# **692.** *The Scope and Mechanism of Carbohydrate Osotriazole Formation. Part I. The Action of Copper Sulphate on Glucose Methylphenylosazone and Glucose 2-N'-Methyl-1-N' : 2-N'-diphenylosazone.*

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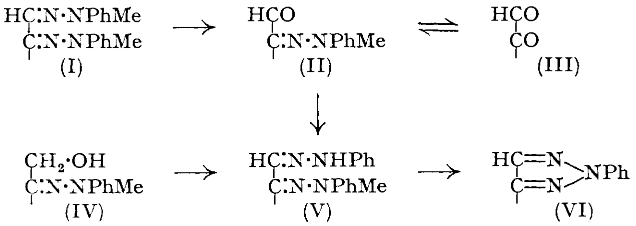
Under the action of copper sulphate glucose 2-*N'*-methyl-1-*N'* : 2-*N'*-diphenylosazone (V) gives an osotriazole, but glucose *N*-methyl-*N*-phenylosazone (I) loses its hydrazone residues stepwise, finally yielding glucosone. This difference is attributed to the presence in the former of hydrogen attached to nitrogen.

Carbohydrate phenylosazones are converted into phenylosotriazoles (VI) and aniline when refluxed in suspension in aqueous copper sulphate (Hann and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 735). Osazones derived from other aromatic monosubstituted hydrazines behave similarly (Hardegger and El Khadem, *Helv. Chim. Acta*, 1947, **30**, 1949; 1950, **33**, 253).

For a similar reaction osazones derived from disubstituted hydrazines would require to lose one of the groups attached to nitrogen, and this seems unlikely. In accordance with this, the reaction of glucose methylphenylosazone (I) with aqueous copper sulphate, although vigorous, was found to yield glucosone 2-methylphenylhydrazone (II), one hydrazone residue being eliminated by hydrolysis. On further treatment of (II), or on prolonged treatment of (I), with copper sulphate the second hydrazone residue was also eliminated and glucosone (III) was obtained in nearly 80% yield. This behaviour is similar to that of carbohydrate hydrazones, which with copper sulphate yield the parent sugar nearly quantitatively; the hydrazones are first hydrolysed and the hydrazines produced are then oxidised with copper sulphate (El Khadem, Diss., Zurich, 1950).

The structure of (II) was established by comparison with glucosone methylphenylhydrazone prepared, according to Fischer (*Ber.*, 1889, **22**, 90), by treating glucosone (III) with *N*-methyl-*N*-phenylhydrazine; the crystalline tetra-acetates and tetrabenzoates were also identical. Fischer did not establish whether the methylphenylhydrazone residue was attached to $C_{(1)}$ or $C_{(2)}$. To settle this, the hydrazone (II) was treated with phenylhydrazine; the resultant mixed osazone (V) was identical with glucose 2-*N'*-methyl-1-*N'* : 2-*N'*-diphenylosazone, (V), prepared according to Percival (*J.*, 1941, 750) by treating fructose methylphenylhydrazone (IV) with phenylhydrazine.



$$\begin{tikzcd} \begin{array}{l} HC{:}N{\cdot}NPhMe \\ \;C{:}N{\cdot}NPhMe \\ \quad (I) \end{array} \arrow[r] & \begin{array}{l} HCO \\ \;C{:}N{\cdot}NPhMe \\ \quad (II) \end{array} \arrow[r, shift left] \arrow[d] & \begin{array}{l} HCO \\ \;CO \\ \quad (III) \end{array} \arrow[l, shift left] \\ \begin{array}{l} CH_2{\cdot}OH \\ C{:}N{\cdot}NPhMe \\ \quad (IV) \end{array} \arrow[r] & \begin{array}{l} HC{:}N{\cdot}NHPh \\ \;C{:}N{\cdot}NPhMe \\ \quad (V) \end{array} \arrow[r] & \begin{array}{l} HC{=}N \\ \;C{=}N \end{array}\!\!>NPh \\ & & \quad (VI) \end{tikzcd}$$

Glucose 2-*N'*-methyl-1-*N'*- : 2-*N'*-diphenylosazone (V) with copper sulphate yielded glucose phenylosotriazole and methylaniline; this osazone has a hydrogen atom attached to a nitrogen atom, resembling in this respect the simple osazones. Osotriazole formation probably takes place by the elimination of this hydrogen atom together with the NPhMe group from the neighbouring methylphenylhydrazone residue, forming methylaniline.

These experiments indicate that for the conversion of an osazone into an osotriazole at least one hydrazone residue must carry a hydrogen atom attached to the nitrogen atom. If this hydrogen atom is replaced by an alkyl group stepwise hydrolysis of the hydrazine residue occurs, yielding, as final product, the osone in good yield. The latter reaction can advantageously be used as a starting point for the synthesis of ascorbic acid analogues.

Further experiments are in progress.

## EXPERIMENTAL

*Glucosone* 2-*Methylphenylhydrazone.*—Glucose methylphenylosazone (7 g.) in dioxan (100 ml.) was added in portions to a boiling solution of copper sulphate (5 g.) in water (100 ml.); after the initial vigorous reaction had subsided the mixture was refluxed for 10 min. and filtered hot from the precipitated copper. The excess of copper sulphate was removed by passing in hydrogen sulphide, filtering, adding barium carbonate, and filtering again. The clear filtrate was evaporated to dryness; on addition of a few drops of methanol the residue crystallised and was purified by recrystallisation from hot water. The pure product, which was faintly yellow, melted at 168°, alone or mixed with glucosone methylphenylhydrazone prepared by Fischer's method (*loc. cit.*) (Found: C, 55·2; H, 6·6; N, 10·1. Calc. for $C_{13}H_{18}O_5N_2$: C, 55·3; H, 6·4; N, 9·9%); it had $[\alpha]_D$ −266° (*c*, 1·15 in pyridine).

The *tetra-acetate*, m. p. and mixed m. p. 118° (from methanol), $[\alpha]_D$ +83° (*c*, 1 in MeOH) (Found: C, 55·8; H, 5·9; N, 6·5. $C_{21}H_{26}O_9N_2$ requires C, 56·0; H, 5·8; N, 6·2%), and *tetrabenzoate*, m. p. and mixed m. p. 187° (from methanol), $[\alpha]_D$ +38° (*c*, 1·09 in $CHCl_3$) (Found: C, 70·6; H, 5·1; N, 4·3. $C_{41}H_{34}O_9N_2$ requires C, 70·5; H, 4·9; N, 4·1%), were prepared from both samples of the hydrazone by treatment with acetic anhydride or benzoyl chloride respectively in pyridine for 24 hr. at room temperature.

*Glucosone.*—(a) *From glucosone* 2-*methylphenylhydrazone.* The hydrazone (0·5 g.) was suspended in water (10 ml.) and added in portions to a boiling solution of copper sulphate (0·5 g.) in water (12 ml.), and the mixture was refluxed for 1 hr. and filtered hot. The filtrate was freed from excess of copper sulphate as above, decolourised with charcoal, and evaporated to dryness, giving a colourless glassy mass of glucosone. To eliminate all traces of inorganic matter, the crude osone was redissolved in water (20 ml.) and passed through a cation-exchange and then through an anion-exchange resin. On evaporation of the solution, glucosone was obtained (0·5 g., 79%), having $[\alpha]_D$ −3° (*c*, 1 in $H_2O$).

(b) *From glucose methylphenylosazone.* The osazone (2 g.) was suspended in a solution of copper sulphate (1 g.) in water (25 ml.). The mixtue was refluxed for 1 hr., filtered hot, and then treated as in (a). The product (0·7 g., 75%) had $[\alpha]_D$ −3° (*c*, 1·1 in $H_2O$).

A 10% solution of this glucosone in water (15 ml.) reacted in the cold with phenyl hydrazine (2 g.) and acetic acid (0·5 ml.) to give glucose phenylosazone (2·9 g., 97%).

When the glucosone was applied to Whatmann No. 1 filter paper, chromatographed with collidine, and sprayed with ammoniacal silver nitrate only one spot developed which had $R_F$ = 0·21; the $R_F$ value in phenol–water was 0·13. No movement occurred with butanol saturated with water.

*Glucose* 2-N′-*Methyl*-1-N′ : 2-N′-*diphenylosazone.*—Glucose methylphenylhydrazone (1 g.) in water (5 ml.) was treated with phenylhydrazine (0·4 g.) in 10% acetic acid (5 ml.) and left at 30° for 2 hr. The crystalline osazone which separated was twice recrystallised from alcohol–water; it had m. p. 193°, $[\alpha]_D$ $-59·7° \longrightarrow +5°$ (*c*, 1·09 in pyridine) (Found: C, 61·6; H, 6·7; N, 15·2. Calc. from $C_{19}H_{24}O_4N_4$: C, 61·3; H, 6·6; N, 15·1%).

This osazone, prepared by Percival's method (*loc. cit.*), had m. p. and mixed m. p. 193°, $[\alpha]_D$ $-59·5° \longrightarrow +6°$ (*c*, 1 in pyridine) (Found: C, 61·1; H, 6·6%).

*Glucose Phenylosotriazole.*—The foregoing osazone (0·5 g.) was suspended in water (10 ml.) and added in portions to a boiling solution of copper sulphate (0·5 g.) in water (10 ml.), then refluxed for 1 hr. and filtered hot. The filtrate was freed from excess of copper sulphate as before, the solution evaporated to dryness, and the residue (0·25 g.) recrystallised from ethanol. The product had m. p. and mixed m. p. 196°, $[\alpha]_D$ −81·7° (*c*, 1 in pyridine).

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