alkylaminoethanols and monoalkylamino-β,β-dimethylethanols with various organic acids have been prepared.

2. The reaction of a monoalkylaminoethanol with an aromatic acid chloride in the presence of aqueous alkali results in the formation of an N-alkyl-N-(β-hydroxyethyl) amide.

3. The β-hydroxyamides formed can be rearranged to corresponding β-alkylaminoethyl esters by treatment with strong acid.

4. A new method for the preparation of mono-alkylaminoethyl esters has been described, which consists in allowing the corresponding amino alcohol and aromatic acid to react in the presence of concentrated sulfuric acid.

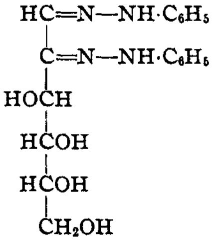
NEW YORK, N. Y. RECEIVED JANUARY 16, 1945

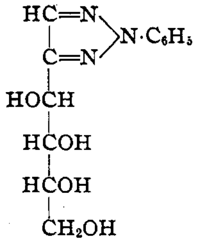
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

The Action of Copper Sulfate on the Phenyl Osazones of the Sugars. II. Some New Osotriazoles

BY W. T. HASKINS, RAYMOND M. HANN AND C. S. HUDSON

Recently[1] it was shown that phenyl D-glucosazone (I) was readily decomposed in hot aqueous copper sulfate solution with the formation of a compound (II) to which the common name phenyl D-glucosotriazole was given. Because of its great stability, low solubility, spontaneity of crystallization, high specific rotation ($[\alpha]^{20}D$ −81.6° in pyridine) and sharp melting point (195–196°) this osotriazole proves to be a valuable reference substance in confirming the identity of phenyl D-glucosazone.


(I)
Phenyl D-glucosazone


(II)
Phenyl D-glucosotriazole

The transformation of sugar phenyl osazones to phenyl osotriazoles by copper sulfate is apparently a general reaction, as is evident from the conversion of typical phenyl osazones of the pentose (D-xylose), hexose (D-galactose, D-altrose and L-sorbose) and compound sugars (lactose, cellobiose, maltose and turanose) to the corresponding phenyl osotriazoles. The ready formation from phenyl turanosazone of crystalline phenyl D-turanosotriazole[2] (m. p. 193–194°; $[\alpha]^{20}D$ +74.5° in water) and the acid hydrolysis of the latter derivative, as well as that of phenyl D-maltosotriazole, to form D-glucose and phenyl D-glucosotriazole (II) constitute proof that the phenyl osazones of turanose and maltose have an atom of nitrogen attached to each of their carbon atoms at positions 1 and 2 and are accordingly osazones of normal structure.

In the present communication we describe the preparation of the phenyl osotriazoles from xylose, galactose, sorbose, altrose, lactose and cellobiose and some of their acetyl and benzoyl derivatives. Thanks are expressed to Mr. Harry W. Diehl for assistance in the experimental work and to Dr. A. T. Ness for carrying out the microchemical analyses.

Experimental

Phenyl D-Xylosotriazole (III).—A solution of 20.0 g. of phenyl D-xylosazone and 16.7 g. (1.1 molecular equivalents) of copper sulfate pentahydrate in 1200 cc. of water was heated to boiling under a reflux condenser for thirty minutes, allowed to cool to room temperature and filtered to separate the fine red precipitate which had deposited. The filtrate was concentrated *in vacuo* to a volume of 25 cc., diluted with 10 cc. of absolute alcohol, and allowed to stand at 5° for eighteen hours; the crystalline precipitate which had formed was separated by filtration and recrystallized several times from 100 parts of warm ether. The yield was 5.8 g. (40%). The pure phenyl D-xylosotriazole melted at 88–90°, showed $[\alpha]^{20}D$ −32.3° in aqueous solution (*c*, 0.81), and crystallized as colorless, glistening plates; it is soluble in cold methyl and ethyl alcohols, acetone and acetic acid, warm ether, chloroform and benzene, and nearly insoluble in cold ether, chloroform, benzene and petroleum ether.

Anal. Calcd. for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57. Found: C, 56.13; H, 5.46.

Phenyl D-Xylosotriazole Triacetate.—A solution of 1.0 g. of phenyl D-xylosotriazole in a mixture of 5 cc. of pyridine and 5 cc. of acetic anhydride was allowed to stand at 20° for forty-eight hours and then poured upon crushed ice. The mixture was extracted with chloroform and the washed extract was concentrated by a current of air to a sirup which was crystallized by cooling, with ether and Dry Ice, its solution in a mixture of ether and petroleum ether. The compound was recrystallized from 5 parts of alcohol; it formed small elongated plates which melted at 57–58° and rotated $[\alpha]^{20}D$ −62.4° in chloroform (*c*, 0.83). The yield of pure product was 2.4 g. or 77%. It is readily soluble in cold methyl and ethyl alcohols, acetone, acetic acid and benzene and nearly insoluble in petroleum ether.

Anal. Calcd. for $C_{17}H_{19}N_3O_6$: C, 56.50; H, 5.30; CH_3CO, 35.7. Found: C, 56.57; H, 5.33; CH_3CO, 35.6.

Phenyl D-Xylosotriazole Tribenzoate.—To an ice-cold solution of 1.0 g. of phenyl D-xylosotriazole in 10 cc. of pyridine, 2.5 cc. of benzoyl chloride was added and the mixture was allowed to stand for twenty-four hours at 20° and then poured upon crushed ice. The reaction product was extracted with chloroform and the washed chloroform extract was evaporated to a sirup and dissolved in 10 cc. of absolute alcohol. The tribenzoate crystallized as small irregularly shaped prisms which after

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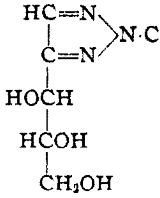
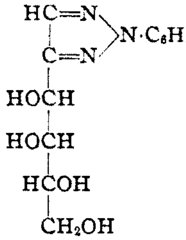
[1] Hann and Hudson, THIS JOURNAL, **66**, 735 (1944).

[2] Hudson, *J. Org. Chem.*, **9**, 470 (1944).



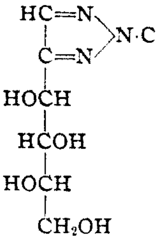
(III)

Phenyl D-xylosotriazole



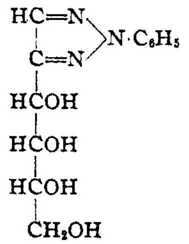
(IV)

Phenyl D-galactosotriazole



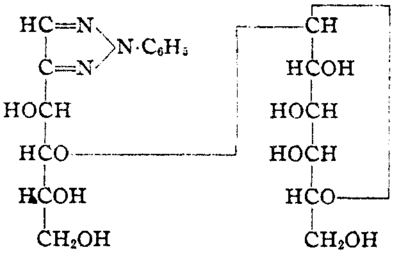
(V)

Phenyl L-sorbosotriazole



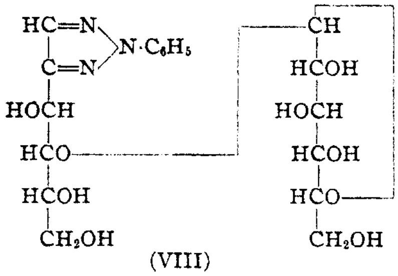
(VI)

Phenyl D-altrosotriazole



(VII)

Phenyl lactosotriazole



(VIII)

Phenyl cellobiosotriazole

recrystallization from 15 parts of absolute alcohol to constant rotation melted at 78–79° and showed a specific rotation $[\alpha]^{20}D$ −24.3° (*c*, 0.80) in chloroform. The yield was 2.0 g. (87%). The compound was readily soluble in cold acetone, acetic acid, chloroform and benzene and in hot methyl and ethyl alcohols and nearly insoluble in cold methyl and ethyl alcohols, water and petroleum ether.

Anal. Calcd. for $C_{32}H_{25}N_3O_6$: C, 70.19; H, 4.60; C_6H_5CO, 57.6. Found: C, 70.02; H, 4.59; C_6H_5CO, 57.3.

Phenyl D-Galactosotriazole (IV).—A solution of 20 g. of phenyl D-galactosazone and 15.4 g. of copper sulfate pentahydrate in 1200 cc. of water was refluxed for one hour, the precipitate was separated by filtration, and the filtrate was concentrated *in vacuo* to a volume of 25 cc., diluted with 20 cc. of absolute alcohol and allowed to stand at 5° for eighteen hours. The precipitate (11.0 g.) of light yellow crystals was removed and the mother liquor was concentrated to half volume and kept at 2° overnight to yield a further 7.0 g. of product. These fractions, which in addition to the osotriazole contained some aniline sulfate, were combined and recrystallized several times from 5 parts of water. The pure phenyl osotriazole crystallized in the form of minute plates which melted at 110–111° and showed specific rotations $[\alpha]^{20}D$ −13.3° in chloroform (*c*, 0.20) and −30.6° in pyridine (*c*, 0.29). The compound is readily soluble in warm methyl and ethyl alcohols, less soluble in warm acetone and relatively insoluble in ether. The yield was 7.0 g. (47%).

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.44; H, 5.60; N, 15.77.

Phenyl D-Galactosotriazole Tetraacetate.—The acetylation of 2.0 g. of phenyl D-galactosotriazole in pyridine solution by acetic anhydride gave 3.1 g. (94%) of the tetraacetate. This compound, which was readily soluble in chloroform, pyridine, ethyl acetate, toluene and acetone and nearly insoluble in water and cold dioxane, crystallized in the form of glistening prisms which melted at 105–106° and rotated $[\alpha]^{20}D$ −28.3° in chloroform (*c*, 0.84).

Anal. Calcd. for $C_{20}H_{23}N_3O_8$: C, 55.42; H, 5.35; CH_3CO, 39.7. Found: C, 55.37; H, 5.26; CH_3CO, 39.4.

Phenyl D-Galactosotriazole Tetrabenzoate.—Benzoyl chloride (4.0 cc.) was added dropwise to an ice-cold solution of 1.0 g. of phenyl D-galactosotriazole in 10 cc. of pyridine. After standing for forty-eight hours at 22° the mixture was poured into cold water and the reaction product was extracted with chloroform. The solid which remained upon evaporation of the chloroform extract was recrystallized from 25 parts of absolute alcohol. The tribenzoate crystallized as small irregularly shaped prisms which melted at 93–94° and showed a specific rotation $[\alpha]^{20}D$ +6.5° in chloroform (*c*, 0.85). It is soluble in chloroform, acetone and ethyl acetate and nearly insoluble in water. The yield was 2.2 g. (85%).

Anal. Calcd. for $C_{40}H_{31}N_3O_8$: C, 70.47; H, 4.58; C_6H_5CO, 61.7. Found: C, 70.47; H, 4.53; C_6H_5CO, 61.9.

Phenyl L-Sorbosotriazole (V).—A suspension of 10.0 g. of phenyl L-sorbosazone in a solution of 7.7 g. of copper sulfate pentahydrate in 1200 cc. of water was heated to boiling under a reflux condenser. Solution of the phenyl osazone and the concurrent development of a red color occurred in ten minutes and shortly thereafter a fine red precipitate was deposited from the solution. After thirty minutes, the precipitate was separated by filtration and on concentrating the filtrate *in vacuo* to 500 cc. crystallization occurred; the fine needles (2.4 g.) were filtered from the cooled solution and a second crop of 1.3 g. (total yield, 3.7 g.; 50%) was obtained by concentration of the mother liquor. The phenyl osotriazole, upon recrystallization from 20 parts of water, formed colorless slender prisms which melted at 158–159° and rotated $[\alpha]^{20}D$ −46.7° in pyridine (*c*, 0.80). The substance is practically insoluble in chloroform, ether, acetone, cold alcohol and cold water and soluble in pyridine, glacial acetic acid and hot water.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70. Found: C, 54.50; H, 5.64.

Phenyl L-Sorbosotriazole Tetraacetate.—This compound was obtained in quantitative yield by the acetylation of the phenyl osotriazole in pyridine solution with acetic anhydride. It was recrystallized by solution in 5 parts of warm alcohol and the addition of 4 parts of water; the colorless elongated plates melted at 95–96° and showed a specific rotation $[\alpha]^{20}D$ −104.6° in chloroform (*c*, 0.81). The compound is soluble in alcohol, ether, acetone and chloroform and nearly insoluble in water and petroleum ether.

Anal. Calcd. for $C_{20}H_{23}N_3O_8$: C, 55.42; H, 5.35; CH_3CO, 39.7. Found: C, 55.30; H, 5.23; CH_3CO, 39.7.

Phenyl L-Sorbosotriazole Tetrabenzoate.—This compound was obtained in quantitative yield by the benzoylation of phenyl L-sorbosotriazole in cold pyridine solution with benzoyl chloride. It crystallized from its solution in 25 parts of alcohol as clusters of minute rod-like crystals which melted at 124–125° and rotated $[\alpha]^{20}\text{D}$ −47.8° in chloroform (*c*, 0.88). The tetrabenzoate is soluble in ether, chloroform, acetone and hot alcohol and nearly insoluble in water, petroleum ether and cold alcohol.

Anal. Calcd. for $C_{40}H_{31}N_3O_8$: C, 70.47; H, 4.58; C_6H_5CO, 61.7. Found: C, 70.36; H, 4.64; C_6H_5CO, 61.3.

Sodium Periodate Oxidation of Phenyl L-Sorbosotriazole.—To a suspension of 0.2072 g. of phenyl L-sorbosotriazole in 25 cc. of water was added 7.0 cc. of 0.432 *M* aqueous sodium periodate (3.88 molecular equivalents) and the mixture was agitated at room temperature (22°) on a shaking machine. The solid phase changed from long slender prismatic crystals to shorter and more thickened ones; after twenty-one hours the change seemed complete and the crystals of the new type were separated by filtration and recrystallized by solution in 2 cc. of alcohol and the addition of 4 cc. of water. They melted at 68–69° in agreement with the melting point of 2-phenyl-4-formylosotriazole obtained previously[1] by the similar oxidation of phenyl D-glucosotriazole; a mixed melting point with the aldehyde from that source showed no depression. Following the filtration of the aldehyde, analyses of the aqueous filtrate showed that 3.25 molecular equivalents of sodium periodate had been consumed and 1.98 molecular equivalents of formic acid had been generated. The agreement of these data with those obtained in the oxidation of phenyl D-glucosotriazole is a proof of the structure of phenyl L-sorbosotriazole and confirmation of the view that the transformation of sugar phenyl osazones to phenyl osotriazoles by copper sulfate is a general reaction.

Phenyl D-Altrosotriazole (VI).—The phenyl D-altrosotriazole was obtained in a yield of 4.6 g. (62%) upon treatment of 10 g. of phenyl D-altrosazone by the method employed for the preparation of phenyl L-sorbosotriazole. The substance was purified by recrystallization from 5 parts of water; it formed clusters of fine rod-like crystals which melted at 134–135° and showed a specific rotation $[\alpha]^{20}\text{D}$ +28.0° in pyridine (*c*, 0.84). It is soluble also in glacial acetic acid, warm water and warm alcohol and nearly insoluble in ether, chloroform, acetone, cold water and cold alcohol.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70. Found: C, 54.36; H, 5.85.

Phenyl Lactosotriazole (VII).—A suspension of 10 g. of phenyl lactosazone in one liter of water was heated to the boiling point and a solution of 5.3 g. of copper sulfate pentahydrate (1.1 molecular equivalents) in 100 cc. of water was added. Solution of the phenyl osazone took place rapidly and a finely divided red precipitate was deposited from the solution. The mixture was heated under reflux for thirty minutes from the time of addition of the copper sulfate solution, then cooled and filtered; the copper still present in the solution was removed as sulfide and the filtrate, after neutralization with 4.0 g. of calcium carbonate, was extracted with ether to remove aniline and then concentrated *in vacuo* to dryness. The crystalline residue was extracted with hot alcohol and the reaction product (5.1 g.; 62%) which crystallized from the extract was recrystallized from 14 parts of alcohol, separating as clusters of glistening elongated platelets which melted at 180–181° and rotated $[\alpha]^{20}\text{D}$ −43.6° in water (*c*, 0.80). It is soluble in pyridine and nearly insoluble in acetone, ether and cold alcohol.

Anal. Calcd. for $C_{18}H_{25}N_3O_9$: C, 50.58; H, 5.90. Found: C, 50.54; H, 5.80.

Phenyl Cellobiosotriazole (VIII).—Phenyl cellobiosazone was converted to the corresponding osotriazole by the same procedure that has been described for the lactose derivative. The impure phenyl osotriazole (5.1 g.; 62%) was recrystallized from 5 parts of alcohol or 18 parts of absolute alcohol; the pure crystals of phenyl cellobiosotriazole formed clusters of small elongated prisms which rotated $[\alpha]^{20}\text{D}$ −50.8° in water and melted at 164–165°. The compound is soluble in pyridine and hot alcohol and nearly insoluble in acetone, ether and cold alcohol.

Anal. Calcd. for $C_{18}H_{25}N_3O_9$: C, 50.58; H, 5.90. Found: C, 50.65; H, 5.86.

Phenyl Cellobiosotriazole Heptaacetate.—The acetylation of 1.0 g. of phenyl cellobiosotriazole in pyridine solution by acetic anhydride at room temperature (23°) for twenty-four hours gave a quantitative yield (1.7 g.) of the heptaacetate. The latter compound was recrystallized from 7 parts of alcohol; it formed small glistening plates which melted at 130–131° and rotated $[\alpha]^{20}\text{D}$ −35.5° in chloroform (*c*, 0.88); it is soluble in ether, benzene and hot alcohol and nearly insoluble in water, petroleum ether and cold alcohol.

Anal. Calcd. for $C_{32}H_{39}N_3O_{16}$: C, 53.26; H, 5.45; CH_3CO, 41.8. Found: C, 53.32; H, 5.45; CH_3CO, 41.7.

Summary

Attention is directed to the general nature of the reaction of hot aqueous solutions of copper sulfate with the phenyl osazones of the sugars, which is evident from the preparation of typical phenyl osotriazoles from pentose, hexose and disaccharide phenyl osazones. The phenyl osotriazoles of D-xylose, D-galactose, D-altrose, L-sorbose, lactose and cellobiose, and several of their acetyl and benzoyl derivatives, are described.

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