shift between C_1 H_e and C_1 H_a was large,[8] the C_2 H was treated as the X portion of an AMX system. The values of the coupling constants found for the signals at τ 5.0 were 1.8 and 4.5 Hz and indicated a β-axial configuration for the nitro group.[9]

The same reaction performed on the 3-ethyl enol ether of testosterone acetate[10] (Ib) gave a compound[11] (IIb) with spectral data closely similar to those of compound IIa; we therefore concluded that even in the case of the 19-CH_3 steroids the reaction afforded the 2-nitro derivative.[12]

Experimental Section[13]

2β-Nitro-3-ethoxyestra-3,5-dien-17β-ol Acetate (IIa).—To a suspension of 3-ethoxyestra-3,5-dien-17β-ol acetate[2] (Ia, 3.4 g) in anhydrous ethyl ether (30 cc), tetranitromethane (1.2 cc) was added dropwise within 10 min at room temperature. The steroid went rapidly into solution. After the solution had been allowed to stand for 1 hr, the crystalline material formed was filtered off and washed with ethyl ether–petroleum ether to give 2 g of IIa with mp 198–200°. Recrystallization from ethyl ether–petroleum ether afforded the analytical sample with mp 203–206°; $[\alpha]_D$ −298°; uv max 246 mμ (ϵ 20,630); ir (KBr) 1730 (acetate), 1660 and 1635 (C=C enol ether), 1553 (NO_2) cm^{-1}; nmr τ 4.47 (s and dd, 2H, C_4 H and C_6 H), 5.00 (dd, 1 H, J = 4.5 and 1.8 Hz, C_2H), 5.38 (m, 1 H, C_{17} H), 6.12 (q, 2 H, J = 7 Hz, OCH_2CH_3), 7.97 (s, 3 H), 8.72 (t, 3 H, J = 7 Hz, CH_2CH_3), 9.18 (s, 3 H, angular CH_3).

Anal. Calcd for $C_{22}H_{31}NO_5$: C, 67.84; H, 8.02. Found: C, 67.98; H, 7.74.

2α-Nitroestr-4-en-17β-ol-3-one Acetate (III).—IIa (2.0 g) in acetone (40 cc) and concentrated hydrochloric acid (1 cc) were refluxed for 10 min, the solution was then cooled and diluted with water, and the steroid was extracted with ethyl acetate. The organic layers were washed with water, dried over anhydrous Na_2SO_4, and evaporated to dryness; the crude residue was crystallized from ethyl ether to give III (1.35 g) of mp 170–171°. An analytical sample obtained by recrystallization from ethyl ether had mp 170–172°; $[\alpha]_D$ +89°; uv max 246 mμ (ϵ 15,300); nmr τ 4.05 (s, 1 H, C_4H), 4.75 (dd, 1 H, J = 5 and 14 Hz, C_2H), 5.37 (m, 1 H, $C_{17}H$), 7.98 (s, 3 H), 9.15 (s, 3 H, angular CH_3).

Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.22; H, 7.41; N, 4.00.

2-Nitroestra-1,3,5(10)-triene-3,17β-diol 17-Acetate (Va).—To an ice-cooled suspension of III (2.3 g) in anhydrous ethyl ether (75 cc) a few drops of a saturated solution of hydrobromic acid in acetic acid were added dropwise, followed by the addition, with stirring, of a solution of bromine (1.02 g) in acetic acid (10 cc). The reaction mixture was stirred at 0° for 15 min, and diluted with water. The steroid was extracted with ethyl acetate, and the organic layers were washed with diluted $NaHCO_3$ solution, and water, then dried over anhydrous Na_2SO_4, and evaporated to dryness. The crude residue (3.06 g) was dissolved in dimethylformamide (44 cc) and treated, under nitrogen, with anhydrous LiCl (1.15 g) for 2.5 hr on a steam bath. After cooling, the dark solution was diluted with water and the steroid extracted with ethyl acetate. After the usual work-up, the residue was crystallized from methanol to give Va (730 mg) with mp 192–195°. The analytical sample was recrystallized from the same solvent and afforded the pure compound with mp 195–197°; $[\alpha]_D$ +66°; uv max 294 mμ (ϵ 8020); nmr τ −0.32 (s, 1 H, OH phenyl), 2.02 (s, 1 H, C_1 H), 3.15 (s, 1 H, C_4 H), 5.28 (m, 1 H, C_{17} H), 7.93 (s, 3 H), 9.15 (s, 3 H, angular CH_3).

Anal. Calcd for $C_{20}H_{25}NO_5$: C, 66.83; H, 7.01; N, 3.90. Found: C, 66.77; H, 7.03; N, 3.97.

2-Nitroestradiol (Vb).—Va (300 mg) in MeOH (30 cc) and H_2SO_4 (20%, 1 cc) was warmed for 2 hr on a steam bath. The solution was diluted with water and the steroid extracted with ethyl acetate. The organic layers were washed with water, dried over anhydrous Na_2SO_4, and evaporated to give a crude residue which, crystallized from methanol, afforded 2-nitroestradiol (Vb, 130 mg) with mp 168–170°; $[\alpha]_D$ +125°; uv max 295 mμ (ϵ 8100) (lit.[6] mp 167–168°; uv max 293 mμ (ϵ 8100); ir (KBr) 3500 (17-OH), 3300 (3-OH), 1635 and 1575 (aromatic), 1520 (NO_2) cm;$^{-1}$ nmr τ −0.33 (s, 1 H, OH phenyl), 2.03 (s, 1 H, C_1 H) 3.15 (s, 1 H, C_4 H), 6.22 (m, 1 H, C_{17} H), 9.18 (s, 3 H, angular CH_3).

Chromic acid oxidation of Vb carried out in acetic acid at room temperature afforded the known[6,7] 2-nitroestrone (Vc).

2β-Nitro-3-ethoxyandrosta-3,5-dien-17β-ol Acetate (IIb).—To a solution of 3-ethoxyandrosta-3,5-dien-17β-ol acetate[10] (Ib, 1.67 g) in anhydrous ethyl ether (16.5 cc), tetranitromethane (0.72 cc) was added dropwise at room temperature in 10 min; after a few minutes a crystalline product was formed. The reaction mixture was allowed to stand at room temperature for 30 min; the crystals were filtered off and washed with ethyl ether–petroleum ether to give 800 mg of IIb with mp 195–197°. Recrystallizations from acetone afforded the analytical sample with mp 219–221°; $[\alpha]_D$ −197°; uv max 247.5 mμ (ϵ 22,000); ir (KBr) 1730 (acetate), 1660 and 1635 (C=C enol ether), 1553 (NO_2) cm^{-1}; nmr τ 4.50 (s, 1 H), 4.58 (dd, 1 H), 5.17 (dd, 1 H, J = 7 and 1.8 Hz, C_2 H), 5.38 (m, 1 H, C_{17} H), 6.10 (q, 2 H, J = 7 Hz, OCH_2CH_3), 7.97 (s, 3H), 8.68 (t, 3 H, J = 7 Hz, CH_2-CH_3), 9.03 (s, 3 H, C_{19} protons), 9.18 (s, 3 H, C_{18} protons).

Anal. Calcd for $C_{23}H_{33}NO_5$: C, 68.46; H, 8.24; N, 3.47. Found: C, 68.56; H, 8.00; N, 3.44.

Registry No.—IIa, 21429-98-1; IIb, 21429-99-2; III, 21430-00-2; Va, 21430-01-3.

Acknowledgments.—The authors gratefully thank Professor B. Camerino, Director of this institute, for his sustained interest in this work, Mr. A. Alemanni for microanalytical data, and Mr. R. Botta for assistance in the preparation of the compounds.

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[8] N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 47.

[9] Other 2β-substituted 3-ethoxy-$\Delta^{3,5}$ steroids have been reported: F. Mancini, and R. Sciaky, *Gazz. Chim. Ital.*, **97**, 431 (1967).

[10] S. K. Pradhan and H. J. Ringold, *J. Org. Chem.*, **29**, 601 (1964).

[11] This compound showed the same chemical and spectral data as reported by Liisberg[1] for the compound to which he assigned the structure of 3-ethyl enol ether of 6-nitrotestosterone acetate in the provisional specification of ref 1, p 5.

[12] Some examples of nitration by tetranitromethane have been reported: L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 1147.

[13] Melting points were determined with a Fisher-Johns apparatus and are uncorrected. The ultraviolet spectra were carried out in ethanolic solution. A Perkin-Elmer M 237 spectrophotometer was employed for the infrared spectra using KBr pellets. All rotations were measured in chloroform solution (c 1%) at the sodium D line. The nmr spectra were determined with a Varian A-60A spectrometer with TMS as internal standard and $CDCl_3$ as solvent.

Hydrogenation of Some Unsaturated Phosphines as Their Nickel Chloride Complexes[1]

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Received May 28, 1969

A number of unsaturated cyclic phosphines (phospholenes) are available from dehalogenation of diene–phosphonous dihalide adducts,[2] or reduction of the phosphine oxides formed on hydrolysis of these adducts.[3] We attempted to hydrogenate catalytically some of these phosphines to obtain the corresponding phospholanes. However, no consumption of hydrogen occurred at room temperature and atmospheric pressure with palladium as catalyst. Since a poisoning effect

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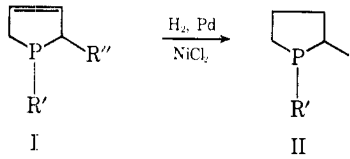
[1] Supported in part by Public Health Service Research Grant CA-05507 from the National Cancer Institute.

[2] L. D. Quin in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press Inc., New York, N. Y., 1967, Chapter 3.

[3] H. Fritzsche, U. Hasserodt, F. Korte, G. Friese, K. Adrian, and H. Arenz, *Chem. Ber.*, **98**, 1681 (1965).

by the phosphines on the catalyst seemed an obvious cause of the difficulty, the reduction was attempted in an acidic medium, where it was believed the electron pair on phosphorus would be protonated and consequently less available for interaction with the catalyst surface. Again no hydrogen uptake occurred. For a similar reason, complexes of the phosphines with metal salts were considered as substrates for the reduction. Such complexes are quite stable, and should release only a low concentration of free phosphine to the medium; yet they can be broken readily by appropriate reagents. This approach was successful, and is described in this paper.

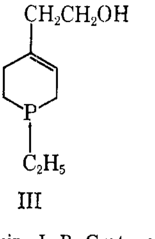
The deep purple nickel chloride complexes of phospholenes Ia--c were prepared in ethanol solution. Isolation of the complexes was unnecessary, although it can be accomplished readily. The solutions still retained a phosphine odor, even when excess nickel chloride was used. With a catalyst of 10% palladium on charcoal, the solutions were hydrogenated at atmospheric pressure. Hydrogen uptake proceeded slowly and ceased after 3 days for Ia, 5 days for Ib, and 9 days for Ic. The volume consumed was 70–100% of theory. Decomplexation was accomplished with an aqueous basic solution of EDTA, and the phospholane was then extracted with ether. No attempt was made to isolate the phospholanes; they were converted to the more readily handled benzyl bromide salts for characterization. Any unreduced phospholene would also form a salt, but there was no evidence for their presence in the products, either by analysis or by the appearance of nmr signals for olefinic protons.



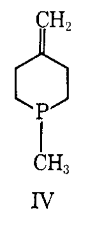
a, $R' = CH_3$, $R'' = H$
b, $R' = R'' = CH_3$
c, $R' = C_6H_5$, $R'' = CH_3$

Phospholene Ib has been shown to exist in stable *cis,trans* forms,[4] and the same is probably true for Ic. Phospholanes derived from them should exhibit the same isomerism. The phospholanes have not yet been studied directly; however, their benzyl bromide salts were found by nmr spectroscopy to consist of an isomer mixture. Thus, the salt of IIb had two PCH_3 doublets, at δ 2.31 (J = 14.1 Hz) and 2.32 (J = 14.1 Hz), and had two overlapping four-line signals for the 2-methyl group (coupled with the 2 proton and with phosphorus). Similarly, the salt of IIc had two CCH_3 signals.

The hydrogenation technique has been extended successfully to one other unsaturated phosphine (III). Its behavior was similar to that of the 3-phospholenes; hydrogen uptake proceeded slowly and was complete in about 7 days. In this case, the phosphine itself was isolated and characterized. A related phosphorinane derivative (IV), however, failed to undergo the reduction in numerous attempts.



III



IV

A survey of the literature has so far revealed very few instances of successful catalytic hydrogenation of unsaturated tertiary phosphines.[5,6] The method described in the present paper may prove to be of value in the reduction of unsaturated phosphines of other types than those described herein.

Experimental Section

All operations involving phosphines and their nickel chloride complexes were conducted under nitrogen. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Nmr spectra were obtained with a Varian A-60 spectrometer; external TMS was used as reference.

Reduction of 1-Methyl-3-Phospholene (Ia).—Addition of 1.5 g (0.012 mol) of nickel chloride to 0.10 g (0.010 mol) of Ia[7] in 40 ml of absolute ethanol caused precipitation of the complex. Solution was effected by briefly heating the mixture, and 0.10 g of 10% palladium on charcoal was added. The mixture was hydrogenated at 1 atm. After 3 days, hydrogen uptake ceased, about 80% of the theoretical amount having been consumed. After the catalyst was filtered, the ethanol was removed on a rotary evaporator. The residual solid complex was treated with 200 ml of a solution saturated with the disodium salt of EDTA, sodium carbonate, and sodium bicarbonate. The purple color of the phosphine complex disappeared, and the blue color of the Ni–EDTA complex remained. The free phosphine was then extracted from the aqueous solution with four 50-ml portions of ether. Isolation of the phosphine was not attempted; it was converted to the benzyl bromide salt by addition of 5 ml of benzyl bromide. The salt that had precipitated after 1 day was filtered from the solution. The filtrate was extracted with water, and the water layer was evaporated to leave some additional salt. The salt was recrystallized from ethyl acetate–methanol: mp 184.0–184.5°.

Anal. Calcd for $C_{12}H_{18}BrP$: C, 52.76; H, 6.64; P, 11.34. Found: C, 52.80; H, 6.57; P, 11.08.

The nmr spectrum of the salt (0.087 g of 0.449 g of D_2O) showed the aromatic protons as a singlet at δ 7.39, the benzyl protons as a doublet (J = 15.4 Hz) centered at δ 3.75, and the methylene and methyl protons as a complex multiplet around δ 2. No vinyl proton absorption due to the salt of unreduced Ia was detected.

Reduction of 1,2-Dimethyl-3-phospholene (Ib).—The nickel chloride complex of Ib[4] was formed by adding 0.666 g (0.00585 mol) of *cis,trans* Ib to a solution of 4.0 g (0.16 mol) of nickel chloride in about 40 ml of absolute ethanol. The solution was briefly heated to effect solution of the complex. The solution was reduced over 0.25 g of 10% palladium on charcoal. After 5 days, hydrogen uptake had ceased, with about 70% of the theoretical amount of hydrogen consumed. The phosphine was released from the complex with EDTA, as in the preceding example, and was extracted with four 100-ml portions of ether. To 300 ml of the extract was added 5 ml of benzyl bromide. After 1 day, the benzyl bromide salt (0.545 g) was filtered from the solution and dried. It was recrystallized from ethyl acetate–methanol: mp 195.5–197.5°.

Anal. Calcd for $C_{13}H_{20}BrP$: C, 54.35; H, 7.19; P, 10.78. Found: C, 54.21; H, 7.19; P, 10.79.

The nmr spectrum of the salt (0.094 g in 0.530 g of D_2O) showed the aromatic protons as a singlet at δ 8.05 and the benzyl protons as a doublet (J = 15.8 Hz) at δ 4.32. The PCH_3 protons of the *cis,trans* forms appeared as two doublets at δ 2.30 (J = 14.1 Hz) and 2.32 (J = 14.1 Hz). The CCH_3 signal was a multiplet centered at δ 1.75.

Some of the original ether extract of the free phosphine was gas chromatographed on an SE-30 column at 75°; only a single

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[4] L. D. Quin, J. P. Gratz, and R. E. Montgomery, *Tetrahedron Lett.*, 2187 (1965).

[5] J. Chatt, F. Hart, and H. C. Fielding, British Patent 859,391 (Jan. 25, 1961).

[6] A. M. Aguiar and D. Daigle, *J. Amer. Chem. Soc.*, **86**, 2299 (1964).

[7] L. D. Quin and D. A. Mathewes, *J. Org. Chem.*, **29**, 836 (1964).

peak, different from that for Ib, was obtained, suggesting that the hydrogenation was more complete than hydrogen uptake indicated. (A less likely explanation is that any unreduced Ib was not extracted from the decomplexed mixture.)

Reduction of 1-Phenyl-2-methyl-3-phospholene (Ic).—The complex formed from 1.71 g (0.0097 mol) of *cis,trans* Ic[8] and 4.0 g (0.16 mol) of nickel chloride in 20 ml of absolute ethanol was reduced over 0.35 g of 10% palladium on charcoal. After 9 days, hydrogen uptake had stopped, with 96% of the theoretical amount of hydrogen consumed. (In another experiment, the measured hydrogen uptake was 71%.) The complex was broken with EDTA as before, and the phosphine was extracted with five portions of ether totaling 450 ml. To 245 ml of the extract was added 5 ml of benzyl bromide. After 3 days, enough of the benzyl bromide salt had formed to permit characterization. It was filtered from the solution; water extraction of the ether solution gave some additional salt. There was obtained 0.281 g, which was recrystallized from ethyl acetate–methanol: mp 202.1–202.5°.

Anal. Calcd for $C_{18}H_{22}BrP$: C, 61.90; H, 6.35; P, 8.87. Found: C, 61.67; H, 6.50; P, 8.96.

The nmr spectrum of the salt (0.067 g in 0.776 g of D_2O, a saturated solution) showed a complicated phenyl region from δ 7.4 to 8.4. Overlapping CCH_3 signals around δ 1.58 indicate a mixture of *cis* and *trans* isomers in the product. The solution was too dilute to gain any other information from the spectrum.

Reduction of 1-Ethyl-4-(2-hydroxyethyl)-1,2,5,6-tetrahydrophosphorin (III).—The nickel chloride complex of phosphine III[9] was formed by adding 10 g (0.058 mol) of III to 7.2 g (0.030 mol) of nickel chloride in 70 ml of absolute ethanol. The complex was hydrogenated over a palladium-on-charcoal catalyst for 7 days at 48 psi, with absorption of 95% of the theoretical amount of hydrogen. The phosphine was then released from the complex as before. The solution was extracted with four 50-ml portions of benzene. The benzene was removed on a rotary evaporator to leave a residue of 6 g (59% crude yield). The residue was fractionated on a spinning-band column to give a 3-g fraction of 1-ethyl-4-(2-hydroxyethyl)phosphorinane at 83–85° (0.15 mm). The infrared spectrum showed no double-bond absorption around 1600 cm^{-1}, and the nmr spectrum showed no vinyl protons.

Anal. Calcd for $C_9H_{19}OP$: C, 62.04; H, 10.99; P, 17.78. Found: C, 61.90; H, 10.98; P, 17.59.

Registry No.—Reduced Ia (benzyl bromide salt), 21473-48-3; reduced Ib (benzyl bromide salt), *cis*, 21473-24-5; reduced Ib (benzyl bromide salt), *trans*, 21492-05-7; reduced Ic (benzyl bromide salt), *cis*, 21473-25-6; reduced Ic (benzyl bromide salt), *trans*, 21473-26-7; 1-ethyl-4-(2-hydroxyethyl)phosphorinane, 21473-27-8.

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[8] L. D. Quin and T. P. Barket, unpublished results.

[9] L. D. Quin and J. W. Russell, Jr., unpublished work.

Phosphorylation of D-Ribose in Aqueous Solution

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Received February 7, 1969

In the context of prebiological chemistry, the phosphorylation of sugars in aqueous solution is of interest in view of the biological importance of the products. The only relevant work with which we are familiar is that of Calvin,[2] who mentioned that dicyandiamide promotes the formation of ribose 5-phosphate from ribose and orthophosphate. No details were given. We report here our studies on the phosphorylation of ribose using cyanogen and cyanamide as condensing agents.

β-D-Ribofuranose 1-phosphate is the only sugar phosphate (10–20%) formed in the reaction of D-ribose with orthophosphate in the presence of cyanogen or cyanamide. This reaction is an order of magnitude more efficient than the phosphorylation of nucleosides (which lack the reactive sugar hemiacetal function) under comparable conditions.[3]

The reactive phosphorylating species in these reactions are presumably adducts of orthophosphate and cyanogen or cyanamide[3] of the same type as those proposed in related reactions of carbodiimides.[4] We think it unlikely that adducts between ribose and either cyanamide or cyanogen[5] undergo a nucleophilic displacement by orthophosphate.

Two observations suggest that the 2-hydroxyl group of ribose is involved in the reaction. Firstly, 2-deoxy-D-ribose is not phosphorylated under the conditions of our reaction; secondly, only the β-phosphate is formed from ribose. It is noteworthy that only the furanose phosphate can be detected, whereas a large number of reactions of ribose are known to produce mixtures of furanose and pyranose isomers.[6]

This reaction may be useful in the synthesis of β-ribofuranose 1-phosphate. Previously reported syntheses involve protected sugars; enzymatic reactions produce exclusively α-ribofuranose 1-phosphate.[4,7]

Experimental Section

Condensation with Cyanogen.—Stirred aqueous solutions of D-ribose and orthophosphate (both initially 0.1–0.2 *M*), at pH's in the 7.0–8.8 range and at 25°, were evacuated through rubber septa. Cyanogen gas was then added by syringe to give final concentrations ranging from 0.02 to 0.44 *M*. After a few minutes, the solutions turned yellowish brown. Samples were withdrawn at intervals for analysis. The phosphate-containing products were studied in various chromatographic systems (see Table I). D-ribose-1-^{14}C was used in some experiments to facilitate the identification of products.

A. Formation of Acid-Labile Phosphate Esters.—The uptake of orthophosphate was measured by the colorimetric method of Lowry and Lopez.[8] A maximal uptake of 18–22% was obtained after 1 day from solutions 0.2 *M* in orthophosphate, cyanogen, and ribose. Chromatography after treatment of the reaction mixture with 0.1 *N* hydrochloric acid for 10 min at 100° showed that all of the sugar phosphate had been hydrolyzed. Only aldose 1-phosphates are so sensitive to acid hydrolysis.[7,9]

B. Test for Alkali-Labile Phosphate Esters.—There was no decomposition of the sugar phosphate formed in the experiment described in A after the reaction mixture had been heated with 0.1 *N* sodium hydroxide for 10 min at 100°. Under such conditions, we found that ribose 5-phosphate was completely destroyed, while both α- and β-ribofuranose 1-phosphates were stable. It had previously been reported that ribose 5-, and 3-, and 2-phosphates readily decompose in aqueous alkali, while aldose 1-phosphates are alkali stable.[9]

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[1] On leave from The Weizmann Institute of Science, Rehovot, Israel.

[2] M. Calvin, *Proc. Roy. Soc.*, **A**, **288**, 441 (1965).

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[5] R. A. Sanchez and L. E. Orgel, *J. Mol. Biol.*, in press.

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[9] L. F. Leloir and C. E. Cardini in "Comprehensive Biochemistry," Vol. 5, M. Florkin and E. H. Stolz, Ed., Elsevier Publishing House, Amsterdam, 1963, p 113, and references therein.