and refluxing for one hour, the reaction mixture was poured on ice. Vacuum distillation yielded 9.0 g. (90%) of a pale green liquid, b. p. 147–148° at 3 mm., m. p. 76–78°. A sample recrystallized from alcohol for analysis melted at 77.0–78.0° cor. A mixed melting point with the decarboxylation product was not depressed.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.7; H, 8.0. Found[b]: C, 85.7, 85.6; H, 7.9, 8.0.

Summary

Evidence is provided that when Grignard reagents react with phthalic anhydride types, the mechanism involves reaction both by addition to the carbonyl group and metathetical reaction by cleavage of the carbon–oxygen single bond. A series of reactions of 3,6-dimethylphthalic anhydride with Grignard reagents and with aromatic hydrocarbons is described.

COLUMBUS, OHIO RECEIVED JANUARY 10, 1944

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

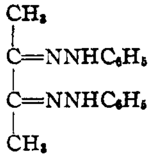
The Action of Copper Sulfate on Phenylosazones of the Sugars. Phenyl-D-glucosotriazole

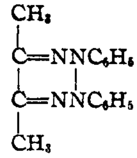
BY RAYMOND M. HANN AND C. S. HUDSON

In a previous communication[1] it was shown that the phenylhydrazides of the aldonic acids of the sugar group are readily decomposed in hot aqueous copper sulfate solution with the production of nitrogen, benzene and the free sugar acid; the reaction appears to proceed quantitatively, as is evident from the fact that upon removal of the inorganic materials and concentration of the solution, a nearly theoretical yield of lactone of the acid is obtained. It seemed of interest to test the action of copper sulfate solutions on the phenylosazones of the sugars. They are known to reduce Fehling solution but no record has been found of a test with copper sulfate under acid conditions.

In the initial experiments a suspension of pulverized phenyl-D-glucosazone (5.0 g.) in 600 cc. of an aqueous solution containing two molecular equivalents (7.0 g.) of copper sulfate pentahydrate was boiled under reflux,[2] most of the osazone dissolved in one hour and as the reaction progressed the precipitation of a small amount of copper or cuprous oxide was noted and the color of the solution changed from blue to green. At the end of a second hour only traces of undissolved osazone remained; the mixture was filtered hot and from the filtrate, while still warm, glistening needle crystals separated. They were filtered from the cooled solution and a second crop was obtained by concentration of the mother liquor to 100 cc.; the total yield of product, which proved to be nearly pure though its color was tan from adsorbed dye, was 2–3 g. It was obtained as colorless pure asbestos-like crystals by recrystallizing once or twice from one hundred parts of boiling water and filtering through a bed of decolorizing carbon in a steam-heated Buchner funnel. The substance melts sharply at 195–196° without decomposition and the cooled melt crystallizes; the compound is very stable. It is not sufficiently soluble in water at ordinary temperatures to permit observation of its rotation, but in pyridine its specific rotation $[\alpha]^{20}D$ was −81.6° (*c*, 0.8). The crystals are anhydrous and their analysis showed 54.44% carbon, 5.71% hydrogen and 15.78% nitrogen (Dumas), values which lead to the formula $C_{12}H_{15}O_4N_3$.

It will be observed that the empirical formula of the substance differs from that of phenyl-D-glucosazone by the elements of aniline, as though the reaction might be $C_{18}H_{22}O_4N_4 = C_{12}H_{15}O_4N_3 + C_6H_5NH_2$. Aniline was indeed detected in the mother liquor by removing the copper as sulfide, making the solution alkaline, extracting it with ether and converting the oily residue from the evaporation of the ether extract to acetanilide (yield, 20%). The evidence led to the possibility that the substance might belong to the class of osotriazoles of v. Pechmann,[3] which are very stable substances. In the case of diacetyl diphenylhydrazone (I), he showed that it was converted by oxidation with potassium dichromate in dilute acetic acid to an osotetrazone (II), which with stronger acidity (HCl) gave a 20% yield of the osotriazole (III). The latter reaction is evidently complex; much tar was produced and aniline was detected.


(I)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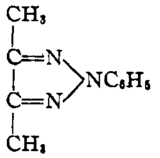
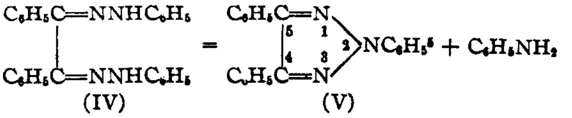

(III)

A direct conversion of an osazone type of compound to the corresponding osotriazole was reported by Auwers and Victor Meyer,[4] who heated benzil diphenylhydrazone (IV) in alcohol solution at 200° and obtained 2,4,5-triphenylosotriazole (V) and aniline.


(IV) (V)

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[1] Hann and Hudson, THIS JOURNAL, **56**, 957 (1934).

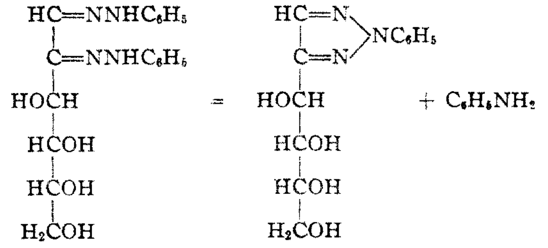
[2] The osazone is difficult to wet and foaming during the first half hour was troublesome; in later experiments this was much reduced by the addition of a few cc. of *n*-butyl alcohol. It was also found that the reaction proceeds equally well but somewhat slower on the steam-bath; the best solvent that has been found so far is acidified 40% isopropyl alcohol at its boiling point, as is described further on.

[3] v. Pechmann, *Ber.*, **21**, 2751 (1888); *Ann.*, **262**, 265 (1891).

[4] Auwers and Victor Meyer, *Ber.*, **21**, 2806 (1888).

[5] The numbering is that of formula No. 77 of Patterson and Capell's "The Ring Index," Reinhold Publishing Corporation, New York, N. Y., 1940. The name osotriazole, introduced by v. Pechmann, implies the 2,1,3-triazole that is related to osazones.

An analogous course for the phenyl-D-glucosazone reaction would be expressed by formulas (VI) and (VII).



(VI) Phenyl-D-glucosazone

(VII) Phenyl-D-glucosotriazole[6]

As previously mentioned, the analysis of the derivative agrees well with this postulated osotriazole structure; it was also found that the substance yields a crystalline tetraacetate and tetrabenzoate, as would be expected if it possesses this structure.

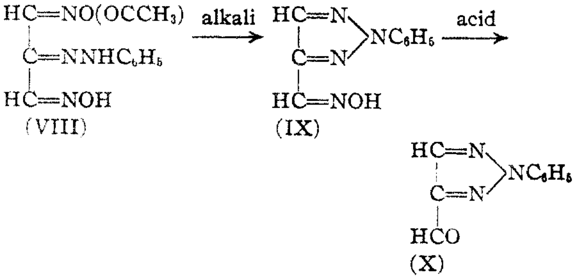
Phenyl-D-glucosotriazole Tetraacetate.—A solution of 1.0 g. of the osotriazole in a mixture of 15 cc. of pyridine and 15 cc. of acetic anhydride was kept at 25° for eighteen hours and then poured upon crushed ice; the product, which was obtained in nearly quantitative yield, was recrystallized from 5 parts of methyl alcohol. The pure substance melts at 81–82°, shows $[\alpha]^{20}\mathrm{D}$ −25.6° in chloroform (c, 0.92), and its minute needle crystals are easily soluble in acetone and ethyl acetate and insoluble in water.

Anal. Calcd. for $C_{20}H_{23}O_8N_3$: C, 55.42; H, 5.35; CH_3CO, 39.7. Found: C, 55.53; H, 5.49; CH_3CO, 39.7.

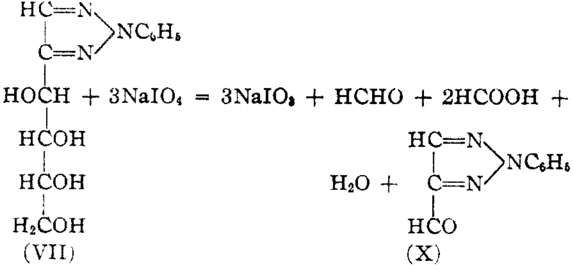
Phenyl-D-glucosotriazole Tetrabenzoate.—Benzoyl chloride (4.0 cc.) was mixed with an ice-cold solution of 1.1 g. of the osotriazole in 15 cc. of pyridine and the mixture kept at room temperature for eighteen hours. On pouring it into water the gummy benzoate precipitated; this mass was repeatedly triturated with fresh water and after several days it crystallized in nearly quantitative yield, and was recrystallized from 15 parts of alcohol. The fine needles show m. p. 112–113° and $[\alpha]^{20}\mathrm{D}$ +3.0° in chloroform (c, 0.92); they are soluble in acetone, ether and hot alcohol and insoluble in water.

Anal. Calcd. for $C_{40}H_{31}O_8N_3$: C, 70.47; H, 4.58; C_6H_5CO, 61.7. Found: C, 70.34; H, 4.63; C_6H_5CO, 61.7.

Proof of the structure (VII) was obtained through a study of the oxidation of the compound by sodium periodate. It would be expected (see reaction equation) that an excess of the oxidant would generate in quantitative manner one mole of formaldehyde, two moles of formic acid and one mole of the aldehyde (X), and that three moles of the oxidant would be reduced. Luckily, the substance having structure (X) is known; it was produced by v. Pechmann fifty-four years ago through the acid hydrolysis of the oxime (IX) that resulted from the action of alkali on monoacetyl dinitrosoacetone phenylhydrazone (VIII). The quantitative measurements confirmed these expectations, and v. Pechmann's aldehyde (X) was obtained from this oxidation in a high yield.



(X) 2-Phenyl-4-formyl osotriazole (m. p. 70°)



Sodium Periodate Oxidation of Phenyl-D-glucosotriazole.—A suspension of 0.5078 g. of phenyl-D-glucosotriazole in a mixture of 50 cc. of water and 15 cc. of 0.428 M aqueous sodium periodate solution (3.35 molecular equivalents) was agitated at 25° for twenty-four hours; the appearance of the suspended crystals changed from that of long fine needles to shorter and more thickened ones; the crystals were removed by filtration and washed well with cold water, the filtrate and washings being finally adjusted to a volume of 100 cc. and analyzed as described in the following paragraph. The crystals melted at 68–69° and this value was not changed by recrystallization, which was accomplished by dissolving them in sixteen parts of alcohol and adding thirty-two parts of water. The substance possesses a faint sweetish odor, as was noted by v. Pechmann, who records the m. p. as 70°. Warming the crystals in the closed palm of the hand accentuates the odor, which we would describe as being suggestive of that from geraniol. The crystals weighed 0.28 g., which corresponds to 0.84 mole per mole of phenyl-D-glucosotriazole. The method makes this rare and interesting aldehyde, 2-phenyl-4-formyl-osotriazole, easily available from common phenylglucosazone through the easily prepared phenylglucosotriazole.

Anal. Calcd. for $C_9H_7ON_3$: C, 62.41; H, 4.07. Found: C, 62.46; H, 4.07.

The filtrate from the crystals of the aldehyde was analyzed for other oxidation products as follows: one 20-cc. aliquot was titrated for excess periodate by the usual iodine–arsenite procedure and it was found that 3.03 molecular equivalents of oxidant had been reduced; a second 20-cc. aliquot was titrated with 0.1 N sodium hydroxide, using methyl red as indicator, and the observed 7.38 cc. of alkali indicated the production of 1.93 molecular equivalents of formic acid; a third 20-cc. aliquot was added to 100 cc. of 0.4% dimethone solution and the 0.1130 g. of formaldimethone which crystallized corresponded to the formation of 1.01 molecular equivalents of formaldehyde.

The transformation of phenyl-D-glucosazone to phenyl-D-glucosotriazole (m. p. 195–196°, yield 67%) by copper sulfate is apparently a general reaction with all the sugar phenylosazones.

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(6) The systematic name of this compound is 2-phenyl-4-[L-*arabino*-tetrahydroxybutyl]-osotriazole, which indicates in only a veiled way the genetic relationship of the substance to phenyl-D-glucosazone. We give it an alternative common name **phenyl-D-glucosotriazole.** An additional reason for such a designation is the fact that the systematic names in the disaccharide group are so very complicated that common names (phenyllactosotriazole, etc.) seem necessary in those cases and advisable consequently in the monose series.

Crystalline phenylosotriazoles, the sharp melting points and yields of which are indicated, have been prepared by this reaction from the phenylosazones of the following additional sugars; L-sorbose (158–159°, 50%), D-galactose (110–111°, 47%), D-altrose (134–135°, 62%), D-xylose (88–90°, 40%), cellobiose (164–165°, 62%), lactose (180–181°, 62%), and turanose (193–194°, 70%). These will be described at length in a later article. All of them are much more soluble in water than the glucose derivative. The exceptionally low solubility of phenyl-D-glucosotriazole, its ease of spontaneous crystallization, stability and sharply characteristic m. p., rotation and crystalline appearance, lead us to recommend this substance for use in confirming the identity of phenylglucosazone, especially in the case of small samples.

Confirmatory Test for Phenyl-D-glucosazone.—A suspension of 0.2 g. of powdered osazone in a solution composed of 18 cc. water, one cc. 0.5 *N* sulfuric acid, 0.6 g. of copper sulfate pentahydrate and 12 cc. of isopropyl alcohol, is refluxed for one hour, using a piece of porous plate to ensure even boiling. The osazone dissolves within fifteen minutes and the solution shows a deep red color. During the next half hour the red fades to orange and finally to yellowish green. The solution is concentrated on the steam-bath by an air current to about 5 cc.; crystallization of the osotriazole occurs during this operation and is increased by keeping the mixture three hours in the refrigerator. The tan colored precipitate is removed by filtration, washed with water, boiled with 30 cc. water and 0.1 g. decolorizing carbon, and the solution filtered hot. On keeping the colorless filtrate cold overnight the long needle crystals of pure osotriazole separate; wt. 20–40 mg., m. p. 195–196°; 18.3 mg. in 25 cc. pyridine solution rotated α_D −0.23° in a 4-dm. tube, the calculated value being −0.24°. Methyl alcohol may be substituted for isopropyl alcohol in these directions if the refluxing time is increased to two hours; yield, 56 mg., m. p. 195–196°, observed rotation for 50 mg. in 25 cc. of pyridine solution, 4-dm. tube, −0.64°, calculated −0.65°. Obviously, the test would be applicable likewise to a small sample of phenyl-L-glucosazone, and dextro-rotation would be observed for its osotriazole; any aid to the positive detection in nature of the L-forms of glucose, mannose or fructose seems worth mentioning because of the biological interest that is involved.[7]

Phenyllactosotriazole is hydrolyzed by acids at nearly as fast a rate as lactose; on cooling the hydrolysis solution, phenyl-D-glucosotriazole crystallizes rapidly and the filtrate from this substance yields crystalline D-galactose readily after removal of the mineral acid.

Curiosity naturally arises concerning the mode of action of copper sulfate in bringing about so easily this splitting of the phenylosazone molecule to phenylosotriazole and aniline. The gross equation of the reaction does not show any role of the copper salt. Some reduction of the latter is always noticed but this may be the result of side reactions, the occurrence of which is indicated by the fact that the yields of osotriazole are always much below quantitative. The great stability of the osotriazole ring may be the factor underlying the reaction; apparently the presence of the copper salt opens a path by which the reaction can proceed at good speed. Independent of speculations, it is demonstrable that the main reaction takes place in two successive stages, which are visually apparent if conditions are favorable for fairly rapid solution of an osazone. Phenylturanosazone (8.6 g.) was readily soluble in 170 cc. water at 90° to form an ordinary yellow osazone solution; a hot solution of 13 g. of copper sulfate pentahydrate in 90 cc. water was prepared separately; on mixing the two solutions an intense red color appeared instantly, indicating that the formation of the osazone–copper ion complex is instantaneous when the components are in solution; on the steam-bath the solution lightened in color to become orange and finally green, all within ten minutes, which gives an approximate measurement of the speed of the second stage of the reaction in the case of this osazone. The complex is red colored, the osotriazole is colorless and the green color is that of residual copper sulfate in the presence of aniline and products from the side reactions. The following experiment shows the formation of the complex at room temperature: when a mixture of 2 g. of phenyllactosazone and 1 g. of copper sulfate crystals was shaken with 200 cc. of 85% methyl alcohol the osazone and some copper sulfate dissolved in one hour to yield a clear brownish-red solution, which did not change in twenty-four hours. Decanting this solution and removing the copper from it as sulfide, left a light yellow filtrate from which crystalline phenyllactosazone was recovered in good yield by concentration *in vacuo* to 50 cc. When phenylglucosazone is refluxed with aqueous copper sulfate solution no red color is noticed; evidently the rate of solution is so slow that the complex is never present in sufficient quantity to affect the blue or green color of the copper salt. However, in the confirmatory test for phenylglucosazone the rate of solution is rapid and the gradual change of color from red to orange and finally green, is observed. The rate of the second stage of the reaction is doubtless a characteristic of each osazone as it appears to be more rapid for phenylturanosazone than for phenylglucosazone; mild mineral acidity appears to increase the rate of this second stage. The various experiments lead us to believe that the role of the copper sulfate in the osazone–osotriazole reaction is that of a promoter which forms an unstable complex with the osazone and thereby opens a path for a speedy formation of the highly stable osotriazole ring by the splitting out of aniline from the osazone.

Thanks are expressed to Dr. W. T. Haskins for assistance in the experimental work and to Dr. A. T. Ness for carrying out the microchemical analyses.

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(7) Although L-glucose has been reported to occur in *Grindelia robusta* [Power and Tutin, *Pub. Wellcome Chem. Research Lab.*, **57**, 1 (1905)], in capsularin, a glycoside from jute (*Corchorus capsularis*) [Saha and Choudhury, *J. Chem. Soc.*, **121**, 1044 (1922)], and collagen [Beek, THIS JOURNAL, **63**, 1483 (1941); *J. Research Natl. Bur. Standards*, **27**, 507 (1941)], the evidence is not conclusive in any case.

Summary

The preparation of a new type of sugar derivative is described. The heating of a suspension of phenyl-D-glucosazone with an aqueous solution of copper sulfate causes the production of aniline and a very stable substance which proves to be a substituted osotriazole, now named phenyl-D-glucosotriazole. Proof of the structure of the substance has been obtained through the oxidation by sodium periodate to yield v. Pechmann's 2-phenyl-4-formyl-osotriazole. The role played by the copper sulfate apparently concerns an osazone-copper ion complex, of deep red color, the formation of which is readily observable in the case of easily soluble osazones. Phenyllactosotriazole is hydrolyzed by mineral acids at nearly as fast a rate as lactose and yields phenyl-D-glucosotriazole and D-galactose. The phenylosotriazoles from several other sugars are mentioned, in advance of later full publication; the reaction is a general one for sugar phenylosazones and the yields are good. Owing to the very low solubility of phenyl-D-glucosotriazole and its high tendency to crystallize, its production from phenyl-D-glucosazone is a useful confirmatory test for the latter substance, especially for small quantities of it.

BETHESDA, MARYLAND RECEIVED FEBRUARY 16, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Hydrolysis of Trimethylethylene Bromide. Mechanism of Ketone Formation

BY C. M. SUTER[1a] AND HARRY D. ZOOK[1b]

It has long been known that the hydrolysis of certain olefin bromides results in the formation of carbonyl compounds. Eltekoff[2] obtained acetaldehyde and ethylene glycol from ethylene bromide or chloride, acetone and propionaldehyde from the propylene halides, isobutyraldehyde from isobutylene bromide and methyl isopropyl ketone from trimethylethylene bromide. His procedure consisted in heating the halide with lead oxide and water to 140-150°. The formation of methyl isopropyl ketone also has been studied by Ipatieff[3a] and more recently by Whitmore and Evers,[3b] who found the use of lead oxide or a high temperature unnecessary. This reaction is now the most convenient source of the ketone.[4] Some other olefin bromides give aldehydes or ketones on hydrolysis but the yields are not large.[5]

Little consideration has been given to the mechanism by which the olefin halides are converted to the carbonyl compounds. Eltekoff[2] found that the longer a halide was heated with water and lead oxide the larger the yield of aldehyde or ketone and the smaller the amount of glycol. He concluded, therefore, that the dehydration of the glycol in the slightly acidic solution was the source of the carbonyl compound. He further found that trimethylethylene glycol was converted to the ketone when its aqueous solution was heated to 220°. Ayres[6] has shown that tetramethylethylene bromohydrin when heated to 100° in the dry state or when shaken with aqueous silver nitrate or oxide yields pinacolone directly without intervention of the glycol. Some time ago Whitmore[7] suggested that ketone formation from a dibromide occurred without involving either a bromohydrin or glycol as an intermediate.

$$(CH_3)_2CBrCHBrCH_3 \xrightarrow{H_2O} [(CH_3)_2C^+CHBrCH_3] \longrightarrow$$

$$[(CH_3)_2CHC^+BrCH_3] \xrightarrow{H_2O} (CH_3)_2CHCOCH_3$$

However, behavior of indene bromide where the halogen adjacent to the benzene ring shows about the same activity as that of a tertiary alkyl halide, is not in accord with this mechanism.[8] Here indene bromohydrin is the primary hydrolysis product and this may be converted to 1-indanone or through the glycol to 2-indanone. If the bromohydrin were an intermediate in the hydrolysis of trimethylethylene bromide, ketone formation could occur either directly with the shift of a methyl group or indirectly by way of the glycol, but in the case of isobutylene bromide, the bromohydrin should give methyl ethyl ketone, whereas only isobutyraldehyde has been observed. Here, at least, it seemed clear that if the bromohydrin is an intermediate, so also is the glycol. In the present investigation a detailed study has been made of the hydrolysis of trimethylethylene and isobutylene bromides, mostly in dioxane-water mixtures.

As was pointed out recently by Vaughan and Rust,[9] pure trimethylethylene bromide has not been described. The action of bromine upon *t*-amyl alcohol gives a product from which a mix-

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(1) (a) Present address, Winthrop Chemical Company, Rensselaer, N. Y. (b) Present address, Pennsylvania State College, State College, Pa.

(2) Eltekoff, *J. Russ. Phys.-Chem. Soc.*, **10**, 215 (1878); *Ber.*, **11**, 989 (1878).

(3) (a) Ipatieff, *J. prakt. Chem.*, (2) **53**, 266 (1896); (b) Whitmore and Evers, THIS JOURNAL, **55**, 812 (1933).

(4) Whitmore, Evers and Rothrock, "Organic Syntheses," **13**, 68 (1933); Calonge, *Bull. soc. chim.*, [5] **3**, 501 (1936).

(5) Froebe and Hochstetter, *Monatsh.*, **23**, 1082 (1902); Evers, Rothrock, Woodburn, Stahly and Whitmore, THIS JOURNAL, **55**, 1136 (1933).

(6) Ayres, *ibid.*, **60**, 2956 (1938).

(7) Whitmore, *ibid.*, **54**, 3274 (1932).

(8) Porter and Suter, *ibid.*, **57**, 2022 (1935).

(9) Vaughan and Rust, *ibid.*, **61**, 215 (1939); Conn, Kistiakowsky and Smith, *ibid.*, **61**, 216 (1939).