Note

Action of Cu(II) salts on osazones: side reactions of osotriazole formation

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It is known¹⁻³ that sugar phenylosazones undergo cyclization in aqueous CuSO₄ to give phenylosotriazoles in yields ranging from 45-70%. In order to identify the side reactions responsible for the low yields, Cu(II) salts were treated with two bis(phenylhydrazones) and two mono(phenylhydrazones) and the products analyzed by g.l.c.m.s. and h.p.l.c. The substrates used were *D*-arabino-hexulose phenylosazone, benzil bis(phenvlhydrazone), D-mannose phenvlhydrazone, and benzaldehyde phenvlhydrazone. It was found that all four coumpounds underwent hydrolysis⁴ to give the parent carbonyl compound and phenylhydrazine. During the reaction, phenylhydrazine was oxidized to benzene, nitrogen, and water by the Cu(II) salt, which explains why reduced Cu and Cu₂O are procipitated during osotriazole formation⁵. The mono(phenylhydrazones) studied afforded hydrolysis products, whereas the bis(phenylhydrazones) yielded cyclization and hydrolysis products. Thus, D-mannose phenylhydrazone yielded mannose and benzene, whereas benzaldehyde phenylhydrazone yielded benzaldehyde and benzene, all in quantitative yields (see Table I). Treatment of *D*-arabino-hexulose phenylosazone with CuSO₄ afforded two cyclization products, D-arabino-hexulose phenylosotriazole and aniline, in 68% yield and two hydrolysis products, D-arabinohexosulose and benzene, in 11% yield. Because of the low solubility of benzil bis-

TABLE I

Starting hydrazones	Salt	Yield of products (%)	
		Triazole and aniline	Carbonyl compds. and benzene
D-arabino-Hexulose phenylosazone	CuSO,	68	11
Benzil bis(phenylhydrazone)	CuCl,	50	6
D-Mannose phenylhydrazone	CuSO,	0	100
Benzaldehyde phenylhydrazone	CuSO	0	100

Yields of the main reaction products formed when bis- and mono-(phenylhydrazones) are treated with Cu(II) salts

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(phenylhydrazone) in water, the reaction had to be carried out in ethanol, using CuCl, as catalyst. This resulted in the formation of a large number of chlorinated aromatic compounds by Sandmeyer-type reactions, which decreased the yields of the cyclization and hydrolysis products. As a result, the cyclization products, 2.4.5-triphenyl-1.2.3triazole and aniline, were formed in 50% yield and the hydrolysis products, benzil and benzene, were formed in 6% yield. To identify the by-products, the mixture was separated into basic, neutral, and acidic extracts and fractionated in the gas chromatograph of a g.l.c.-m.s. instrument. The major components were then identified by comparing their mass spectra with the mass spectra of authentic samples or of reference spectra from the NIH library. The basic fraction was found to contain aniline, chloroaniline, and dichloroanilines. The neutral fraction contained 2,4,5-triphenyl-1,2,3-triazole, benzene, and chlorobenzene as well as a degradation product 2-phenyl-1,2,3triazole, of uncertain origin. The acid fraction contained considerable amounts of benzoic acid, probably formed by hydrolytic degradation of benzil (see Table II). The accompanying formulas show possible pathways leading to the formation of these compounds. When glyoxal bis(phenylhydrazone) was treated in the same manner with CuCl₂, it afforded 2-phenyl-1,2,3-triazole, aniline, and benzene as well as some of the by-products obtained from the reaction of benzil bis(phenylhydrazone), such as chlorobenzene, chloroanilines, and benzoic acid. In addition, it yielded several rearrangement products such as biphenyl, chlorobiphenyls, and aminobiphenyls, naphthalene, and naphthylamine (see Table II).



TABLE II

	Benzil bis(phenylhydrazone)	Glyoxal bis(phenylhydrazone)
Basic fraction:	aniline, chloroaniline, dichloroaniline	aniline, chloroaniline, naphthyl- amine, biphenylamine
Neutral fraction:	2,4,5,triphenyl-1,2,3-triazole, 2-phenyl-1,2,3-triazole, benzene, chlorobenzene	2-phenyl-1,2,3-triazole, benzene, biphenyl, naphthalene, chlorobenzene, chlorobiphenyl
Acidic fraction:	benzoic acid	benzoic acid

Products obtained when benzil bis(phenylhydrazone) and glyoxal bis(phenylhydrazone) are refluxed with $CuCl_2$ in ethanol

It seems that cyclization of bis(phenylhydrazones) with $CuSO_4$ or $CuCl_2$ is always accompanied by hydrolysis, which decreases the yield of the triazoles and that the reaction with $CuCl_2$ is accompanied by extensive chlorination and rearrangement not usually observed with $CuSO_4$.

EXPERIMENTAL

General methods. — Benzene was estimated by the head-space method⁶ on a Hewlett–Packard 5995A g.l.c.–m.s. instrument fitted with a bonded FSOT RSL-150 $15m \times 0.25mm$ (0.2µm) column heated from 20 to 150° at a rate of 3°/min. When helium was used as the carrier gas, the retention time of benzene was 4.40 min. H.p.l.c. analysis was performed on a Beckman silica (5µm) column attached to a Waters 501 h.p.l.c. pump. The elution solvent, 1:1 hexane–CH₂Cl₂ was pumped at a rate of 1 mL/min. The detector, a Waters Lambda-Max Model 481 l.c. spectrophotometer was connected to a Hewlett–Packard 3392A intergrator. The retention times of the standards were: benzene, 1.68 min.; aniline, 1.87 min.; benzaldehyde, 4.53 min.; 2,4,5tripheny1-1,2,3-triazole, 4.59 min., and benzil, 5.66 min.

Oxidation of phenylhydrazine. — Phenylhydrazine (5 g) was refluxed in a solution of $CuSO_4 \cdot 5H_2O(10 g)$ in water (50 mL) for 20 h and then left to cool to room temperature. In one set of experiments, head space sample were analysed by g.l.c.-m.s. to confirm the formation of benzene and in another, the benzere formed was distilled and estimated by h.p.l.c. Benzene was produced in quantitative yields.

Reaction of benzil bis(phenylhydrazone) with $CuCl_2$. — (a) Estimation of the main reaction products. A suspension of benzil bis(phenylhydrazone) (5 g) in a solution of $CuCl_2 \cdot 2H_2O$ (10 g) in EtOH (50 mL) was refluxed for 20 h and then cooled to room temperature. Head-space samples analyzed by g.l.c.-m.s. confirmed the presence of benzene, and h.p.l.c. was used to estimate benzene and aniline in the distillate. To estimate 2,4,5-triphenyl-1,2,3-triazole and benzil, the residue of the distillation was extracted with 1:1 hexane-CH₂Cl₂ and analyzed by h.p.l.c. (b) Identification of the by-products of cyclization with $CuCl_2$. A solution of benzil bis(phenylhydrazone) or of glyoxal bis(phenylhydrazone) (10 g) in EtOH (250 mL) was refluxed with $CuCl_2 \cdot 2H_2O$ (5 g) and then diluted with water and extracted with ether. The extract was separated into basic, acidic, and neutral fractions and injected in the g.l.c.-m.s. The major components were identified by comparing their mass spectra with those of authentic samples or of reference spectra from the NIH library of spectra (see Table II).

Reaction of D-arabino-hexulose phenylosazone with $CuSO_4$. — A suspension of the osazone (5 g) in a solution of $CuSO_4 \cdot 5H_2O(10 g)$ in water (50 mL) was refluxed for 20 h. Estimation by h.p.l.c. was carried out as already described under (a).

Hydrolysis of D-mannose phenylhydrazone and benzaldehyde phenylhydrazone with $CuSO_4$. — A suspension of D-mannose phenylhydrazone or benzaldehyde phenylhydrazone (5 g) in a solution of $CuSO_4 \cdot 5H_2O(10 g)$ in water (50 mL) was refluxed for 20 h and then analysed as described under (a).

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