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PHOSPHONIC ACIDS—IX[1]

STEROIDAL 21a-PHOSPHONATE ESTERS[2]

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Abstract—Dialkyl esters of steroidal 21a-phosphonic acids, which may be regarded as phosphonate analogs of 21-phosphate esters with the oxygen link replaced by a methylene group, were synthesized by the reaction of a trialkyl phosphite with a quaternary salt of a Mannich base derivative of a 20-keto steroid. In this way, the 21-dialkoxyphosphinylmethyl group, $(RO)_2P(O)CH_2$—, was introduced into pregnenolone, 17α-hydroxypregnenolone and 17α-acetoxypregnenolone, and the products converted by oxidation to the corresponding progesterone derivatives. The same steroid phosphonates also were obtained by the reaction of alcoholic trialkyl phosphite with the 20-keto-$\Delta^{21(21a)}$-steroid formed by thermal decomposition of the Mannich base salt. Monodealkylation of the 21a-dialkyl phosphonate esters to furnish the corresponding monobasic acids was effected smoothly by warming with alcoholic sodium propylmercaptide, except in the case of 17α-acetoxy-20-ketosteroids where this reagent caused a condensation between the acetoxy group and the side chain accompanied by D-homoannulation. Although the reaction of 21-iodoprogesterone with triethyl phosphite or sodium diethylphosphonate gave only progesterone, 21-tosyloxyprogesterone reacted with triethyl phosphite to yield 21-diethoxyphosphinylprogesterone.

THE synthesis of steroidal phosphate esters, particularly in the cortical series, has been the subject of frequent investigation[3] stimulated by the use of the 21-phosphate monoesters in clinical therapy.[4] The water-solubilizing property of the P(V) ester group,[3d] which renders possible the administration of aqueous solutions of the hormone by intravenous injection, apparently is not correlated with any loss in physiological activity.

The present study is directed towards the preparation of 21- and 21a-phosphonic acid anolags of 21-phosphonate esters, differing from the latter by either omission of the oxygen atom which serves to link the phosphorus group to the steroid or its replacement by a methylene unit. Such compounds should retain the desirable water solubility of the phosphates,[3d] but differ from the latter in one important respect. Specifically, the stability to hydrolytic cleavage of the carbon-phosphorus bond[5] of

[1] Paper VIII. R. G. Harvey and E. V. Jensen, *J. Org. Chem.* **28**, 470 (1963).

[2] This investigation was supported by contract SA-43-ph-1759 with the Cancer Chemotherapy National Service Center, National Institutes of Health. A preliminary report was presented at the International Symposium on the Chemistry of Natural Products, Kyoto, Japan (1964).

[3a] T. Reichstein and W. Schindler, *Helv. Chim. Acta* **23**, 669 (1940); [b] T. Reichstein and E. Schlittler, U.S. patent 2,183,589 (1939); [c] L. Sarett, U.S. patent 2,779,775 (1957); [d] F. A. Cutler, Jr., J. P. Conbere, R. M. Lukes, J. F. Fisher, H. E. Mertel, R. Hirschmann, J. M. Chemerda, L. H. Sarett, and K. Pfister, 3rd *J. Amer. Chem. Soc.* **80**, 6300 (1958); [e] J. Elks and G. H. Phillips, U.S. patent 2,950,298 (1960); *Ibid.* 2,936,313 (1960); Brit. patent 902,254 (1962); [f] J. M. Chemerda, R. J. Tull, and J. F. Fisher, U.S. patent 2,939,873 (1960); [g] K. Irmscher, *Chem. Ind.* 1035 (1961); [h] Y. Mori, *Yakugaku Zasshi Japan* **81**, 1667,1674 (1961); [i] J. Fried, U.S. patent 3,050,535 (1962); Belg. patent 613,053 (1962); U.S. 3,053,834 (1962); U.S. patent 3,069,439 (1962); [j] K. Irmscher and W. Schumann, Ger. patent 1,134,075 (1962); [k] G. I. Poos, R. Hirschmann, G. A. Bailey, F. A. Cutler, Jr., L. H. Sarett and J. M. Chemerda, *Chem. Ind.* 1260 (1958); [l] A. L. Nussbaum and R. Tiberi, *Tetrahedron* **20**, 2467 (1964).

[4] J. C. Melby and R. H. Silber, *Amer. Pract. Dig. Treat.* **12**, 156 (1961).

[5] L. Freedman and G. Doak, *Chem. Revs.* **57**, 479 (1957).

Chart 1

alkyl phosphonic acids and esters should prevent the removal of the phosphinyl group *in vivo*. Thus, biological evaluation of these compounds should throw light on whether the presence of a terminal phosphinyl group on the steroid side chain is compatible with biological activity, a matter of interest in connection with the problem of the existence of naturally occuring phosphorylated intermediates in steroid metabolism.[6,7]

This paper describes the synthesis of such steroidal phosphonate derivatives in the 11-deoxy series. The synthetic pathway (Chart 1) which ultimately led to 21-dialkatephosphinyl[8] derivatives of progesterone (V) *via* the corresponding pregnenolone analogs (IV and III) involves the sequence of steps: (1) Mannich reaction of the 20-ketosteroid; (2) formation of quaternary methiodide; (3) displacement of the nitrogen function with a phosphite ester; (4) deacetylation of the 3β-acetate; (5) oxidation of the 3-*ol* and isomerization of the double bond into conjugation; and finally, (6) dealkylation or hydrolysis of the phosphonate ester.

Conversion of 3β-acetoxypregnenolone to its Mannich base (I; X = H) in the conventional solvents for this reaction,[9] ethyl or isoamyl alcohol, was found to be very slow and accompanied by extensive decomposition of the product to form the unsaturated ketone (II; X = H). As described in a preliminary report,[10] the Mannich bases of pregnenolone, 17α-hydroxypregnenolone and their acetates can be prepared in high yield by employing pyrrolidine as the amine and 1,2-dimethyoxyethane (DME) as the solvent. The reaction of 17α-hydroxypregnenolone diacetate proved to be extremely slow even under the improved conditions; the corresponding Mannich base (I; X = OAc) was most conveniently prepared by acetylation of the 17α-hydroxypregnenolone-3-acetate Mannich base (I; X = OH) with acetic anhydride and pyridine.

To establish unequivocally that condensation takes place at the 21 and not at the 17 position of pregnenolone, the Mannich base of this steroid was also synthesized by an alternative route (Chart 2). Treatment of pregnenolone with ethyl formate in the presence of sodium methoxide furnished 21-hydroxymethlyenepregnenolone[11] (VI). This compound possesses a single, rather broad absorption maximum in the UV at 270 mμ (ε = 8,150), comparable in intensity to the maxima in this region exhibited by hydrogen-bonded enolizable aliphatic β-diketones, e.g. acetylacetone (λ_{max} 270 mμ; ε = 10,000)[12]. The pyrrolidyl enamine obtained from VI underwent reduction with LAH to furnish a Mannich base identical in all respects with that obtained *via* the direct route.

The methiodides of the various steroidal Mannich bases were converted smoothly

[6] G. W. Oertel and K. B. Eik-Nes, *Acta Endocrinol* **30**, 93 (1959).

[7] I. E. Bush and M. M. Gale, *Acta Endocrinol.* Suppl. **51**, 1027 (1960).

[8] Throughout this paper, the nomenclature used for organic phosphorus compounds conforms to the new rules adopted in 1952 by American and British chemical journals; see *Chem. Eng. News* **30**, 4515 (1952).

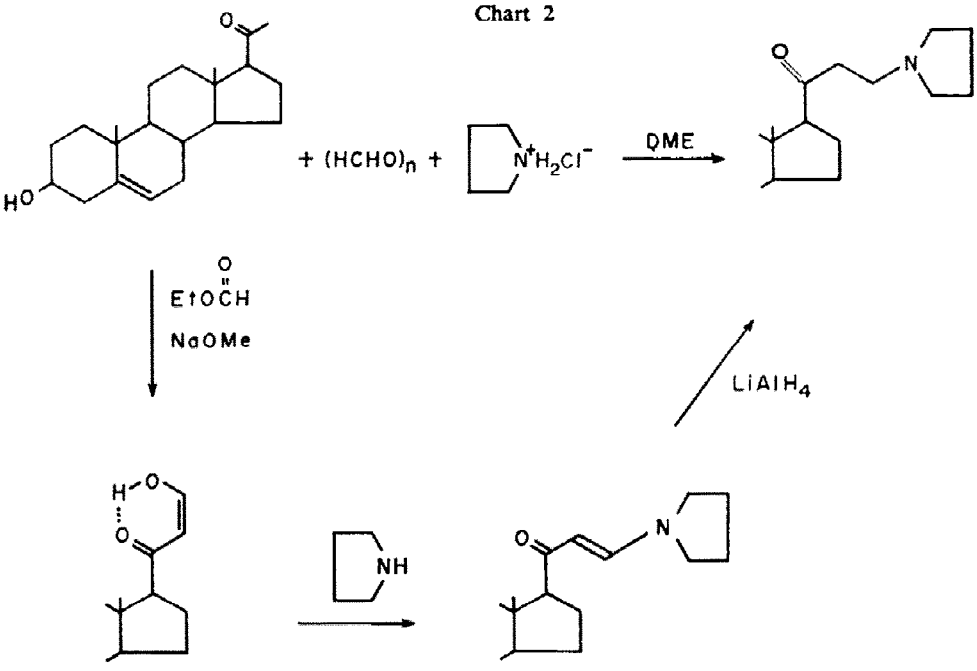
[9] F. F. Blicke in *Organic Reactions* (Edited by R. Adams) Vol. 1; p. 303. J. Wiley, New York (1942).

[10] S. Hirai, R. G. Harvey and E. V. Jensen, *Tetrahedron Letters* 1123 (1963).

[11] This product showed a different m.p. than that reported in the patent literature. M. Bockmühl, G. Ehrhart and H. Ruschig, Ger. patent 871,451 (1953).

[12] R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, *J. Amer. Chem. Soc.* **71**, 1068 (1949); G. S. Hammond, W. G. Borduin and G. A. Guter, *Ibid.* **81**, 4682 (1959).

Chart 2



VI

to the corresponding phosphonate esters, III (Table 1) by heating in boiling triethyl or triisopropyl phosphite[13] for 1 to 4 hr in a nitrogen atmosphere.

The most probable mechanism involves either (A) *direct displacement* of the nitrogen function (Eq. 1) to furnish a phosphonium intermediate (VII) which undergoes a valency expansion[14] leading to a phosphonate, or (B) indirect production of the

TABLE 1. 3β-ACETOXY-21-DIALKOXYPHOSPHINYLMETHYLPREGN-5-EN-20-ONE (III) DERIVATIVES

X	R	Reaction time (hr)	m.p.	% Yield	$[\alpha]_D$	C		H		P	
						Calc.	Found	Calc.	Found	Calc.	Found
H[a]	Et	4	99–100°	65							
H[b]	Et	3	100–101°	72	+3·9°	66·12	66·34	8·92	8·98	6·09	6·22
OH[a]	Et	1·5	149–150°	91							
OH[b]	Et	3	149–150°	39	−29·8°	64·09	63·88	8·65	8·77	5·90	5·36
OH[a]	i-Pr	1·5	119–120°[c]	71	−26·9°	65·19	65·23	8·94	8·98	5·60	5·76
OH[a]	i-Pr	2	136–136·5°[c]	85		65·19	65·20	8·94	9·17	5·60	5·75
OAc[a]	Et	1	139–140°	72	−46·1°	63·57	63·84	8·36	8·21	5·47	5·44
OAc[a]	i-Pr	2	165–166°	61	−43·0°	64·62	64·75	8·64	8·63	5·21	5·17

[a] Mannich base prepared from pyrrolidine.

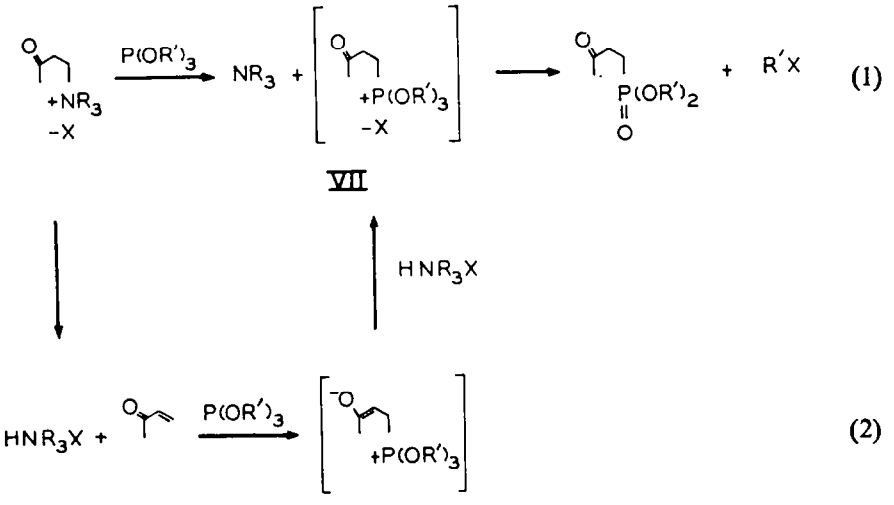
[b] Mannich base prepared from dimethylamine.

[c] These substances appear to be polymorphic since they were identical in all other respects except for IR spectra in KBr discs.

[13] T. C. Myers, R. G. Harvey and E. V. Jensen, *J. Amer. Chem. Soc.* 77, 3101 (1955).

[14] R. G. Harvey and E. R. DeSombre in *Topics in Phosphorus Chemistry* Vol. I; pp. 55–111. Interscience, New York (1964).

same intermediate by *decomposition of the Mannich base to a vinyl ketone*, which is attacked by the nucleophilic phosphorus reagent to furnish an intermediate which in turn is transformed into VII (Eq. 2). In view of this mechanistic problem, it was of interest to synthesize the 21-methylenepregnenolone acetates (II; X = H or OH) and investigate their reactions with triethyl phosphite. The results of these experiments will be described later in this paper.



When the reaction of triethyl phosphite with the pyrrolidine Mannich base methiodide of a 17α-hydroxy steroid (I; X = OH) was prolonged (3 hr) beyond that required for complete conversion to the 21a-phosphonate (1½ hr), ester interchange of triethyl phosphite with the 17-hydroxyl group took place to yield a product containing both a phosphonate and a phosphite ester substituent (III; X = O—P(OEt)$_2$; R = Et). Under the same conditions, the corresponding dimethylamine Mannich base methiodide gave only the expected 21a-phosphonate with no evidence of a phosphite-containing product.

TABLE 2. 3β-HYDROXY-21-DIALKOXYPHOSPHINYLMETHYLPREGN-5-EN-20-ONE (IV) DERIVATIVES

X	R	m.p.	% Yield	$[\alpha]_D$	C		H		P	
					Calc.	Found	Calc.	Found	Calc.	Found
H	Et	110–111°	74	+6·6°	66·91	66·81	9·29	9·53	6·64	6·59
OH	Et	135–136°	94	−29·2°	64·71	64·71	8·93	8·89	6·42	6·20
OH	i-Pr	158–159°	78	−27·8°	65·86	66·36	9·28	9·39	6·07	5·81
OAc[a]	Et	178–179°	59	−48·3°	64·09	64·29	8·65	8·89	5·90	5·79
OAc[a]	Et	164·5–165·5°	81	−47·5°	64·09	64·22	8·65	8·89	5·90	5·85
OAc	i-Pr	153–154°	90	−44·0°	65·19	65·04	8·94	9·05	5·60	5·68

[a] These compounds, differing only in m.p., were obtained in separate runs. IR spectra in CCl_4 were superimposable, and oxidation with Jones reagent furnished the same product.

The free 3β-hydroxy compounds (IV) listed in Table 2 were obtained by alcoholysis at room temperature of the corresponding acetates (III) in dilute ethanolic hydrochloric acid. Under these conditions no appreciable hydrolysis of the phosphonate group takes place.

Oxidation of the 3β-hydroxyl function was achieved satisfactorily by treatment of a cold solution of IV in acetone with Jones reagent[15] for 5 min. Dilution with water generally furnished a crystalline precipitate which was removed by filtration, taken up in alcohol containing several drops of sulfuric acid and heated for 5 min to isomerize the double bond into conjugation. Use of 10% potassium hydroxide instead of sulfuric acid as a catalyst for this isomerization considerably depressed the yield. The 21-dialkoxyphosphinylmethyl derivatives of progesterone, V (Table 3) obtained by this means possessed IR absorption spectra consistent with the postulated structures. They all were crystalline solids with the exception of the 17-deoxy compound, 21-diethoxyphosphinylmethylpregn-4-ene-3,20-dione (V; X = H; R = Et), which was prepared both by chromium trioxide oxidation and by Oppenauer oxidation of the related 3β-ol, but which failed to solidify despite purification by various methods including column chromatography and molecular distillation.

TABLE 3. 21-DIALKOXYPHOSPHINYLMETHYLPROGESTERONE (V) DERIVATIVES

X	R	m.p.	% Yield	$[\alpha]_D$	C		H		P	
					Calc.	Found	Calc.	Found	Calc.	Found
H[a]	Et	oil	82	+108·3°	67·20	66·75	8·90	9·24	6·67	6·70
OH	Et	166–167°	84	+67·6°	64·98	64·94	8·60	8·64	6·45	6·48
OH	i-Pr	151–152°	67	+80·8°	66·12	66·44	8·92	9·08	6·09	6·06
OAc	Et	132–133°	42	+54·8°	64·35	64·36	8·29	8·13	5·93	5·93
OAc[b]	i-Pr	116–117°	48	+52·4°	65·43	65·28	8·60	8·80	5·63	5·63

[a] Analytical sample was prepared by Oppenauer oxidation of IV (X = H; R = Et) and purified by chromatography on Florisil and molecular distillation.

[b] In addition there was also obtained 6β-hydroxy-21a-diisopropoxyphosphinylprogesterone (10%).

In addition to the expected product from the chromium trioxide oxidation of IV (X = OAc; R = i-Pr), there was isolated a second substance differing structurally from V (X = OAc; R = i-Pr) only in the presence of an additional hydroxyl function. Inasmuch as Δ^5-3-ketones are susceptible to oxidation at C-6, and Δ^4-3,6,diones are occasionally encountered as by-products in the Jones oxidation of Δ^5-3β-ols,[16,17] it appears probable that the hydroxyl is located at C-6.

The final step in the synthesis of the desired 21-homoprogesteronephosphonic acid, and its 17-hydroxy and 17-acetoxy derivatives, involves the conversion of the diethyl or diisopropyl phosphonate esters to the corresponding free acids. So far only the monobasic acids have been obtained successfully. The vigorous conditions commonly employed[5,13,18] for the complete hydrolysis of simple P(V) esters (e.g. heating overnight in concentrated hydrochloric or other mineral acid) appear to be too severe for these steroidal phosphonates. Satisfactory products could not be isolated in any case where this method was attempted. Our unsuccessful preliminary experiments along

[15] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).

[16] P. Crabbe, E. A. Azpeitia and C. Djerassi, *Bull. Soc. Chim. Belg.* 70, 168 (1961).

[17] J. Iriarte, J. N. Shoolery and C. Djerassi, *J. Org. Chem.* 27, 1139 (1962).

[18] [a] G. Kosolapoff, *Organophosphorus Chemistry*. J. Wiley, New York, N.Y. (1950); [b] W. Gerrard, W. Green and R. Nutkins, *J. Chem. Soc.* 4076 (1952); [c] E. DeSombre, Dissertation, University of Chicago (1963).

these lines, taken with the knowledge of the comparatively facile rearrangement[19] of 17-hydroxy-20-ketosteroids into D-homo derivatives under both acidic and basic conditions, led us to explore alternative methods of phosphonate dealkylation.

Thermal decomposition, reported to be an effective method for the dealkylation of phosphinite, phosphonate[20] and phosphate[21] esters, when applied to V (X = OH; R = i-Pr) afforded an acidic product which could not be obtained in a pure state.

Anionic dealkylation with inorganic salts, a valuable alternative to hydrolytic methods for the cleavage of sensitive phosphate and pyrophosphate esters,[21,22] proved more successful. Treatment of the 21a-diethoxyphosphinyl esters III and IV (X = OH; R = Et) with lithium chloride in boiling ethoxyethanol for 22 hr provided the monoethyl esters in modest yields, 30% and 40%, respectively (Table 4). Similar treatment of the 3-keto compound, (V; X = OH; R = Et) with lithium chloride or with calcium iodide gave the corresponding monoacid as an oil which could be obtained crystalline only as a 2,4-dinitrophenylhydrazone derivative.

The best method for preparing the free monoacids from phosphonate esters in the 17α-hydroxy series was found to be treatment of the diester with alcoholic sodium ethyl or propyl mercaptide. The striking ability of mercaptide ions to effect monodealkylation of phosphate and phosphonate esters has been reported previously.[23] Although mercaptides will add to unhindered α,β-unsaturated ketones, the steroidal Δ^4-3-ketone group appears to be inert to this reagent. In contrast to lithium chloride or calcium iodide, treatment of V (X = OH, R = Et) with alcoholic mercaptide afforded the corresponding monoacid in crystalline form. So far dealkylation with mercaptide has not been investigated with phosphonate esters in the 17-deoxy series.

When a 17α-acetoxy substituent is present in the phosphonate ester, dealkylation with alcoholic sodium mercaptide is accompanied by a side reaction involving condensation of the side chain with the acetoxy group. This phenomenon was studied most thoroughly with 3β-hydroxy-21-diisopropoxyphosphinylmethyl-5-pregnen-20-one (IV; R = i-Pr, X = OAc), in which case dealkylation takes place at a slow enough rate that both a neutral and an acidic condensation product can be obtained. Elemental analyses of these two substances correspond to loss of the elements of water from the original diisopropyl ester and its monoacid, respectively. In the IR spectra of both products the original 20-ketone and acetoxy carbonyl bands are absent; instead there are strong bands of approximately equal intensity at 1693 and 1633 cm^{-1}, a pattern characteristic of an α,β-unsaturated ketone of cisoid structure.[24] Both compounds show rather strong UV absorption at 273 mμ (ε = 8,100 and 8,230, respectively). The NMR spectrum of the neutral product shows clearly that only one vinyl hydrogen is present, namely, that at C_6 which exhibits a peak at 4·6 τ.

The simplest explanation of an interaction between the side chain and the acetoxy substituent to form an unsaturated ketone is that the sodium mercaptide catalyzes a

[19] H. Stavely, *J. Amer. Chem. Soc.* **63**, 3127 (1941); R. Turner, *Ibid.* **75**, 3484 (1953).
[20] A. Canavan, B. Dowden and C. Eaborn, *J. Chem. Soc.* 331 (1962).
[21] J. Lecocq and A. Todd, *J. Chem. Soc.* 2381 (1954); H. E. Baumgarten and R. A. Setterquist, *J. Amer. Chem. Soc.* **79**, 2605 (1957); C. E. Higgins and W. H. Baldwin, *J. Org. Chem.* **30**, 3173 (1965).
[22] R. J. W. Cremlyn, G. W. Kenner, J. Mather and A. Todd, *J. Chem. Soc.* 528 (1958).
[23] R. G. Harvey, H. I. Jacobson and E. V. Jensen, *J. Amer. Chem. Soc.* **85**, 1623 (1963).
[24] R. L. Erskine and E. S. Waight, *J. Chem. Soc.* 3425 (1960).

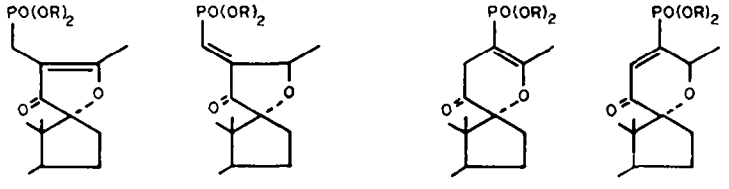
TABLE 4. MONOALKYL ESTERS OF STEROIDAL 21A-PHOSPHONIC ACIDS

Parent phosphonate	X	R	Reagent	m.p.	$[\alpha]_D$	C		H		P		$C_6H_{11}NH_3^+$ salt	
						Calc.	Found	Calc.	Found	Calc.	Found	m.p.	$[\alpha]_D$
	OH	Et	LiCl	141–142°	−23·6	60·68	60·52	8·42	8·11	6·02	5·79	120–122°	−14·4
III	OH	i-Pr	CaI_2	178–179°	−27·9	63·51	63·21	8·49	8·54	6·07	6·12	146–150°	−15·8
	OAc	Et	LiCl	oil		(64·02	64·27	8·85	8·94	4·86	4·75)[a]	172–175°	−35·0
	H	Et	KOH (on III)	170–171°	+5·2	65·73	65·72	8·96	9·03	7·06	7·52		
	OH[b]	Et	LiCl	173–174°								218–220°	−14·4
IV	OH[b]	Et	EtSNa	173–174° (181–183°)[c]	−17·4	63·41	63·41	8·65	8·60	6·82	6·63		
	OH[b]	i-Pr	CaI_2	239–240° dec	−27·1	64·08	63·69	8·82	8·70	6·61	6·59	222–224°	−22·6
	OAc[b]	Et	LiCl	oil		(64·51	64·32	9·14	9·17	5·20	5·07)[a]	192–194°	−38·6
	OH	Et	LiCl or CaI_2	oil		(55·73	55·66	6·66	6·63	4·76	4·59)[d]		
V	OH	Et	EtSNa	183–184·5°	+89·5	63·70	63·70	8·24	8·09	6·85	6·89		
	OH	Et	n-PrSNa	192–193°	+99·9	63·70	63·74	8·24	8·28	6·85	6·81		

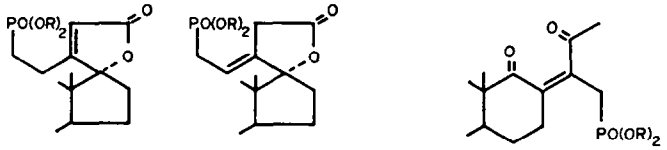
[a] Analytical data for cyclohexylammonium salt. [b] This compound was also prepared by treatment of corresponding 3-acetate with dilute alcoholic HCl at room temp overnight. [c] This crystalline modification formed the same cyclohexylammonium salt as did the lower melting form. [d] Analytical data for 2,4-dinitrophenylhydrazone monohydrate.

Claisen type condensation of either the 21 or the 21a methylene group with the acetoxy carbonyl, or of the acetoxy methyl group with the 20-ketone to give products with structures VIII, IX or X, respectively. However, none of these structures are compatible with all the spectral data.[25] All of these substances possess an additional vinyl hydrogen substituent except for structures VIIIa and IXa, which should not exhibit UV absorption at 273 mμ. Moreover, VIIIa and IXa represent enol ethers which should be unstable to acid, whereas the monodealkylated product, which is a strong acid, is stable in aqueous solution.

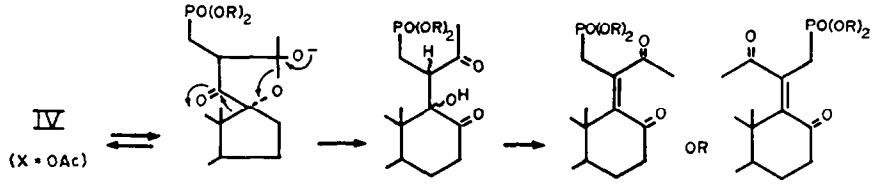
A more satisfactory explanation, consistent with all present experimental evidence, is that the base-catalyzed interaction of the 21-methylene group with the carbonyl group of the 17-acetoxy substituent is accompanied by D-homoannulation to produce a conjugated enedione (Eq. 3). On the basis of the known course of alkali-catalyzed D-homo rearrangements of 17α-hydroxy-20-ketosteroids[26] a product resulting from the migration of the C_{13}–C_{17} bond (XI) is considered more probable than one involving C_{16}–C_{17} bond cleavage (XII). The stabilization achieved from the conversion of the *trans*-fused five-membered ring system to a six-membered ring system provides a



VIII a VIII b IX a IX b



X a X b XII



XI a XI b

(3)

[25] The authors are indebted to Professor Josef Fried for his helpful discussion of spectra interpretation.

[26] N. L. Wendler in *Molecular Rearrangements* (Edited by P. de Mayo) Part 2; p. 1114. Interscience, New York (1964).

substantial driving force, so that the reaction proceeds with facility even though the concentration of initiating anions produced by such a weak base as sodium mercaptide must be fairly low.

The proposed enedione structure may exist in two isomeric forms, XIa and XIb, either of which is compatible with the observed properties. Neither possesses a vinyl hydrogen except at C_6. Each contains one rigid cisoid unsaturated ketone grouping, consistent with the strong IR absorption observed in the double bond region.[24] The expected position of the UV absorption maximum depends on the overall configuration of the enedione chromophore,[27] which, because of free rotation in the side chain, is difficult to predict. The cisoid-transoid structures illustrated (XIa or XIb) represent one planar form of the enedione chromophore for which an absorption maximum at 273 mμ is not unreasonable. A similar structure is present in the rigid hydrindene system of 3β-hydroxyetiojerva-5,13(17a)-diene-3,11-dione acetate,[28] which shows UV absorption at 267 mμ (ε = 14,500). At this time, the assignment of a D-homo steroid structure (XIa or XIb) to the condensation products resulting from the action of sodium mercaptides on 17α-acetoxy-20-keto-21-dialkoxyphosphinylmethyl steroids is tentative; definite proof must await chemical evidence, which is outside the scope of the present paper.

In the 17-deoxy series, alkaline hydrolysis of the phosphonate ester (III; X = H, R = Et) with potassium hydroxide in refluxing aqueous dioxan afforded the corresponding deacetylated monoacid (Table 4) in rather low yield. Dealkylation with metal salts or sodium mercaptide has not been systematically investigated with phosphonate esters of the 17-deoxy series and may prove to be the method of choice.

The 21-methylenepregnenolone acetates (II; X = H or OH), possible intermediates in the phosphite-Mannich base reaction (Mechanism B), were synthesized in order to test their ability to participate in this transformation. Decomposition of the methiodides of I(X = H) or its 21-dimethylaminomethyl analog in boiling ethanol led predictably to the 21-methylene compound (II; X = H). When initially isolated this substance melted at 140–142° and exhibited bands at 1688 (w) and 1667 (s) cm^{-1}. Chromatography and recrystallization elevated the m.p. to 150–2° and led to a reversal in the relative intensity of these absorptions. Although neither form could be isolated completely free of the other, it may be reasonably inferred on the basis of a shift of this magnitude and direction in the carbonyl frequency[24] that the higher melting compound is cisoid and the lower melting is transoid. Similar decompositions of the 17-hydroxylated derivatives of the same Mannich base methiodides provided only a single conformer of II (X = OH), presumed to be cisoid on the basis of ν_{max} 1681 (C=O) cm^{-1}. Acetylation with acetic acid-acetic anhydride in the presence of *p*-toluenesulfonic acid at room temperature furnished the 17-acetoxy derivative of II (X = OAc) melting sharply at 177° with ν_{max} 1666 (C=O) cm^{-1} indicative of transoid conformation.

Quaternization of the nitrogen function is not essential since elimination of pyrrolidine or dimethylamine from the free Mannich bases themselves occurred readily in refluxing acetic acid-acetic anhydride, providing moderate yields of II (X = H or OH). However, the susceptibility of methylene ketones to addition of acetic acid, as

[27] A. I. Scott, *Interpretation of the Ultraviolet Spectra of Natural Products* Chap. 2. Pergamon Press, Oxford (1964).

[28] J. Fried and A. Klingsberg, *J. Amer. Chem. Soc.* 75, 429 (1953).

evidenced by the isolation of 21-acetoxymethylpregnenolone acetate as a major side product from the decomposition of 21-dimethylaminomethylpregnenolone acetate under these conditions, limits the applicability of this approach.

In order to determine whether the 21-methylene-20-ketosteroids (II) were capable of furnishing III via interaction with a phosphite ester and a proton donor, II (X = H or OH) was treated with triethyl phosphite in ethanol and triisopropyl phosphite in isopropanol.[14,29] In confirmation of expectation, the same γ-ketophosphonate esters (III; R = Et or i-Pr; X = H or OH) were obtained as were previously provided from reaction of the corresponding Mannich base methiodides with these P (III) esters. These findings, while they provide rather clear-cut evidence for an elimination mechanism (B), do not represent a rigorous proof that this is the major pathway. This must await a thorough kinetic study.

Introduction of the phosphonate grouping into the terminal position of the progesterone side chain proved to be less straightforward than anticipated. Although either β-ketophosphonate esters or enolphosphate esters may be produced by interaction of simple α-haloketones and phosphite esters (via Michaelis-Arbuzov[14] or Perkow[30] reactions, respectively), optimim yields of the former are reported to be obtained with α-iodoketones[31] utilizing ether as solvent.[30] However, treatment of 21-iodoprogesterone with triethyl phosphite (Eq. 4) in dry ether or acetone or with sodium diethyl phosphonate in dry tetrahydrofuran furnished progesterone as the sole product in 9, 71 and 78% yield, respectively. Reduction of other alkyl halides by P(III) esters has been observed only with compounds negatively substituted on the carbon bearing halogen, and mechanisms consistent with this limitation have been suggested.[14]

In contrast with these results, reaction of 21-tosyloxyprogesterone with triethyl phosphite (Eq. 4) afforded 21-diethoxyphosphinylprogesterone (XIII) as a noncrystalline oil.

Finally, interaction of sodium diethyl phosphonate with this same tosylate (Eq. 5) led to a compound assigned the structure 20-diethoxyphosphinyl-20,21-epoxyprogesterone (XIV) on the basis of its IR spectrum, analysis and the obvious close relationship of this reaction to an analogous reaction entered into by α-haloketones.[32]

Introduction of the dialkoxyphosphinyl group into the 1, 7 and 16 positions of the steroid ring system has also been achieved in this laboratory. A subsequent paper will be concerned with the synthesis of 1-dialkoxyphosphinylprogesterone, testosterone, hydrocortisone and cortisone; 7-dialkoxyphosphinyltestosterone; and 16-dialkoxyphosphinylprogesterone and pregnenolone by reaction of the appropriate conjugated ketone function with a trialkyl phosphite in alcohol or phenol.[14]

EXPERIMENTAL

All reactions were carried out in a N_2 atmosphere, and unless otherwise specified optical rotations were measured in $CHCl_3$, UV spectra in EtOH and IR absorption spectra in solid KBr. M.p.s are uncorrected.

[29] Alcohol, rather than the hydroiodides of trimethylamine or N-methylpyrrolidine, was chosen for this purpose since the facile addition of amine hydrohalides to α,β-unsaturated ketones would have prevented distinction between mechanism A or B.

[30] F. W. Lichtenthaler, *Chem. Revs.* **61**, 607 (1961).

[31] H. I. Jacobson, M. J. Griffin, S. Preis and E. V. Jensen, *J. Amer. Chem. Soc.* **79**, 2608 (1957).

[32] B. A. Arbuzov, *Chem. Soc., London, Spec. Publ. No.* 8, 47 (1959).

(4)
(5)
XIII
XIV
P(OR)3 or NaPO(OR)2
Y = I
P(OR)3
Y = OTs
NaPO(OR)2
Y = OTs
PO(OR)2
Y
O

Tetrahydrofuran (THF) was purified either by distillation from CaH_2 or by passage through a column of alumina. Pyridine was purified by distillation over KOH. Commercial triethyl phosphite (TEP) and triisopropyl phosphite (TIPP) were redistilled before use. 21-Iodoprogesterone[23] was prepared by the action of NaI on deoxycorticosterone *p*-toluenesulphonate. Sodium diethyl phosphonate was conveniently prepared by reaction of a 50% oil dispersion of NaH (Anderson Chemical Company) with diethyl phosphonate as previously described.[23]

21-*Hydroxymethylenepregnenolone* (VI)

A solution of pregnenolone (3·22 g, 10 mmoles) in 20 ml dry benzene plus 20 ml THF was added to a stirred mixture of ethyl formate (2·38 g, 32 mmoles) and NaOMe (prepared from 740 mg Na) in 16 ml dry benzene. A yellowish precipitate gradually formed. The reaction mixture was stirred overnight at room temp, then partitioned between water and ether. The organic layer was washed with water and the washings were combined with the aqueous layer, acidified with cold conc. HCl and extracted twice with benzene. The organic extracts were washed with water, dried over Na_2SO_4 and evaporated to a white solid. Recrystallization from benzene provided VI (1·53 g in two crops, m.p. 155–158°; $(\alpha)_D^{24}$ +38·5°; λ_{max} 204 mμ (ε = 6,400), 270 mμ (ε = 8,150); ν_{max} 3435 (O—H), 1595 (C=C) cm^{-1}). (Found: C, 76·76; H, 9·41. $C_{22}H_{32}O_3$ requires: C, 76·70; H, 9·36%.)

21-N-*Pyrrolidylmethyl-3β-hydroxypregn-5-en-20-one*

(a) *From pregnenolone.* The Mannich base route was previously described in the preliminary report.[10]

(b) *From* VI *via* 21-N-*pyrrolidylmethylene-3β-hydroxypregn-5-en-20-one.* A solution of 600 mg VI and 0·6 ml pyrrolidine was heated in 50 ml dry benzene at reflux for a period of 4 hr as the water formed was collected in a Dean-Stark trap. Removal of benzene and excess amine *in vacuo* left a residue of 21-pyrrolidylmethylenepregnenolone. To a solution of this Mannich base in 30 ml THF, LAH (100 mg) in 30 ml ether was added, and the mixture heated at reflux for 150 min and allowed to stand at room temp overnight. Treatment with a saturated solution of sodium potassium tartrate, followed by extraction with ether, drying over Na_2SO_4 and evaporation *in vacuo* left a residue, which upon recrystallization from benzene and acetone gave a product (389 mg, m.p. 176–178°, $(\alpha)_D$ +17·7°) identical in every respect (including IR spectra and m.m.p.) with the Mannich base[10] prepared by the direct route (a). (Found: C, 77·52; H, 9·71; N, 3·99. $C_{26}H_{41}O_2N$ requires: C, 78·13; H, 10·34; N, 3·51%.)

The methiodide and the 3β-acetate (I; X = H) prepared from this product were also identical with those obtained from the product of the direct Mannich reaction. (Found: C, 59·80; H, 8·00; N, 2·63; I, 23·65. $C_{27}H_{44}O_2NI$ requires: C, 59·88; H, 8·19; N, 2·59; I, 23·44%.)

Reaction of phosphite esters with Mannich base methiodides

The experimental method developed earlier[13] was employed with the modification that the products were purified by chromatography on Florisil. Reaction times, yields and physical properties of the resulting steroidal phosphonates (III) are summarized in Table 1. A period of 90 min in boiling TEP (10 ml) was sufficient for the transformation of I(X = OH) methiodide (6·89 g) to the expected phosphonate (III; R = Et, X = OH). However, prolonged reaction (3 hr) of 780 mg methiodide and 10 ml TEP led instead to III (R = Et, X = O—P(OEt)$_2$; 282 mg) which after recrystallization from ether and hexane provided the analytical sample (m.p. 97–97·5°, $(\alpha)_D^{24.5}$ −40·3°). (Found: C, 59·30; H, 8·19; P, 9·69. $C_{32}H_{54}O_6P_2$ requires: C, 59·61; H, 8·44; P, 9·61%.)

Oxidation and isomerization of IV *to* V

The following method is representative. Standard chromium trioxide reagent[24] (9 ml) was added rapidly to a stirred solution of 2·70 g of IV (R = Et, X = OH) in 400 ml acetone chilled in an ice bath. After 5 min, 2 l. water was added. The crystalline precipitate was filtered off, washed with water, dissolved in 20 ml EtOH containing 4 drops of 10N H_2SO_4 and heated at reflux for 5 min. The mixture was again diluted with water and extracted with ether. Conventional workup of the extracts furnished 1·64 g of the crude 3-keto compound, which upon recrystallization from acetone and pentane, afforded 1·41 g of V(X = OH; R = Et), m.p. 166–167° and a second crop of 86 mg,

[23] P. Tannhauser, R. Pratt and E. V. Jensen, *J. Amer. Chem. Soc.* **78**, 2658 (1956).
[24] C. Djerassi, R. Engle and A. Bowers, *J. Org. Chem.* **21**, 1547 (1956).

m.p. 162–164°; λ_{max} 241 mμ (ε = 19,200); ν_{max} 3360 (O—H), 1706 (C=O at C-20), 1675 (C=O at C-3), 1615 (C=C), 1225 (P=O), 1055 and 1025 (P—O—C) cm^{-1}.

Chromatographic separation on Florisil of the products derived from IV (X = OAc, R = i-Pr) furnished, in addition to V (X = OAc, R = i-Pr), a hydroxylated derivative, probably 6β,17α-dihydroxy-21-diisopropoxyphosphinylmethylprogesterone 17-acetate, $(\alpha)_D^{23.5}$ +32·7 (c = 1·065 in EtOH); λ_{max} 238 mμ (ε = 17,100); ν_{max} 3335 (OH), 1729, 1248 (acetoxy), 1710 (C=O), 1672, 1628 (Δ⁴-3-ketone), 1110, 1005, and 975 (P(O)(O—i-C_3H_7)$_2$) cm^{-1}. (Found: C, 63·29; H, 8·73; P, 5·66. $C_{30}H_{47}O_6P$ requires: C, 63·58; H, 8·36; P, 5·47%.)

Decomposition of Mannich bases and their methiodides

(a) *3β-Acetoxy-21-dimethylaminomethylpregn-5-en-20-one.* A solution of 650 mg of the corresponding methiodide was heated in 40 ml refluxing alcohol for 5 hr. After removal of the solvent *in vacuo*, the residue was dissolved in ether–benzene and the solution washed with water, dried over $MgSO_4$ and evaporated to dryness. The ether soluble portion of this crude product was recrystallized from hexane to give 117 mg of II (X = H) (m.p. 140–142°); $(\alpha)_D^{24°}$ +41·7; λ_{max} 209·5 mμ (ε = 11,100); ν_{max} 1725 (acetoxy), 1688 (w), and 1667 (s) (C=O), and 1612 (C=C) cm^{-1}. (Found: C, 77·42; H, 9·02. $C_{24}H_{34}O_3$ requires: C, 77·80; H, 9·25%.)

Chromatography on Florisil followed by recrystallization from ether and hexane provided what is apparently a cisoid conformer, m.p. 150–1·52° and differing from the lower melting, presumably transoid conformer, only in the relative intensity of the 1688 and 1667 cm^{-1} bands in the IR spectrum.

Decomposition of the free Mannich base (1·0 g) was carried out in a refluxing solution of 5 ml AcOH and 5 ml Ac_2O for 2 hr. Removal of the majority of the solvent *in vacuo*, addition of water, followed by extraction with ether and washing of the extracts with N Na_2CO_3 and with water, and concentration gave the crude product which was chromatographed on Florisil. Elution with 2% acetone in pet. ether gave 311 mg of II (X = H; m.p. 146–147°). Further elution with 10% acetone in pet. ether provided 182 mg of 21-acetoxymethylpregnenolone acetate m.p. 100–101°; $(\alpha)_D^{24°}$ +20·5; ν_{max} 1725 (acetoxy), 1700 (C=O) cm^{-1}. (Found: C, 72·40; H, 8·86. $C_{26}H_{38}O_5$ requires: C, 72·52; H, 8·89%.)

(b) *3β-Acetoxy-21N-pyrrolidylmethylpregn-5-en-20-one* (I; X = H). A solution of 703 mg of the methiodide in 150 ml EtOH was maintained at reflux temp for 8 hr, and then the reaction mixture was worked up as in the preceding experiment. The crude product (322 mg) after recrystallization from ether–hexane gave 230 mg of II (X = H), m.p. 145–148°. It did not depress the m.p. of an analytical sample from the foregoing experiment.

(c) *3β-Acetoxy-17α-hydroxy-21-dimethylaminomethylpregn-5-en-20-one.* A similar reaction of 100 mg of this methiodide in 25 ml EtOH for 6 hr furnished 43 mg of II (X = OH; m.p. 194–196°; $(\alpha)_D^{24°}$ −55·5; λ_{max} 206·5 and 217 mμ (ε = 7,730 and 7,420, respectively); ν_{max} 3510 (O—H), 1726 (acetoxy), 1681 (C=O) and 1612 (C=C) cm^{-1}). (Found: C, 74·20; H, 8·90. $C_{24}H_{34}O_4$ requires: C, 74·60; H, 8·87%.)

(d) *3β-Acetoxy-17α-hydroxy-21-pyrrolidylmethylpregn-5-en-20-one* (I; X = OH). A solution of 900 mg of the methiodide in 100 ml boiling EtOH was heated for 18 hr and provided 600 mg of crude II (X = OH). Recrystallization from acetone–hexane gave 475 mg (m.p. 188·5–190°; m.p. with an analytical sample of II (X = OH) was not depressed).

Decomposition of the free Mannich base (500 mg) was carried out in a mixture of 2·5 ml each of AcOH and Ac_2O at reflux temp for 2 hr. Purification of the product as in (a) provided 217 mg of II (X = OH) eluted from a Florisil column with pet. ether–ether (4:1). Recrystallization from acetone–hexane furnished pure II (X = OH) (118 mg, m.p. 193–195°).

Preparation of 3β,17α-diacetoxy-21-methylenepregn-5-en-20-one (II; X = OAc)

A solution of 100 mg II (X = OH) and 100 mg *p*-toluenesulphonic acid monohydrate in a mixture of 4 ml AcOH and 7 ml Ac_2O was allowed to stand at room temp overnight. The reaction mixture was diluted with ice water, made alkaline with Na_2CO_3aq and extracted with ether. The extracts were washed with water, dried over Na_2SO_4, concentrated to dryness *in vacuo* and recrystallized from ether–hexane to give 79 mg II (X = OAc; m.p. 176–177°; $(\alpha)_D^{24°}$ −39·4; λ_{max} 207·5 and 214 mμ (ε = 11,400 and 10,900, respectively); ν_{max} 1735 (acetoxy), 1698 and 1666 (C=O) and 1609 (C=C) cm^{-1}). (Found: 72·57; H, 8·36. $C_{26}H_{36}O_5$ requires: C, 72·87; H, 8 47%.)

21-Diethoxyphosphinylprogesterone (XIII)

A suspension of 1 g of the tosylate in 10 ml TEP was maintained at gentle reflux for 3 hr. Concentration to dryness *in vacuo* left an oily residue which was chromatographed on Florisil. Elution with ether furnished ethyl tosylate (362 mg; m.p. 32–33° after recrystallization). Further elution with ether–acetone (4:1) gave 673 mg of an oil, purified first by molecular distillation then by rechromatography on Florisil. The first substance eluted proved to be progesterone (59 mg; m.p. 116–118° after recrystallization). Elution with ether–acetone furnished XIII as a viscous oil ($[\alpha]_D$ +122·2; $\nu_{max}^{CHCl_3}$ 1702 and 1663 (C=O); 1615 (C=C); 1252 (P=O); 1161 (POEt); 1050 and 1025 (P—OC) cm^{-1}). (Found: C, 66·59; H, 8·96; P, 6·88. $C_{35}H_{39}PO_5$ requires: C, 66·64; H, 8·73; P, 6·72%.)

Reaction of 21-tosyloxyprogesterone with sodium diethyl phosphonate

A solution of 950 mg of the tosylate in 30 ml abs EtOH was added to a solution of sodium diethyl phosphonate prepared from 390 mg diethyl hydrogen phosphonate in a solution of 56 mg Na in 10 ml abs EtOH. The mixture was heated at reflux for 5 hr; then the alcohol was evaporated *in vacuo* and the residue partitioned between ether and water. The ether extracts were dried, evaporated and chromatographed on Florisil. The major product (XIV; 601 mg) was a viscous oil ($[\alpha]_D$ 80·0; λ_{max} 240 (ε = 17,100); ν_{max} 1666 (C=O); 1616 (C=C); 1250 (P=O); 1160 (POEt); 1053 and 1025 (POC) cm^{-1}). Found: C, 66·25; H, 8·68; P, 6·81. $C_{35}H_{39}PO_5$ requires: C, 66·64; H, 8·73; P, 6·72%.)

Reaction of phosphite esters with 20-keto-21-methylene pregnenolone derivatives

Preparation of phosphonate esters from the α,β-unsaturated ketones[14] may be illustrated by reaction of 21-methylene pregnenolone acetate with TEP. A solution of 230 mg of II (X = H) in 0·5 ml TEP and 10 ml EtOH was maintained at reflux for 3 hr. Concentration *in vacuo* followed by chromatography on Florisil gave 173 mg III (R = Et, X = H; m.p. 98–99°). The IR spectrum was identical with that of an analytical sample prepared directly from the methiodide of I (X = H).

Monodealkylation of phosphonate esters

(a) *Inorganic halides.* Treatment of the esters III, IV or V with LiCl or CaI_2 in ethoxyethanol by the method of Todd *et al.*[21,22] resulted in formation of the monoacids summarized in Table 4.

(b) *Sodium ethyl or n-propyl mercaptide.* The experimental procedure is essentially that developed in earlier studies[23] on the interaction between sodium ethyl mercaptide and simple P(III) and P(V) esters. However, the longer reaction periods required for the apparently more inert steroidal phosphonates (e.g. 70 hr for V; X = OH; R = Et) led us to investigate higher boiling mercaptans. With the use of n-propylmercaptan virtually complete cleavage of 500 mg of V (X = OH, R = Et) to acidic products was achieved in 20 hr in a refluxing solution prepared from 200 mg Na in 10 ml of n-propanethiol and 3·5 ml EtOH (Table 4).

Under these conditions, reactions of 600 mg of IV (R = i-Pr, X = OAc) afforded 414 mg of a neutral product and 186 mg of an acidic product from a 24 hr reaction and equal quantities of these substances from a 66 hr reaction. Chromatography on Florisil of the neutral fraction from the shorter reaction gave 365 mg of an oil XI (R = i-Pr) with $[\alpha]_D^{23·5}$ +53·3; (c = 1·044, EtOH); λ_{max} 273 mμ (ε = 8,100) and absorption maxima in the IR at 3400, 1693, 1633 cm^{-1}. Its NMR spectrum exhibited a single vinyl proton at 4·64 τ (C-6), 2 isopropyl protons at 5·20 τ as an apparent sextet (J = 12), 6 isopropyl methyl protons at 8·72 τ as a doublet (J = 6), 3 methyl protons at 8·99 τ (C-19) and 3 methyl protons at 9·07 τ (C-18). (Found: C, 67·32; H, 9·11; P, 5·61. $C_{30}H_{47}O_6P$ requires: C, 67·39; H, 8·86; P, 5·79%.)

Recrystallization of the acidic fraction from acetone–ether furnished the monoacid derived from XI (R = i-Pr; m.p. 205–206°; $[\alpha]_D^{23°}$ +57·7 (c = 1·078, EtOH); λ_{max} 273 mμ (ε = 8,230) shifted to 280·5 mμ (ε = 8,700) in 0·1N NaOH; absorption in the IR at 3400, 2240, 1686, 1615, 1174, 1010 and 986 cm^{-1}). (Found: C, 65·84; H, 8·54; P, 6·40. $C_{27}H_{41}O_6P$ requires: C, 65·82; H, 8·39; P, 6·29%.)

The cyclohexylammonium salt of XI decomposed at 204–206°. (Found: C, 66·94; H, 9·01; N, 2·50; P, 5·13. $C_{33}H_{54}O_6NP$ requires: C, 66·97; H, 9·20; N, 2·37; P, 5·23%.)

An analogous reaction with sodium ethylmercaptide in EtOH–isopropanol for 40 hr afforded neutral products almost quantitatively.

Acetylation of the neutral enedione (276 mg; XI; R = i-Pr) in pyridine–Ac_2O at room temp overnight followed by chromatography on Florisil of the crude product provided the 3-acetate of XI (R = i-Pr) as an oil (218 mg; $[\alpha]_D^{22.5°}$ +57·9 (c = 0·769, EtOH); λ_{max} 273 mμ (ε = 7,850). (Found: C, 66·06; H, 8·57; P, 5·28. $C_{32}H_{49}O_7P$ requires: C, 66·64; H, 8·57; P, 5·37%.)

(c) *Alkaline hydrolysis.* A solution of III (R = Et; X = H) and 320 mg KOH in 5 ml water plus 2 ml dioxan was heated at reflux for 8 hr, then cooled and acidified with 2N HCl. The reaction mixture furnished 87 mg (from acetone) of the related monoethyl ester of IV (Table 4), with absorption in the IR at 3400, 3110, 2710, 2410, 1715, 1225, 1193, 1063, 983 cm^{-1}.