sized this ketone by the application of the Oppenauer oxidation[2] on β-ionylidene ethyl alcohol (I) which was prepared by the reduction of ethyl β-ionylidene acetate with lithium aluminum hydride.[3,4]

Ethyl β-ionylidene acetate (b. p. 141–144° (2–3 mm.); $n^{25}D$ 1.5320; $\lambda_{max.}$ 2850 Å., log ε 4.42) was prepared according to Karrer, *et al.*,[5] by the Reformatsky condensation of β-ionone ($n^{25}D$ 1.5180) and ethyl bromoacetate. The intermediate hydroxy ester was dehydrated with *p*-toluene sulfonic acid in toluene. This ester (180 g.) was reduced in an ethereal solution at 0° with lithium aluminum hydride (32 g.) prepared essentially by the recently published method.[3] The product (163 g.) was recovered after acidification with a mixture of ice and glacial acetic acid and fractionated under reduced pressure and the fraction (113.6 g.) boiling at 137–144° (4 mm.), collected and analyzed; $n^{25}D$ 1.5496; $\lambda_{max.}$ 2740 Å., log ε 4.45.

Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98; unsaturation, 3 ⌐¬; active hydrogen, 1.0. Found: C, 81.42; H, 10.92; unsaturation, 3.12, 3.17 (Pt) ⌐¬; active hydrogen (Zerewitinoff), 0.99, 1.01, 1.02.

β-Ionylidene ethyl alcohol (44.8 g.) was dissolved in a mixture of thiophene-free benzene (1000 cc.) and purified acetone (400 cc.) and to the mixture was added 60 g. of freshly prepared aluminum *t*-butoxide and refluxed in nitrogen for forty-four hours. The mixture was cooled, hydrolyzed with 1 liter of water and filtered and the benzene layer separated from the filtrate, dried and the benzene removed under vacuum; yield of the crude product, 40 g. (active hydrogen, 0.55). This dark brown product was distilled under a high vacuum and the fraction (32 g.) distilling at 80–85° (10^{-4}–10^{-5} mm.) collected and analyzed. Carbon and hydrogen showed the presence of about 10% ketol, so that the product was further dehydrated with 2% *p*-toluene sulfonic acid in toluene. The ketone was recovered and, after preliminary purification in petroleum ether and in methanol at −78°, was fractionated under high vacuum and the fraction (yellow oil, 24.5 g.) boiling at 80–82° (10^{-4}–10^{-5} mm.) was collected and analyzed; $n^{17}D$ 1.5685; $\lambda_{max.}$ 3330 Å., log ε 4.2.

Anal. Calcd. for $C_{18}H_{26}O$: C, 83.67; H, 10.14; unsaturation, 4.0 ⌐¬. Found: C, 83.67; H, 10.43; unsaturation, 4.15 ⌐¬.

The ketone had a negligible active hydrogen (Zerewitinoff) and gave a wine red color with antimony trichloride in chloroform. We expect to carry out a Reformatsky on this ketone, dehydrate the hydroxy ester and reduce the final ester to vitamin A with lithium aluminum hydride.

(2) Batty, Burawoy, Harper, Heilbron and Jones, *J. Chem. Soc.*, 175 (1938).

(3) Finholt, Bond and Schlesinger, THIS JOURNAL, **69**, 1199 1947).

(4) Nystrom and Brown, *ibid.*, **69**, 1197 (1947).

(5) Karrer, Salomon, Morf and Walker, *Helv. Chim. Acta*, **15**, 878 (1932); Karrer, Morf and Schoepp, *ibid.*, **16**, 557 (1933); Karrer, Ruegger and Solmssen, *ibid.*, **21**, 448 (1938).

DEPARTMENT OF CHEMISTRY NICHOLAS A. MILAS
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RECEIVED AUGUST 26, 1947

PHOSPHITE ISOMERIZATION IN THE SYNTHESIS OF THIOPHENE PHOSPHONIC ACIDS

Sir:

In view of the very poor yields heretofore attainable in the preparation of thiophene-substituted phosphonic acids,[1] the classical isomerization of alkylphosphites was tried in an attempt to make the compounds of this type more available for study.

Sodium dibutylphosphite (from 45 g. of dibutyl phosphite) was treated in hexane solution with 31 g. of α-chloromethylthiophene to give, after three hours of reflux, 71% yield of dibutyl α-thienylmethanephosphonate, b. p. 147–150° at 3 mm. Hydrolysis by boiling with hydrochloric acid, followed by evaporation and recrystallization of the residue from water, gave a substantially quantitative conversion of the ester to α-thienylmethanephosphonic acid, which formed yellowish plates; m. p. 108–109°. *Anal.* Calcd.: S, 16.3. Found: S, 16.46.

(1) Sachs, *Ber.*, **25**, 1514 (1892).

CENTRAL RESEARCH DEPARTMENT
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RECEIVED AUGUST 11, 1947

CARCINOGENESIS

Sir:

Concerning the excellent paper by L. F. Fieser and S. T. Putnam on the Oxidation of Carcinogenic Hydrocarbons in the May issue of THIS JOURNAL, I should like to suggest that peroxidation is more important than oxidation in determining their carcinogenicity. Since the ionization potential decreases with the number of conjugation centers, a simple electron transfer process involving the non-localized π electrons can readily occur with these hydrocarbons. This may be followed by a proton transfer resulting in the formation of a free-radical. This radical reacts with oxygen to form a peroxide free-radical capable of initiating a branched-chain, free-radical oxidation of intracellular nutrient material, thus increasing cell-metabolism and cell-growth. In the presence of trace quantities of such materials as chromium, iron, cobalt, arsenic, ascorbic acid, etc., the activation energy required for the decomposition of the hydroperoxides into free radicals may be low enough to accelerate tissue growth to the extent that it is entirely out of proportion to the growth rate of the normal surrounding tissues.

The hydroperoxides will increase until limited by the supply of arterial oxygen. Since they are a

constituent of the protoplasm, they will be transmitted to future generations of cells through cell division. Cell division will increase cellular surface area and consequently the available oxygen so that peroxides will again increase.

The free-radical oxidation chain can be broken by radioactive radiations, certain nitrogen compounds (carbamates, aryl amines, bis-β-chloroethyl substituted tertiary amines, alkyl ureas, etc.), quinones and similar compounds. Consequently, these agents inhibit cancer by retarding the oxidation. The oxidation can be probably completely prevented by lipoid-soluble iodides (quaternary aryl or alkyl ammonium iodides, iodogorgoic acid, etc.) and related materials because compounds of this sort are remarkably effective in destroying hydroperoxides. A free-radical, branched-chain oxidation reaction may be started in the tissues not only by carcinogenic hydrocarbons but also by ultraviolet light, X-rays and radioactive radiations, high temperature, etc. It should be possible to check the validity of the free-radical mechanism of cancer by studying the kinetics of the oxidation of cancerous tissue *in vitro*.

In some cases it would be possible to extract some of these hydroperoxides from the cells. They could then be filtered through a Berkefeld filter and injected into non-neoplastic tissue. Whereupon, if the injected hydroperoxides possess a low activation energy, they could decompose to form free-radicals and thus initiate another branched-chain oxidation reaction so that cancer would result. The hydroperoxide molecules also have the unique property of multiplying in the presence of oxygen and organic molecules containing hydrogen attached to secondary or tertiary carbon atoms. It is not surprising, therefore, that numerous investigators have mistaken these hydroperoxides for viruses.

Despite the pronounced superficial diversity of the multitude of neoplasms, the hydroperoxide theory might possibly be applicable to all types, not only carcinomas but also endotheliomas and sarcomas. It might even be applied with success to many kinds of benign hyperplasia.

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RECEIVED JULY 25, 1947

CRYSTALLINE DERIVATIVES OF 6-α-D-GLUCOPYRANOSIDO-β-D-GLUCOSE FROM STARCH

Sir:

Waxy corn starch (400 g.) was hydrolyzed with a purified amylolytic enzyme prepared from *Aspergillus oryzae*. Fermentable sugars were removed by treatment with bakers' starch-free yeast. Proteins were removed with basic lead acetate, and the liquors further purified by passage through Amberlite–resin exchange IR-4 and IR-100 ion columns. After concentration and treatment of the liquors with methyl, ethyl and butyl alcohols, an amorphous white solid (A) consisting essentially of the non-fermentable fragments of starch was obtained; reducing value 82% of that calculated for maltose monohydrate; $[\alpha]^{25}D$ + 127.6° (*c*, 2 in water); yield 6.3 g.

This solid (A) was esterified with *p*-nitrobenzoyl chloride in pyridine and yielded a crystalline product, presumably octa-*p*-nitrobenzoyl 6-α-D-glucopyranosido-D-glucose; diamond-shaped crystals; $[\alpha]D$ + 22.0° (*c*, 1.27 in acetonylacetone); m. p. 188°.

Anal. Calcd. for $C_{12}H_{14}O_{11}(OC_7H_4NO_2)_8$: C, 53.20; H, 3.02; N, 7.40. Found: C, 53.20; H, 3.27; N, 7.70.

On *acetylation* of solid (A) with acetic anhydride in pyridine at 0° a crystalline compound apparently 6-α-D-glucopyranosido-D-glucose octaacetate (I) was obtained in the form of brush-like clusters of needles; $[\alpha]^{25}D$ + 37° (*c*, 1.23 in chloroform); m. p. 175°.

Anal. Calcd. for $C_{12}H_{14}O_{11}(CH_3CO)_8$: C, 49.6; H, 5.63; CH_3CO, 50.7; mol. wt., 678.6. Found: C, 49.7; H, 5.48; CH_3CO, 50.6; mol. wt. (Rast), 670.

The sirup obtained by deacetylation of this acetate gave the same octa-*p*-nitrobenzoate described above.

In addition to these crystalline compounds, an amorphous octacetate had also been prepared at the time the Communication to the Editor by Georges, Miller and Wolfrom[1] appeared, describing the isolation of the octaacetate of 6-α-D-glucopyranosido-β-D-glucose following the acid hydrolysis of dextran. Our amorphous octaacetate was formed by acetylation of solid (A) with a solution of sodium acetate in acetic anhydride at 100 to 110°; $[\alpha]^{25}D$ + 96.2° (*c*, 2 in chloroform). This acetate has in the meantime crystallized; long prism-shaped crystals; $[\alpha]^{25}D$ + 98.2° (*c*, 1.50 in chloroform); m. p. 142°.

Anal. Calcd. for $C_{12}H_{14}O_{11}(CH_3CO)_8$: C, 49.56; H, 5.63; CH_3CO, 50.7. Found: C, 49.6; H, 5.73; CH_3CO, 50.9.

This acetate (II) has the same physical properties as the octaacetate of 6-α-D-glucopyranosido-B-D-glucose from dextran. The melting point of a mixture of the octaacetate derived from dextran, which was kindly supplied by Dr. Wolfrom, and octaacetate II from starch was 142°. Following Dr. Wolfrom's suggestion, X-ray powder diffraction diagrams of these compounds were taken, and also were found to be identical.

The two crystalline acetates prepared in this work behaved like 1,6- rather than 1,4-disaccharides toward hydrogen bromide in acetic anhydride and acetyl bromide, that is 1,4-disaccharides are ruptured to form acetobromo-monosaccharides, whereas 1,6-disaccharides are not, but in-

(1) L. W. Georges, I. L. Miller and M. L. Wolfrom, THIS JOURNAL, **69**, 473 (1947).