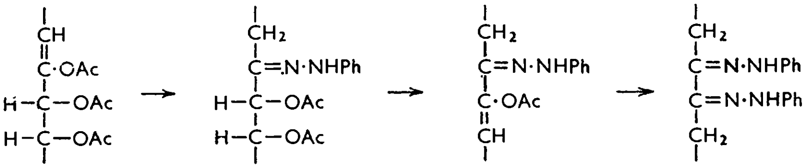
651. *The Reaction of Phenyl- and 2,4-Dinitrophenyl-hydrazine with Some Unsaturated Glucose Derivatives.*

By W. M. Corbett.

The products of reaction of tetra-*O*-acetyl-2-hydroxy-D-glucal, 2-hydroxy-D-glucal, kojic acid, and 2-methoxy-2,3-D-glucal * with phenyl- and 2,4-dinitrophenyl-hydrazine have been examined. The hydrolysis of phenylosazones and alkaline rearrangement of the resulting osones has been described.

The reaction of phenylhydrazine with 2-hydroxy-D-glucal and its acetate has been examined by Bergmann and Zervas.[1] Although the tetra-acetate (I) does not possess a carbonyl group, it reacts readily with phenylhydrazine, giving a phenylosazone whose structure has been shown to be (II). The initial reaction must be attack of the reagent on the 2-acetyl group which is activated by the double bond (cf. Evans's postulation [2] of the occurrence of a similar reaction in alkaline solutions of sugars). It is postulated that this is then followed by a second reaction involving the elimination of the 4-acetyl group, the resulting unsaturated derivative reacting with further reagent to give an osazone.



2-Hydroxyglucal (V) itself reacts with phenylhydrazine in a different way. At room temperature,[1] the product isolated has the structure (VI). The acetyl-free starting material will exist as a mixture of the enol and the carbonyl form, the latter reacting with phenylhydrazine in the normal way to give the osazone. It has now been observed that after reaction at higher temperature, the product has a higher melting point: it is also obtained when Bergmann and Zervas's osazone (VI) is heated with phenylhydrazine and acetic acid. Analysis shows that the osazone undergoes elimination of water at elevated temperatures.

It is well established that water is eliminated when phenylosazones are treated with dilute acid, but the structures of the products have still to be conclusively established. It has been suggested that an anhydro-ring is formed by elimination of water from two hydroxyl groups of the sugar moiety [3] or from a hydroxyl group of the sugar moiety and the amine group of the phenylhydrazine residue.[4] Formation of a cyclic anhydride by either process is unlikely in this particular case because our products are pyranoses, so it is more reasonable that the elimination should be from the sugar unit, yielding an unsaturated derivative. This would lead to an isomer of the phenylosazone (VIII; R = Ph) expected from kojic acid (VII). This derivative (VIII; R = Ph) has been prepared, and shown to differ from the compound prepared from 2-hydroxyglucal. It may be that the relation between the two phenylosazones is similar to that between the similar derivatives of ascorbic acid (IX) and dehydroascorbic acid (X).[5] The reaction of kojic acid with phenyl- and 2,4-dinitrophenyl-hydrazine appears to be normal in that the expected derivatives (VIII) are produced, and, unlike the situation with 2-hydroxyglucal, the

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* 2,3- denotes the position of the double bond.

[1] Bergmann and Zervas, *Ber.*, 1931, **64**, 1434.

[2] Evans, *Chem. Rev.*, 1942, **31**, 537.

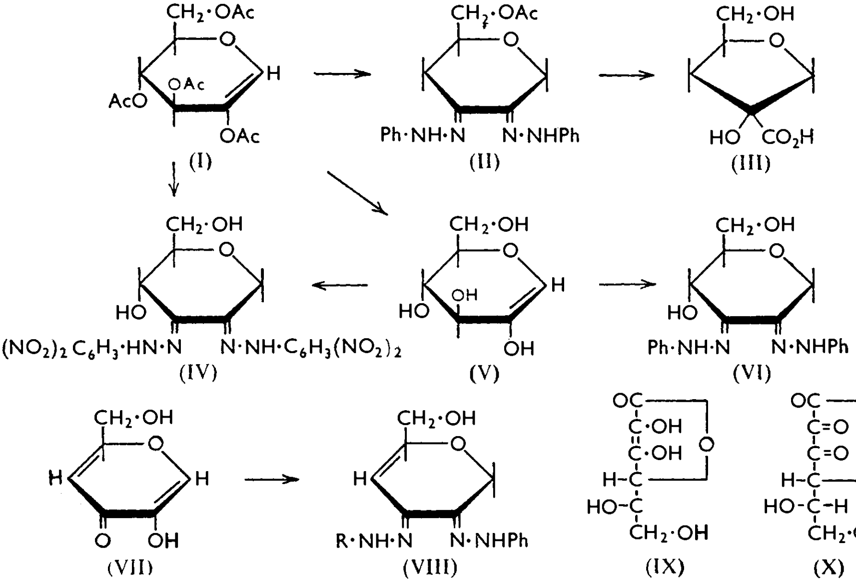
[3] Hardegger and Schreier, *Helv. Chim. Acta*, 1952, **35**, 232, 993; Schreier, Stöhr, and Hardegger, *ibid.*, 1954, **37**, 35, 574; Mester and Major, *J. Amer. Chem. Soc.*, 1955, **77**, 4305.

[4] Percival, *J.*, 1945, 783.

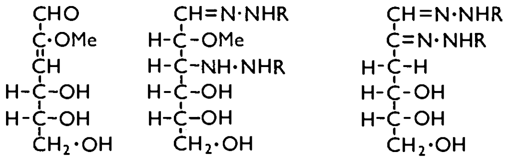
[5] Herbert, Hirst, Percival, Reynolds, and Smith, *J.*, 1933, 1270.

same product is obtained with phenylhydrazine at room temperature and elevated temperatures.

2-Hydroxyglucal tetra-acetate appears not to react with 2,4-dinitrophenylhydrazine in acetic acid or alcohol, possibly owing to the lower reactivity of 2,4-dinitrophenylhydrazine. A solution of the dinitrophenylhydrazine in hydrochloric acid, however, does react with the tetra-acetate. The same product is produced by reaction with 2-hydroxyglucal itself, and analyses indicate structure (IV). Clearly the initial reaction of the reagent with the tetra-acetate is hydrolysis of the acetyl groups.



Kenner and Richards [6] isolated 2-methoxy-2,3-D-glucal * (XI) which with 2,4-dinitrophenylhydrazine gave an osazone whose structure was given as (XIIa). The formation of of such a derivative is contrary to the above findings from which structure (XIIIa) would be predicted. Re-investigation of the osazone has revealed the absence of a methoxyl group.[7] The analyses quoted by Kenner and Richards for the dinitrophenylhydrazine derivative and its triacetate are in close agreement with those calculated for (XIIIa) and its acetate, although the melting point of the osazone is considerably higher than that given for the osazone of 3-deoxy-D-mannose.[8] To provide further evidence for structure (XIII), the phenylhydrazine derivative has been prepared; this too was free from methoxyl groups, and analyses indicated structure (XIIIb).



(XI) (XII) (XIII)

(a) R = $C_6H_3(NO_2)_2$
(b) R = Ph

If the phenylhydrazine derivative is indeed (XIII*b*), it should on mild acid hydrolysis followed by treatment with alkali give α- and β-*meta*saccharinic acid. Because the

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* See footnote, p. 3213.

[6] Kenner and Richards, *J.*, 1956, 2921.

[7] Machell and Richards, personal communication.

[8] Foster, Overend, Stacey, and Vaughan, *J.*, 1953, 3308.

alkaline rearrangement of osones is new, the reactions of glucose phenylosazone and the phenylhydrazine derivative of 2-hydroxyglucal acetate (II) were first examined. Since only small amounts of material were available, the acidic products could be identified only by paper chromatography. Acid-hydrolysis of glucose phenylosazone gave glucosone and a new compound which is probably one of the two possible forms of glucosone monophenylhydrazone, as well as (*a*) a lactone which corresponded to D-mannolactone and (*b*) small amounts of D-gluconolactone. The concentrations of the two lactones increased when the crude material was treated with lime-water. The rearrangement of the osone to acids in acidic solutions is in agreement with Theander's findings.[9] Limited asymmetric synthesis appears to be a feature of the benzilic acid rearrangement of some αβ-dicarbonyl compounds into acids, *e.g.*, the saccharinic acids, of which one form usually predominates. The phenylhydrazine derivative of 2-hydroxyglucal acetate produced an acid which, as expected, was chromatographically identical with the acid of postulated structure (III) produced by the alkaline degradation of hepta-*O*-acetyl-2-hydroxylcellobial.[10] When the phenylhydrazine derivative of 2-methoxy-2,3-D-glucal was similarly treated, a mixture of lactones was isolated which behaved identically with α- and β-*glucometa*saccharolactone. It is evident that the 2,4-dinitrophenylosazone obtained by Kenner and Richards has the structure (XIIIa).

EXPERIMENTAL

Reaction of 2-Hydroxyglucal Tetra-acetate with 2,4-Dinitrophenylhydrazine.—2-Hydroxyglucal tetra-acetate (1·0 g.) was dissolved in ethanol (10 ml.) and the solution was diluted with water (240 ml.), treated with a saturated solution (500 ml.) of 2,4-dinitrophenylhydrazine in 2N-hydrochloric acid, and kept at room temperature for 18 hr. before the bright red precipitate was filtered off and washed with water until free from acid. The product, 1,2,3-*trideoxy*-2,3-*bis*-(2,4-*dinitrophenylhydrazono*)-D-*glucopyranose* (IV) (0·8 g.), had m. p. 186—190°, raised to 234·5—236° by several recrystallisations from acetone—ethanol (Found: C, 41·5; H, 3·4. $C_{18}H_{16}O_{11}N_8$ requires C, 41·5; H, 3·1%).

Reactions of 2-Hydroxyglucal.—(a) *With phenylhydrazine.* 2-Hydroxyglucal (0·80 g.), prepared by a Zemplén deacetylation of the tetra-acetate, was dissolved in 30% acetic acid (10 ml.), and to it was added phenylhydrazine (2 ml.) in 30% acetic acid (4 ml.). The mixture was heated at 95° for $\frac{3}{4}$ hr., and to the cooled solution was added water. The crystals which gradually separated were digested with cold ethanol, then recrystallised twice from ethanol–acetone to give a 1,2,3-*trideoxy*-2,3-*bisphenylhydrazono*-4,5(?)-D-*glucal* * (VI), m. p. 240—241° (Found: C, 67·2; H, 5·6. $C_{18}H_{18}O_2N_4$ requires C, 67·2; H, 5·6%).

Reaction at room temperature gave Bergmann and Zervas's osazone.[1] This (50 mg.) was heated at 90° for 1 hr. with 30% acetic acid (2·5 ml.) and phenylhydrazine (0·5 ml.). On addition of water crystals separated which were digested with ethanol to give an osazone, m. p. 230—235°, undepressed on admixture with that obtained at 95°.

(b) *With 2,4-dinitrophenylhydrazine.* 2-Hydroxyglucal (1·4 g.) was dissolved in a saturated solution (1 l.) of 2,4-dinitrophenylhydrazine in 2N-hydrochloric acid. After several days at room temperature, the red precipitate was centrifuged off, washed with water until free from acid, dried, and extracted with chloroform. Concentration of the extract gave a residue which crystallised from ethanol–acetone to give an osazone (0·2 g.) having m. p. 230—232°, undepressed on admixture with that obtained from the tetra-acetate (Found: C, 41·9, H, 3·1%).

Reaction of Kojic Acid.—(a) *With phenylhydrazine.* Kojic acid (1 g.) was treated in hot water (20 ml.) with phenylhydrazine (1 ml.) in acetic acid (2 ml.), heated at 90° for 1 hr., and then cooled. The dark red syrup which separated was dissolved in a little ethanol and allowed to crystallise. The dark red crystals were filtered off and washed with a little ethanol, to give yellow crystals (0·6 g.). After three recrystallisations from aqueous ethanol, the *phenylosazone* (VIII; R = Ph) had m. p. 169·5—171° (Found: C, 67·3; H, 5·5. $C_{18}H_{18}O_2N_4$ requires C, 67·2; H, 5·6%). Reaction at room temperature gave the same product, m. p. 171—172°.

(b) *With 2,4-dinitrophenylhydrazine.* To 2,4-dinitrophenyhydrazine (1·3 g.) in warm

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* See footnote, p. 3213.

[9] Theander, *Acta Chem. Scand.*, 1958, **12**, 1897.

[10] Corbett and Kidd, *J.*, 1959, 1594.

2N-hydrochloric acid (100 ml.), kojic acid (0·5 g.) was added. The mixture was heated at 70° for 3 hr. during which considerable degradation occurred. The precipitate was crystallised twice from anisole–light petroleum (b. p. 40—60°), to give a 2,4-*dinitrophenylosazone* (0·1 g.), m. p. 221—224° (Found: C, 43·4; H, 3·1. $C_{18}H_{14}O_{10}N_8$ requires C, 43·0; H, 2·8%).

Reactions of 2-*Methoxy*-2,3-D-*glucal*.—(a) *With* 2,4-*dinitrophenylhydrazine*. 2-Methoxy-2,3-D-glucal was prepared and treated with 2,4-dinitrophenylhydrazine as described by Kenner and Richards.[6] The osazone had m. p. 263—264° (Kenner and Richards give m. p. 266—268°, and Foster *et al.*[8] give m. p. 205°, for 3-deoxy-D-mannose 2,4-dinitrophenylosazone) (Found: C, 41·4; H, 3·7; OMe, 0·0. Calc. for $C_{18}H_{18}O_{11}N_8$: C, 41·4; H, 3·5%).

(b) *With phenylhydrazine*. To crude 2-methoxy-2,3-D-glucal (1·28 g.) in water (45 ml.), phenylhydrazine (3 ml.) and acetic acid (3 ml.) were added. After 4 days at room temperature, the precipitate (0·66 g.) was filtered off and digested with ether, to give yellow 3-*deoxy*-D-*glucosazone* (0·25 g.), m. p. 139—140°, depressed on admixture with 5-hydroxymethyl furfuraldehyde phenylhydrazone (Found: C, 62·9; H, 6·4; OMe, 0·0. $C_{18}H_{22}O_3N_4$ requires C, 63·3; H, 6·5%).

Hydrolysis of Phenylosazones.—(a) *Glucose phenylosazone*. Glucose phenylosazone (1·0 g.) was suspended in chloroform (115 ml.), and concentrated hydrochloric acid (18·4 ml.) in water (83 ml.) was added. The mixture was refluxed for ½ hr., then the aqueous layer was washed with chloroform and shaken with *N*-methyldioctylamine [11] (50 ml.) in chloroform (1 l.) until neutral. Addition of 2,4-dinitrophenylhydrazine in hydrochloric acid to a portion of the aqueous solution gave immediately a precipitate which after being washed and dried had m. p. 250—251° (decomp.), undepressed on admixture with glucosazone. The aqueous solution was treated with charcoal and concentrated under reduced pressure to a solid (0·339 g.). The material crystallised partly on trituration with alcohol. After several recrystallisations from ethanol–ether, the very fine, pale yellow needles had m. p. 169—170° (decomp.), depressed on admixture with glucose phenylhydrazone, m. p. 149—150°. They were soluble in water and reduced Fehling's solution in the cold. They were probably one of the two possible forms of *glucosone monophenylhydrazone* (Found: C, 53·6; H, 6·0; N, 10·3. $C_{12}H_{16}O_5N_2$ requires C, 53·8; H, 6·0; N, 10·4%).

The ethanol liquors from the trituration were concentrated to a straw-coloured syrup which reduced cold Fehling's solution, decolorised permanganate, and reacted readily with 2,4-dinitrophenylhydrazine. Chromatography of the acidic syrup in ethyl acetate–acetic acid–water (10 : 1·3 : 1) and in butan-1-ol–pyridine–water (6 : 4 : 3) gave two lactones, detected by permanganate–periodate [12] and hydroxylamine–ferric chloride sprays.[13] The main lactone behaved identically with mannonolactone, and on admixture no separation was observed. The minor component behaved similarly to gluconolactone. The concentrations of these lactones were increased by treatment of the hydrolysis product with calcium hydroxide.

(b) *Phenylosazone of tetra*-O-*acetyl*-2-*hydroxyglucal*. The osazone was deacetylated catalytically with sodium methoxide, to give the unsubstituted osazone, m. p. 178—179° (Bergmann and Zervas [1] give m. p. 183°) (Found: C, 66·7; H, 6·2; N, 16·8. Calc. for $C_{18}H_{22}O_2N_4$: C, 66·6; H, 6·2; N, 17·3%). This osazone (85 mg.) was treated as above, and the resultant product on chromatographing gave a main component (R_{Lactic} 0·45) which was acidic, reacted slowly with periodate, and did not form a lactone. It appeared to be identical with the acid produced by the alkaline degradation of 2-hydroxycellobial acetate.

(c) *Phenylosazone from* 2-*methoxy*-2,3-D-*glucal*. The phenylosazone (*ca.* 50 mg.) was treated as above except that dioxan was used instead of chloroform. Chromatography of the resulting syrup revealed the presence of two lactones of R_{Lactic} 0·47 and 0·56 which behaved similarly to α- and β-*glucometa*saccharolactones. An acid with R_{Lactic} 0·75 was also detected.

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[11] Smith and Page, *J. Soc. Chem. Ind.*, 1948, **67**, 48.

[12] Lemieux and Bauer, *Analyt. Chem.*, 1954, **26**, 920.

[13] Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859.