COMMUNICATIONS TO THE EDITOR

THE USE OF SODIUM IN THE PREPARATION OF METHYLENE-LINKED SILANES

Sir:

The use of sodium in the preparation of compounds of the type $ASi(CH_3)_2[CH_2Si(CH_3)_2]_nB$ has been investigated. These compounds have been made wherein the A and/or B may be methyl, chloride, or ethoxy. The compounds where both A and B are methyl groups have been tentatively called "silahydrocarbons."

Compounds of the above type where A and B are methyl groups may be prepared from reactions of materials such as $(CH_3)_3SiCl$, $CH_3[(CH_3)_2SiCH_2]_nCl$ and sodium. This reaction gives products of the type formula $(CH_3)_3Si[CH_2Si(CH_3)_2]_nCH_3$. Yields of these reactions are 65–70% of the desired product. Two of these compounds also have been prepared by reacting $(CH_3)_3SiCl$ and $(CH_3)_2SiCl_2$ with $(CH_3)_3SiCH_2MgCl$.[1]

The preparation of compounds where both A and B are ethoxy groups may be carried out by (1) and (2) as follows.

$$(1)\quad (CH_3)_2Si(OC_2H_5)_2 + ClCH_2Si(CH_3)_2OC_2H_5 + 2Na \longrightarrow C_2H_5OSi(CH_3)_2[CH_2Si(CH_3)_2]_1OC_2H_5 + NaCl + NaOC_2H_5$$

$$(2)\quad (CH_3)_2Si(OC_2H_5)_2 + ClCH_2Si(CH_3)_2Cl + 2Na \longrightarrow C_2H_5OSi(CH_3)_2[CH_2Si(CH_3)_2]_1OC_2H_5 + 2NaCl$$

In (2) it appears that $NaOC_2H_5$ is formed and reacts with the $ClSi(CH_3)_2SiCH_2(CH_3)_2OC_2H_5$ to give $C_2H_5OSi(CH_3)_2CH_2Si(CH_3)_2OC_2H_5$.

The preparation of compounds where A is a methyl group and B is ethoxy is easily effected by a reaction such as

$$(CH_3)_3SiCl + ClCH_2Si(CH_3)_2OC_2H_5 + 2Na \longrightarrow (CH_3)_3SiCH_2Si(CH_3)_2OC_2H_5 + 2NaCl$$

This reaction gives yields of 75–80% of the desired product and smaller amounts of higher members. The subsequent preparation of higher members of this series is best achieved by conversion of the ethoxy group to the chloride by reaction with acetyl chloride or benzoyl chloride and the reaction of the chloride with $ClCH_2Si(CH_3)_2OC_2H_5$ and sodium. In this way materials of the type $(CH_3)_3Si[CH_2Si(CH_3)_2]_nOC_2H_5$ may be produced.

The reaction of either the ethoxy materials or the chloride-ended materials with Grignard reagents will give the corresponding "silahydrocarbons." The monofunctional ethoxy and chloride compounds also may be hydrolyzed to give materials of the type $[(CH_3)_3Si[CH_2Si(CH_3)_2]_n]_2O$ while hydrolysis of the difunctional compounds gives cyclic materials with the type formula $[[-(CH_3)_2SiCH_2]_nSi(CH_3)_2O-]_m$. Two cyclic materials with formulas $[(CH_3)_2SiCH_2Si(CH_3)_2O]_2$ and $(CH_3)_2Si[CH_2Si(CH_3)_2]_2O$ have been isolated and identified.

A typical experiment in this series of reactions involves the following procedure: 800 g. of toluene and 4 moles of sodium were placed in a flask and heated to 110° with vigorous stirring. A mixture of 2 moles of $(CH_3)_3SiCl$ and 2 moles of $ClCH_2Si(CH_3)_2OC_2H_5$ was added at such a rate that the temperature was maintained at 110°. The materials were then filtered and distilled. Distillation gave 1.57 moles of $(CH_3)_3Si[CH_2Si(CH_3)_2]_1OC_2H_5$, b. p. 160° at 740 mm., $n^{25}D$ 1.4148, d^{25} 0.8060, a yield of 78.5%. *Anal.* Calcd. for $C_8Si_2H_{22}O$: Si, 29.5; C, 50.55; *MR*D, 59.15. Found: Si, 29.65; C, 50.6; *MR*D 58.9. Similar experiments have produced the compounds indicated up to *n* values of 4.

There is a good reason for using $ClCH_2Si(CH_3)_2OC_2H_5$ rather than $ClCH_2Si(CH_3)_2Cl$ in these reactions. The reaction of $ClCH_2Si(CH_3)_2Cl$ with other molecules like itself is so rapid that the simpler members of the series are very difficult to isolate. The products of the reaction of several molecules of $ClCH_2Si(CH_3)_2Cl$ and sodium are materials with high molecular weights and with the basic unit $[Si(CH_3)_2CH_2]_n$ predominating in the molecule.

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J. T. GOODWIN, JR.
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R. R. MCGREGOR

RECEIVED AUGUST 15, 1947

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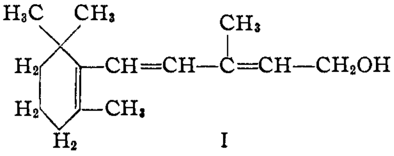
[1] Whitmore, Sommer, Goldberg and Gold, THIS JOURNAL, **69**, 980 (1947).

A NEW SYNTHESIS OF 1-(2',6',6'-TRIMETHYLCYCLOHEXEN-1'-YL)-3-METHYLHEXA-1,3,5-TRIEN-7-ONE (C_{18} KETONE)

Sir:

The C_{18} ketone (II)[1] is an important intermediate in the synthesis of "vitamin A acid" and vitamin A itself. Recently we have synthe-



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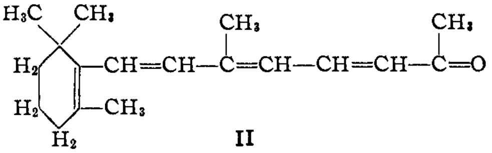

II

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[1] (a) Arens and van Dorp, *Nature*, **157**, 190 (1946); *Rec. trav. chim.*, **65**, 338 (1946); (b) Heilbron, Jones and O'Sullivan, *Nature*, **157**, 485 (1946); *J. Chem. Soc.*, 868 (1946); (c) Karrer, Jucker and Schick, *Helv. Chim. Acta*, **29**, 704 (1946).

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.); $n^{25}\mathrm{D}$ 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 ($n^{25}\mathrm{D}$ 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; $n^{25}\mathrm{D}$ 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; $n^{17}\mathrm{D}$ 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.

DEPARTMENT OF CHEMISTRY NICHOLAS A. MILAS
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASS. THERESE M. HARRINGTON

RECEIVED AUGUST 26, 1947

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[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).

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).

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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.

MONSANTO CHEMICAL COMPANY
PLASTICS DIVISION
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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; $[\alpha]^{25}\mathrm{D}$ + 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; $[\alpha]\mathrm{D}$ + 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; $[\alpha]^{25}\mathrm{D}$ + 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°; $[\alpha]^{25}\mathrm{D}$ + 96.2° (*c*, 2 in chloroform). This acetate has in the meantime crystallized; long prism-shaped crystals; $[\alpha]^{25}\mathrm{D}$ + 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-

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

stead behave anomalously.[2] Thus a quantity of acetate in 10 ml. of a solution of hydrogen bromide in acetic acid and acetyl bromide, calculated to produce 7.576×10^{-4} mole of 1-bromotetraacetyl glucose, assuming the disaccharide is quantitatively converted to this derivative, gave the following end rotations: β-maltose octaacetate, +17.2; gentiobiose octaacetate, +12.2; and octaacetates I and II, + 12.1 and +11.2°, respectively.

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RECEIVED AUGUST 8, 1947

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(2) Allene Jeanes and G. E. Hilbert, presented before the American Chemical Society, Sept. 11-15, 1944.

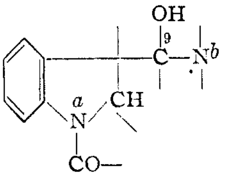
(3) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

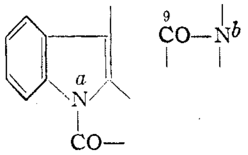
THE STRUCTURE OF STRYCHNINE

Sir:

We have found that the ultraviolet absorption spectrum [$\lambda\lambda_{\max.}$ (log ε): 246(4.15), 270(3.92), 294(3.72)] of strychnone, the neutral product[1] of the action of acidic hydrogen peroxide on *pseudo*strychnine, resembles closely that of model N-acylindoles, and is entirely different from that of strychnine and other N-acyldihydroindoles. This observation can be accommodated on the basis of the change I → II. It is clear that in the imino-carbonyl chain tautomer of I, the oxidizing agent interpolates an oxygen atom between the (potential) carbonyl group at C.9 and the β-carbon atom of the indole nucleus, giving III. The subsequent changes are unexceptional. The new expression leads to $-\overset{|}{\mathrm{N}}{}^{a}\mathrm{H}\ \mathrm{HOO}\overset{|}{\mathrm{C}}$ for strychnone hydrate. N^a is now part of an indole system, and in the hydrate is only very feebly basic, as required. Methoxydihydrostrychnone is simply the ester $-\overset{|\,a}{\mathrm{N}}\mathrm{H}\ \mathrm{MeOO}\overset{|}{\mathrm{C}}$. Like other indoles and N-acylindoles, none of these substances gives, as do N-acyldihydroindoles, the characteristic Otto reaction.

I





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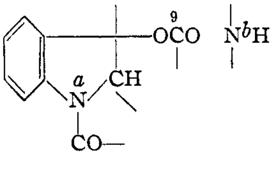
The importance of these considerations is twofold: (i) on the new basis, the formation of strychnone is the long-sought crucial experiment with respect to resolving the remaining dubieties concerning the mode of the linkage of N^b to the indole ring. Consequently, taken with the recent observations of Robinson[2] on the environment of the double bond in the *neo* series, and similar studies in this Laboratory on the replacement by methylene of the ketonic group of methoxymethyl-*chano*dihydrostrychnone, the new evidence completes the inferential proof for a particular expression for strychnine, IV.[3] (ii) In the formation of strychnone, the very involved tightly fused polycyclic system of strychnine has been broken into to an extent not achieved in any of the extensive earlier degradations, which have in the main led only to the destruction of the periphery of the molecule. Thus, the way is now open to build up an unequivocal degradative proof of structure for strychnine.



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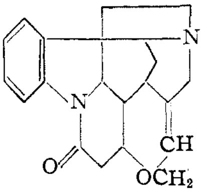

IV

CONVERSE MEMORIAL LABORATORY R. B. WOODWARD
HARVARD UNIVERSITY WARREN J. BREHM
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RECEIVED JULY 28, 1947

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(1) Leuchs, *et al.*, *Ber.*, **77**, 408 (1944).

(2) Chakravarti and Robinson, *Nature*, **160**, 18 (1947).

(3) This expression, which for some years has been considered independently in this Laboratory (*cf. J. Chem. Soc.*, 903 (1946), footnote, p. 904) and in that of Sir Robert Robinson (ref. 2), represents a slight modification of the structure regarded in 1939 by the latter (*J. Chem. Soc.*, 603 (1939)) as the culmination of the strychnine structure problem, on the basis of a long and brilliant logical sequence, much of which had been elaborated as early as 1930 (Robinson, *Proc. Roy. Soc.* (*London*), **130A**, 431 (1931).