYL PHOSPHITE ADDUCT, XIII, WITH ACID CHLORIDES,[a] RCOCl

R in RCOCl	Compd	Mp° or bp (mm)	Molecular formula	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P	Yield, %	Conditions Solvent	Conditions Temp, °C	Conditions Time, hr
CH_3	XVI	87-88 (0.1)	b							78	None	55	16
CF_3[c]	XVII	79-80 (0.1)	$C_8H_{12}O_6F_3P$[d]	32.9	4.1	10.6	32.7	4.1	10.5	70[e]	CH_2Cl_2	10	3
C_6H_5	XXVII	74-75[f]	$C_{13}H_{17}O_6P$	52.0	5.7	10.3	51.7	5.7	10.5	71	$C_2H_4Cl_2$	80	30
p-$NO_2C_6H_4$	XXVIII	103-104[f]	$C_{13}H_{16}O_8NP$[g]	45.2	4.6	9.0	44.8	4.6	8.8	90[h]	CH_2Cl_2	40	24
p-FC_6H_4[i]	XXIX	148-153 (0.02)	$C_{13}H_{16}O_6FP$[j]	49.0	5.0	9.7	48.4	5.2	9.7	85	None	70	24
p-$CH_3OC_6H_4$[k]	XXX	l								ca. 70	None	100	48

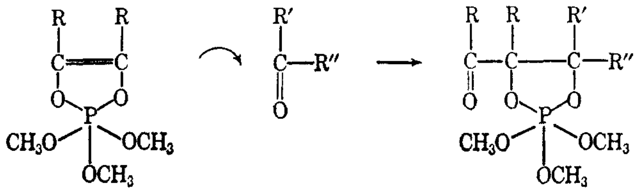
[a] Equimolar amounts of the reagents were allowed to react under the conditions indicated, in a dry N_2 atmosphere. [b] Reference 4a. [c] The gaseous chloride was passed over anhydrous $CuSO_4$ prior to the reaction. [d] Calcd for fluorine: 19.5%. Found: 19.4%. [e] By-products were 15% of $(CH_3O)_3PO$ removed at 50-60° (0.1 mm), 15% of acetyltrifluoroacetylmethylcarbinyl chloride removed below 45° (40 mm), and 5% of dimethyl phosphoacetoin. [f] From benzene-hexane. [g] Calcd for nitrogen: 4.0%. Found: 4.3%. [h] Crude mp 99-102°; 80% after crystallization. [i] By-product, 10% of $(CH_3O)_3PO$. [j] Calcd for fluorine: 5.9%. Found: 5.4%. [k] Two molar equivalents of the adduct XIII were used. The excess of XIII was removed below 70° at 0.1 mm. [l] The phosphate XXX could not be purified by distillation or crystallization; it was hydrolyzed to the hydroxy diketone.

alkoxyphosphonium chloride,[5] VIII or IX, was formed as a fleeting intermediate.

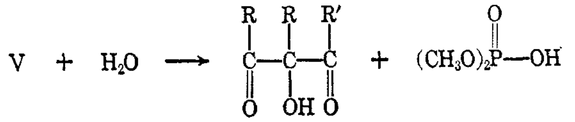


VIII, R′ = alkyl or aryl
IX, R′ = Cl

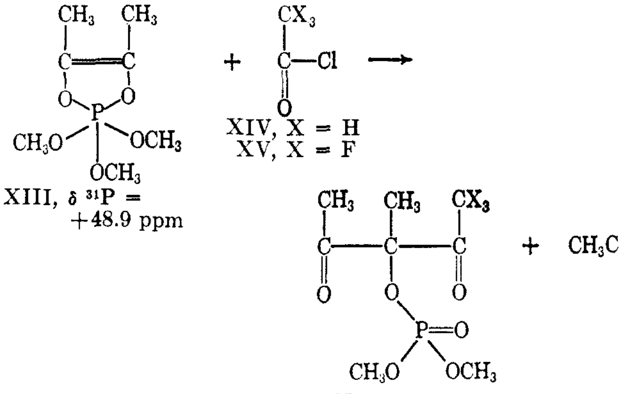
The reaction of the phospholene, VII, with the acid chlorides is a nucleophilic substitution at an unsaturated carbon and should be compared with the related nucleophilic additions of the phospholene to a variety of carbonyl compounds that have been discovered in this laboratory,[6,7] for example, VII + X → XI.



The synthetic scope of the new condensation of phospholenes of type VII with acid chlorides is widened by the extraordinary ease with which phosphate esters of α-hydroxy β-diketones, V, undergo hydrolyses.[4a,8]


XII

Reaction of the Biacetyl–Trimethyl Phosphite 1:1 Adduct, XIII, with Aliphatic Acid Chlorides.—Acetyl chloride reacted smoothly with the biacetyl–trimethyl phosphite adduct XIII under the conditions given in Table I. The product was diacetylmethylcarbinol dimethyl phosphate XVI which had the spectral characteristics listed in Table II.



XVI, X = H
XVII, X = F

The hydroxy diketo phosphate, XVI, was identical with a sample made by a new procedure which involved the nucleophilic addition of the phospholene XIII to ketene.[4a] This reaction gave a cyclic pentaoxyphosphorane, XVIII, having an exocyclic enol-ether function. Treatment of this phosphorane with hydrogen chloride afforded the hydroxy diketo phosphate, XVI, via the same intermediate tetraalkoxyphosphonium chloride (VIII, R = CH_3) previously discussed.

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(5) (a) J. S. Cohen, *J. Amer. Chem. Soc.*, **89**, 2543 (1967); (b) K. D. Berlin, M. Nagabhushanam, and E. T. Gaudy, *Tetrahedron*, **22**, 2191 (1966); (c) D. B. Denney and J. Giacini, *Tetrahedron Lett.*, 1747 (1964); (d) A. Schmidpeter, B. Wolf, and K. Düll, *Angew. Chem. Intern. Ed. Engl.*, **4**, 712 (1965); (e) H. Teichmann, M. Jatkowski, and G. Hilgetag, *ibid.*, **6**, 372 (1967).

(6) (a) F. Ramirez and N. Ramanathan, *J. Org. Chem.*, **26**, 3041 (1961); (b) F. Ramirez, N. Ramanathan, and N. B. Desai, *J. Amer. Chem. Soc.*, **84**, 1317 (1962); (c) F. Ramirez, N. B. Desai, and N. Ramanathan, *Tetrahedron Lett.*, 323 (1963).

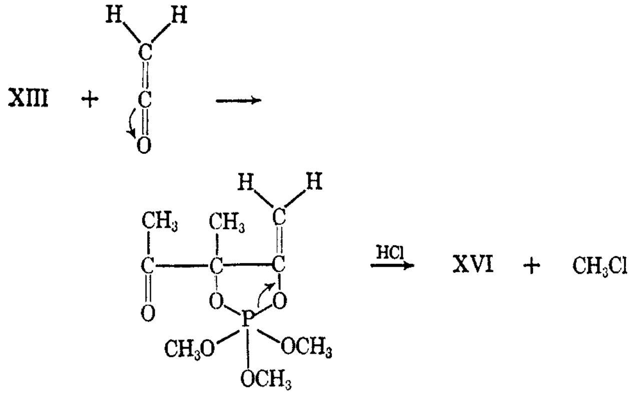
(7) The literature on 2,2-dihydro-1,3,2-dioxaphospholanes has been reviewed: (a) F. Ramirez, *Bull. Soc. Chim. Fr.*, 2443 (1966); (b) F. Ramirez, S. B. Bhatia, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, **32**, 2194 (1967); (c) F. Ramirez, S. B. Bhatia, and C. P. Smith, *J. Amer. Chem. Soc.*, **89**, 3030 (1967).

(8) F. Ramirez, B. Hansen, and N. B. Desai, *ibid.*, **84**, 4588 (1962).

TABLE II
SPECTRAL PROPERTIES OF β-HYDROXY β-DIKETONE DIMETHYL PHOSPHATES[a]

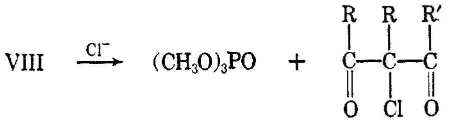
R derived from RCOCl	Compd	$\delta\ ^{31}P$, ppm	H^1 nmr[b]						Ir, μ[c]
			τ (CH_3CO)	τ (CH_3)	τ (CH_3O)	J_{HP}, cps	τ (CH_3O)	J_{HP}, cps	(C=O)
CH_3	XVI	+3.0	7.75	8.27	6.20	11.2			5.80, 5.83
CF_3	XVII	+3.2	7.59	8.15	6.17	11.5	6.19	11.5	5.62, 5.80
C_6H_5	XXVII	+3.0	7.65	8.07	6.30	11.4	6.51	11.4	5.80, 5.90
p-$NO_2C_6H_4$	XXVIII	+2.7	7.55	8.02	6.22	11.5	6.41	11.5	5.80, 5.90
p-FC_6H_4	XXIX	+2.9	7.57	8.03	6.23	11.5	6.42	11.5	5.80, 5.90
p-$CH_3OC_6H_4$[d]	XXX	+3.0	7.66	8.05	6.23	11.5	6.42	11.5	5.80, 5.90

[a] ^{31}P nmr are given in parts per million vs. H_3PO_4 in CH_2Cl_2 at 40.5 Mcps. ^1H Nmr are given in parts per million vs. TMS = 10 in $CDCl_3$ at 60 Mcps. Infrared spectra in CH_2Cl_2. [b] The aromatic hydrogens gave the expected signals. [c] All phosphates had strong bands at 7.85 micron (PO) and 9.6 μ ($POCH_3$). [d] Singlet at τ 6.15 (CH_3O on aromatic ring).



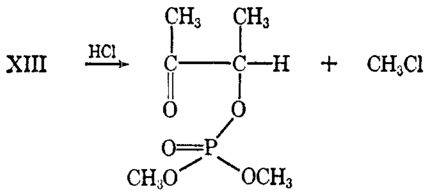
XVIII, $\delta\ ^{31}P$ = +51.4 ppm

Trifluoroacetyl chloride[9] (XV) was extremely reactive toward the phospholene XIII, as can be seen by the conditions given in Table I. Acetyltrifluoroacetylmethylcarbinol dimethyl phosphate (XVII) was isolated in satisfactory yield. Two by-products were also isolated from this reaction, namely, trimethyl phosphate (XIX) and acetyltrifluoroacetylmethylcarbinyl chloride (XX). The formation of these minor products is readily explained as a nucleophilic substitution by chloride ion on the α carbon rather than the methyl group of the tetraalkoxyphosphonium salt, VIII → XIX + XX.

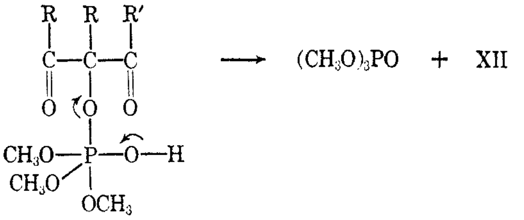


XIX XX, R = CH_3; R′ = CF_3

It should be emphasized that the success of this reaction, and of related ones, requires the absence of hydrogen chloride from the carboxylic acid chloride. It is known[4] that the phospholene XIII is converted into dimethyl phosphoacetoin (XXI) by hydrogen chloride. Strictly anhydrous conditions are demanded by the sensitivity of the reagents to water and by the decomposition of the intermediate VIII into trimethyl phosphate and the hydroxy diketone as shown in formula XXII.

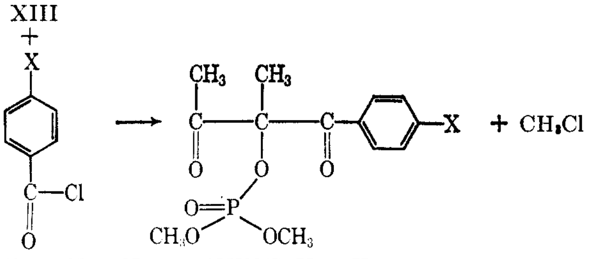


XXI



XXII

Reaction of the Biacetyl-Trimethyl Phosphite 1 : 1 Adduct with Aromatic Acid Chlorides.—The reaction of benzoyl chloride with the phospholene XIII gave acetylbenzoylmethylcarbinol dimethyl phosphate (XXVII) using the conditions given in Table I. The spectral properties are listed in Table II.



XXIII, X = H XXVII, X = H
XXIV, X = NO_2 XXVIII, X = NO_2
XXV, X = F XXIX, X = F
XXVI, X = OCH_3 XXX, X = OCH_3

Electron-withdrawing groups on the aromatic acid chloride, XXIV and XXV, increased their reactivity toward the phospholene. This was illustrated by the syntheses of acetyl-p-nitrobenzoylmethylcarbinol dimethyl phosphate (XXVIII) and of acetyl-p-fluorobenzoylmethylcarbinol dimethyl phosphate (XXIX); cf. Tables I and II. Less than 10% of trimethyl phosphate was formed as a by-product in these reactions.

Acid chlorides with electron-releasing groups on the aromatic ring were distinctly less reactive toward the phospholenes. Note the preparation of acetyl-p-methoxybenzoylmethylcarbinol dimethyl phosphate (XXX) from anisoyl chloride (XXVI).

Reaction of the Biacetyl-Trimethyl Phosphite Adduct with Phosgene.—This reaction was carried out at 0° in methylene chloride and afforded α-methyl

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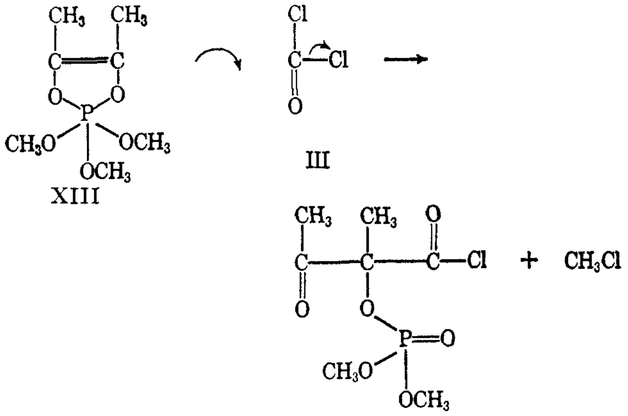
[9] A. L. Henne, R. M. Alm, and M. Smoak, J. Amer. Chem. Soc. 70, 1968 (1948).

TABLE III

ANALYSES AND SPECTRAL PROPERTIES OF α-HYDROXY β-DIKETONES[a]

R derived from RCOCl	Compd	Bp° (mm)	Molecular formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	¹H nmr[b] τ (CH₃CO)	¹H nmr[b] τ (CH₃)	Ir, μ[c]
CH_3	XXXIII	43–44 (4)	*d*					7.76	8.48	5.84
CF_3[e]	XXXIV	71–72 (58)	$C_6H_7O_3F_3$[f]	39.1	3.8	39.4	3.8	7.66	8.32	5.66, 5.80
C_6H_5	XXXV	73–74 (0.01)	$C_{11}H_{12}O_3$	68.7	6.3	67.9	6.3	7.82	8.32	5.80, 5.95
p-$NO_2C_6H_4$	XXXVI	118–119 (0.02)	$C_{11}H_{11}O_5N$[g]	55.7	4.6	55.2	4.8	7.65	8.25	5.80, 5.90
p-FC_6H_4	XXXVII	75–76 (0.01)	$C_{11}H_{11}O_3F$	62.8	5.2	62.5	5.2	7.78	8.30	5.80, 5.92
p-$CH_3OC_6H_4$[h]	XXXVIII	125–126 (0.05)	$C_{12}H_{14}O_4$	64.9	6.3	64.9	6.6	7.82	8.32[i]	5.80, 5.97

[a] A mixture of the phosphate ester, benzene, and water was kept 12 hr at reflux temperature. The water layer was extracted with benzene. The combined benzene solution was extracted with 5% aqueous sodium bicarbonate and distilled. The hydroxydiketones were isolated in about 60–70% yield. [b] Given in parts per million *vs.* TMS = 10 (τ values) in $CDCl_3$; the signals due to the hydroxylic proton were in the range τ 4.75–τ 5.14. [c] The bands due to the OH group were at 2.95 μ. [d] Reference 4a. [e] The phosphate ester, XVII, was very sensitive to water; see Experimental Section. [f] Calcd for fluorine: 31.0%. Found: 31.0%. [g] Calcd for nitrogen: 5.9%. Found: 6.2%. [h] The crude dimethyl phosphate ester was subjected to hydrolysis; the hydroxy diketone was obtained in 40% yield based on the phospholene, XIII. [i] τ 6.16 ($CH_3OC_6H_4$).

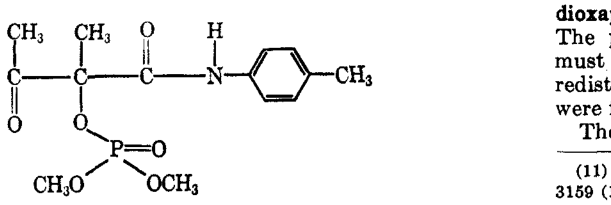


XXXI, δ ³¹P = +3.2 ppm

α-hydroxyacetoacetyl chloride dimethyl phosphate (XXXI) in satisfactory yield.

It was, of course, necessary to remove hydrogen chloride from the phosgene[10] to prevent the conversion of the phospholene XIII into dimethyl phosphoacetoin (XXII). The acid chloride XXXI was quite stable at 20°, in the presence or in the absence of inert solvents. However, the chloride was rapidly transformed into a variety of products when heated above 80°. These transformations, as well as other aspects of the chemistry of this new type of polyfunctional phosphate ester, will be discussed elsewhere.

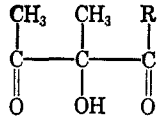
The structure of the acid chloride XXXI was based on the following. (1) The ³¹P nmr shift was typical of a phosphate ester. (2) The ¹H nmr spectrum had singlets at τ 7.61 and 8.15 due to the protons of the acetyl and the C-methyl groups, respectively;[11] the spectrum also had two doublets, one at τ 6.11 and the other at 6.17, both with J_{HP} = 11.5 cps, which were due to the nonequivalent methoxy groups on phosphorus. (3) The infrared spectrum had bands at 5.60 and 5.80 due to the carbonyl functions, and at 7.82 and 9.6 μ due to the phosphate group. (4) The crystalline *p*-toluide derivative, XXXII, had the expected elemental analysis and spectral properties.



XXXII, δ ³¹P = +2.5 ppm

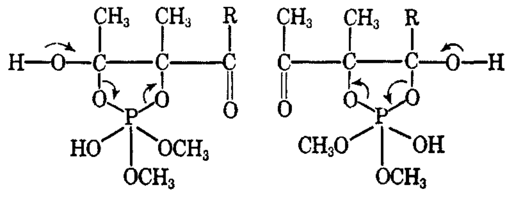
The acid chloride XXXI failed to react with an excess of the phospholene XIII in the temperature range where the chloride was stable.

Hydrolysis of the Phosphate Esters of α-Hydroxy β-Diketones.—These phosphate esters were converted into the α-hydroxy β diketones, XXXIII–XXXVIII, with extraordinary ease. The procedure used and the properties of the alcohols are given in Table III.



XXXIII, R = CH_3
XXXIV, R = CF_3
XXXV, R = C_6H_5
XXXVI, R = p-$NO_2C_6H_4$
XXXVII, R = p-FC_6H_4
XXXVIII, R = p-$CH_3OC_6H_4$

We have suggested[4a,8] that the rapid hydrolysis of the α-ketol phosphates may be due to carbonyl participation and pentaoxyphosphorane formation as shown in formulas XXXIXa and XXXIXb.



XXXIXa XXXIXb

Experimental Section

The analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. The instrumentation was described previously.[12]

Reaction of 2,2,2-Trimethoxy-4,5-dimethyl-2,2-dihydro-1,3,2-dioxaphospholene (XIII) with Carboxylic Acid Chlorides.—The phospholene XIII was prepared as described.[4b,12a] It must be protected against moisture and air; it should be redistilled after storage for several weeks. The acid chlorides were freshly distilled or crystallized.

The reactions of the liquid phospholene XIII with the acid

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(10) I. G. Farbenind A.-G., Belgian Patent 450,648 (June 1943); *Chem. Abstr.*, **41**, 7063*d* (1947).

(11) F. Ramirez, A. V. Patwardhan, and C. P. Smith, *J. Org. Chem.*, **31**, 3159 (1966).

(12) (a) F. Ramirez, A. V. Patwardhan, N. Ramanathan, N. B. Desai, C. V. Greco, and S. R. Heller, *J. Amer. Chem. Soc.*, **87**, 543 (1965); (b) F. Ramirez, A. V. Patwardhan, N. B. Desai, and S. R. Heller, *ibid.*, **87**, 549 (1965).

chlorides were carried out under the conditions indicated in Table I. The reagents were mixed in the absence or in the presence of solvents, depending on the reactivity of the chlorides and on their physical state. The course of the reaction was followed by means of infrared spectrometry on small aliquots. At the end of the reaction, the solvent was evaporated under vacuum. When the products were liquids, purification was effected by vacuum distillation. When the products were solids, the crude phosphates, usually of an acceptable degree of purity, were obtained by addition of cold ether. The phosphates were crystallized from the solvents indicated in Table I.

Reaction of the Phospholene XIII with Phosgene.—The phosgene was condensed in a trap at −70° and was then passed[10] through anhydrous $CuSO_4$ and led into a 5 *M* solution of the biacetyl–trimethyl phosphite adduct, XIII, in methylene chloride at 0°. The addition of the phosgene was carried out over a 2-hr period; the chloride was used in excess (*ca.* 1.7 mol equiv). The solution was kept overnight at 20° and was then freed from solvent at 20° and 10 mm, with protection against moisture. The residue was analyzed by ^1H and ^{31}P nmr and infrared spectrometry. This material consisted of 95% acid chloride XXXI and 5% dimethyl phosphoacetoin. *The acid chloride should be handled with care since it may have a high degree of toxicity.*

The acid chloride XXXI (33 mmol) in benzene (80 ml) was treated at 0° with *p*-toluidine (67 mmol) in benzene (25 ml). The mixture was kept 1 hr at 25° and was then filtered. The filtrate was evaporated at 25° (10 mm) and the residue was washed with pentane. The crude *p*-toluide XXXII (76% yield) had mp 102–103°. The analytical sample had the same melting point (from benzene–hexane).

Anal. Calcd for $C_{14}H_{20}O_6NP$: C, 51.1; H, 6.1; N, 4.2. Found: C, 51.1; H, 6.2; N, 4.3.

The infrared spectrum in CH_2Cl_2 had bands at 3.00, 5.78, 5.95, and 7.80 μ. The ^1H nmr spectrum in $CDCl_3$ had singlets at τ 7.66 ($CH_3C_6H_4$–), 7.70 (CH_3CO), and 8.03 (CH_3C); it had doublets at 6.12 and 6.17, both with $J_{HP} = 11$ cps; it had aromatic protons near 2.7.

Hydrolysis of the Phosphate Esters of α-Hydroxy β-Diketones.—The procedure used and the properties of the resulting alcohols are given in Table III.

Acetyltrifluoroacetylmethylcarbinol dimethyl phosphate (XVII) was very sensitive to water, therefore, the following procedure was used. The phosphate (9.10 g) was dissolved in ether (30 ml) and the solution was cooled to 0°. One molar equivalent of water was added and the mixture was stirred for 30 min at 0° and for 30 min at 20°. The solution was submitted to fractional distillation and gave the hydroxy diketone, XXXIV, in 65% yield; *cf.* Table III.

Acetyltrifluoroacetylmethylcarbinyl Chloride (XX).—As stated in Table I, the reaction of the biacetyl–trimethyl phosphite adduct, XIII, with trifluoroacetyl chloride (XV) gave a by-product which was removed by distillation below 45° at 40 mm. This liquid was distilled and gave the chloro diketone, XX, bp 79–80° at 80 mm.

Anal. Calcd for $C_6H_6O_2F_3Cl$: C, 35.6; H, 3.0; F, 28.2; Cl, 17.3. Found: C, 35.9; H, 3.1.

The infrared spectrum in CH_2Cl_2 had bands at 5.62 and 5.80 with a shoulder at 5.70 μ. The ^1H nmr spectrum in $CDCl_3$ had singlets at τ 7.53 (acetyl) and 8.16 (methyl on C).

Registry No.—XIII, 1665-79-8; XVI, 15088-11-6; XVII, 15186-04-6; XVIII, 15088-10-5; XX, 15138-14-4; XXVII, 15138-15-5; XXVIII, 15138-16-6; XXIX, 15138-17-7; XXX, 15186-02-4; XXXI, 15138-18-8; XXXII, 15215-70-0; XXXIII, 7338-73-0; XXXIV, 15138-20-2; XXXV, 15138-21-3; XXXVI, 15138-22-4; XXXVII, 15186-03-5; XXXVIII, 15138-23-5.

Reaction of Hydriodic Acid with Tertiary Ketols[1]

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The reaction of hydriodic acid in refluxing acetic acid on tertiary ketols can bring about reduction to saturated ketones, rearrangements, and/or eliminations. Many ketols undergo these reactions whereby an intermediary carbonium ion can explain these reaction sequences. If the ketone cannot enolize no reaction takes place.

Recent publications[3–5] by Reusch, *et al.*, on the reduction of saturated and unsaturated α-diketones and secondary α-ketols with hydriodic acid in refluxing acetic acid prompted this publication on the reaction of the same reagent on tertiary ketols. *A priori*, we were interested in a versatile method for the reduction of 17α-hydroxy 20-keto steroids and also in the reduction of the 17,21-dihydroxy 20-keto side chain as an addition to already well-established methods[6–8] of reduction with zinc and acetic acid. Further examples for the study of tertiary ketol reduction by hydriodic acid were carried out in order to assess this method.

Most materials were allowed to react under the same conditions described by Reusch,[3–5] except in the case of 1-acetyl-1-hydroxycyclohexane which required increased temperature and duration of reaction. In all cases an immediate release of iodine was observed which rendered the solution dark. All conversions were free of tar formation[9] and gave in most cases readily separable mixtures.

Thus, 17α-hydroxyprogesterone (**1**) was first rearranged[10] to 17aα-methyl-17aβ-hydroxy-D-homoandrost-4-ene-3,17-dione[11] (**2**), which in turn was reduced to 17aβ-methyl-D-homoandrost-4-ene-3,17-dione (**3**) (see Scheme I). The isomerization[10] of 17α-hydroxyprogesterone with base and the isolation of the resulting isomeric hydroxymethyl-D-homo ketones is described in detail in the Experimental Section.

Both 3β-methyl-3α-hydroxy-5α-androstane-2,17-dione[12] (**7**) and 2β-hydroxy-2α-acetyl-A-nor-5α-androstan-17-one[12] (**10**) gave the identical product, 3β-methyl-5α-androstane-2,17-dione (**6**) (see Scheme II).

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(2) Ayerst Laboratories, Montreal, Que.

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(9) Additional hydroxyls (besides the ketol itself) lead to extensive tar formation.

(10) For pertinent discussion of this rearrangement, see N. L. Wendler in "Molecular Rearrangements II," de la Mare, Ed., Interscience Publishers, Inc., New York, N. Y., 1964, pp 1114–1121, and references therein.

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(12) The synthesis of this compound is described in the experimental part.