204. *Studies on Sugar Osazones. Part VII.* A Comparison of the Phenylosazones prepared from* 3 : 6-*Anhydro*-d-*glucose and* 3 : 6-*Anhydro*-d-*galactose with the Anhydro-osazones prepared from* d-*Galactosazone and* d-*Glucosazone by the Method of Diels and Meyer.*

By E. G. V. Percival.

Evidence is presented that the anhydro-osazone prepared by the method of Diels and Meyer (*Annalen*, 1935, **519**, 157) from galactosazone is identical with 3 : 6-anhydrogalactosazone and structures are proposed for this compound and an isomeric 3 : 6-*anhydrogalactosazone* prepared from 3 : 6-*anhydrogalactosazone diacetate*.

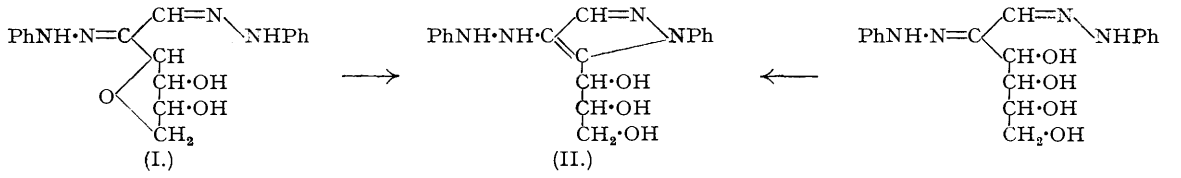
In the glucose series it is shown that 3 : 6-anhydroglucosazone and the anhydro-osazone prepared by Diels' method are not identical and the probable reasons for this and possible structures are discussed.

A new *dehydro*-3 : 6-*anhydroglucosazone* and its *diacetate* are described.

In 1935 Diels and Meyer (*Annalen*, 1935, **519**, 157) isolated osazone anhydrides from galactosazone and glucosazone by boiling with alcohol containing a small quantity of sulphuric acid, and represented these derivatives as the 3 : 6-anhydro-osazones (I), but Diels, Meyer, and Onnen (*Annalen*, 1936, **525**, 94) suggested

* Parts I to VI of this series are as follows: *J.*, 1935, 1398; 1936, 1770; 1937, 1320; 1938, 1384; 1940, 1479; 1941, 750.

that these products were in fact pyrazole derivatives (II) produced as indicated. The suggestion was made (Percival and Percival, *J.*, 1937, 1320) that these compounds like the parent osazones (Percival and Percival,



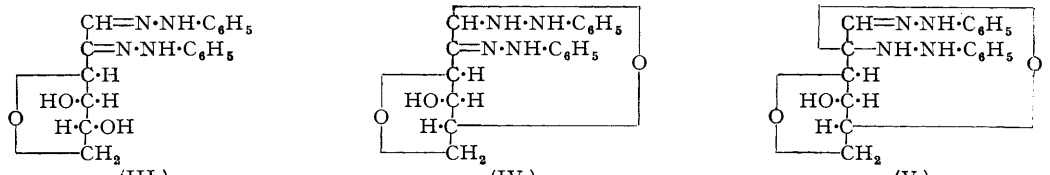
(I.) (II.)

J., 1935, 1398; Muir and Percival, *J.*, 1940, 1479), and the dianhydrohexosazone (Percival, *J.*, 1936, 1770; 1938, 1384) possessed an oxide ring structure since the anhydro-osazones of Diels gave diacetates instead of triacetates. More recently the isolation of a second osazone from 3 : 6-anhydroglucose (this vol., p. 119) was reported, so that it was considered advisable to review the situation.

From the data in the following table it will be seen that whereas the osazone prepared from 3 : 6-anhydro-galactose and that prepared from galactosazone by Diels' method are identical, this is not the case in the glucose series.

	Galactose.	Glucose.
Osazone from 3 : 6-anhydro-sugar	M. p. 215°, $[\alpha]_D^{17°}$ +71° (in methanol)	M. p. 187°, $[\alpha]_D^{17°}$ −150° (in methanol)
Diacetate	M. p. 74—76°, $[\alpha]_D^{17°}$ +62° (in chloroform)	M. p. 190°, $[\alpha]_D^{17°}$ −49° (in chloroform)
Osazone by Diels' method	M. p. 215°, $[\alpha]_D^{17°}$ +71° (in methanol)	M. p. 176—178°, $[\alpha]_D^{17°}$ −157° (in methanol)
Diacetate	M. p. 74—75°. $[\alpha]_D^{17°}$ +64° (in chloroform)	M. p. 90°, $[\alpha]_D^{16°}$ −145° (in chloroform)

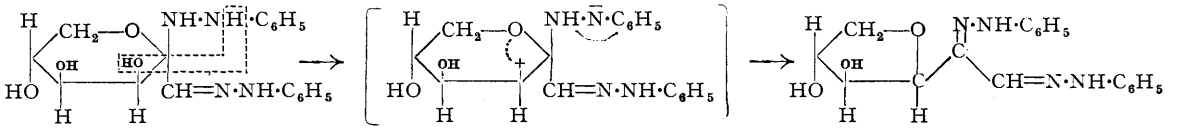
The structure proposed by Diels, Meyer, and Onnen (*loc. cit.*) for the anhydrogalactosazone is, nevertheless, incorrect, since it should yield a triacetate, a monoacetone derivative and a 6-toluene-*p*-sulphonate which would react with sodium iodide (Oldham and Rutherford, *J. Amer. Chem. Soc.*, 1932, **54**, 366). None of these compounds has been isolated, in fact the toluene-*p*-sulphonate could not be isolated by the usual method nor could a triphenylmethyl ether be prepared; it is obvious therefore that Diels' formula for 3 : 6-anhydro-galactosazone must be modified. There seems no reason to depart from the view that the 3 : 6-anhydro ring is still retained in this compound so that formulations (III), (IV), and (V) must be considered since interaction between C_1 and C_4 is rendered impossible on stereochemical grounds in the galactose series.



(III.) (IV.) (V.)

Haworth, Jackson, and Smith (*J.*, 1940, 620) and Haworth, Owen, and Smith (*ibid.*, 1941, 88) have made it clear that compounds of 3 : 6-anhydro-sugars having 1 : 5-pyranose rings are in a state of considerable strain, which in the glucose series may be relieved by the formation of a 1 : 4-furanose ring and in the galactose series by reversion to the acyclic structure. Formulation (IV) is therefore unlikely. No exception can, however, be taken to (V) on these grounds. Deacetylation of 3 : 6-anhydrogalactosazone diacetate gave a small quantity of a second isomeric 3 : 6-*anhydrogalactosazone*, m. p. 226°, $[\alpha]_D^{15°}$ +44° in methanol, which in turn yielded a *diacetate*, m. p. 204°, $[\alpha]_D^{18°}$ −90° in chloroform. This compound also failed to give a triphenylmethyl ether or a toluene-*p*-sulphonate so that the 3 : 6-anhydro ring is presumed to be present in this compound also. The question as to which is (III) and which (V) cannot be decided directly although the lower values of the specific rotations of the last two compounds incline one to the view that this isomeric anhydrogalactosazone is probably (III), and that of m. p. 215° is (V). The possibility that this isomerism is concerned with α and β or *syn*- and *anti*-forms cannot be excluded, however.

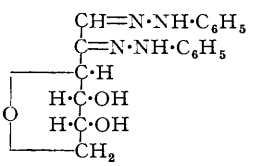
To account for the formation of the same dianhydrohexosazone from *d*-galactosazone and *d*-glucosazone (VII) (*J.*, 1935, 1398), (VI) was suggested as the formula of the former, *i.e.*, the β-tagatopyranosazone. On this basis the ready production of a 3 : 6-anhydro ring can be supposed to take place as follows when *d*-galactosazone is boiled with ethanol containing a little sulphuric acid.

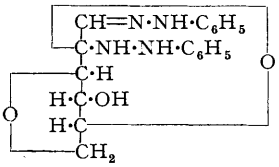


(VI.) (III.)

This reaction could not occur with *d*-glucosazone which was formulated as α-fructopyranosazone (VII) (p. 785), and in fact in this instance the 3 : 6-anhydride is not produced by Diels' process.

The problem is more complicated in the glucose series, but there is no reason to doubt that the 3 : 6-anhydro ring is retained in the osazone prepared from 3 : 6-anhydroglucose, since the osazone failed to give a triphenylmethyl ether, or even a toluene-*p*-sulphonate, although a readily crystallisable *diacetate* was obtained with ease, a compound which is very suitable for the characterisation of 3 : 6-anhydroglucose in small amounts.


(VIII.)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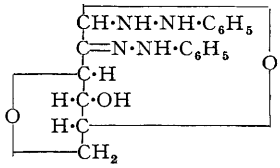
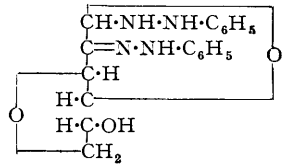
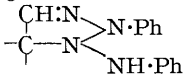

(X.)


(XI.)

Formula (VIII) is not admissible since repeated attempts to condense the osazone with acetone failed, therefore a second oxide ring system must be presumed to be present. Formulæ (IX), (X), and (XI) remain as possibilities. Formula (X) would be expected to be unstable (Haworth *et al.*, *loc. cit.*) so the choice lies between (IX) and (XI); no evidence is available, at present, to decide between these two formulæ.

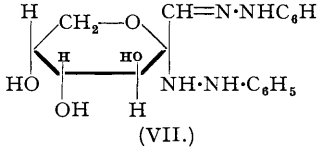
Deacetylation of the diacetate did not yield either a hexosazone dianhydride (*J.*, 1936, 1770) or an isomeric anhydroglucosazone as in the case of galactose, but a new *dehydroanhydro-osazone*, m. p. 232—233°, $[\alpha]_D$ −76° in acetone, which in turn gave a *diacetate*. Diels, Cluss, Stephan, and König (*Ber.*, 1938, **71**, 1189) isolated a number of dehydro-osazones which they considered to be osotriazoles by treating osazones with air or oxygen in alkaline solution. These authors state, however, that their anhydro-osazones could not be dehydrogenated in this way. There is no doubt, however, that a reaction of this kind has taken place with 3 : 6-anhydroglucosazone, as indeed would be expected from either (IX) or (XI) since both are capable of yielding the

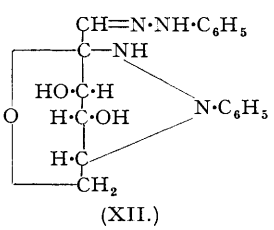


type structure. On the other hand reference to the formulæ (XII) and (XIII) proposed for the Diels' anhydroglucosazone shows that such a transformation could not occur in that case.

The second product, m. p. 108—110°, isolated from 3 : 6-anhydroglucose on osazone formation to which reference has already been made (*J.*, 1945, 119), appears to be a hydrate of the osazone, m. p. 187°, since it gives the same crystalline diacetate, although in diminished yield, and the amorphous fraction accompanying this crystalline product is also a diacetate having the same specific rotation and giving the same dehydroanhydroglucosazone on deacetylation.

The anhydroglucosazone prepared by the method of Diels and Meyer (*loc. cit.*) formed a diacetate as reported previously (*J.*, 1937, 1320) but gave no acetone compound and the toluene-*p*-sulphonate did not react with sodium iodide. It must be concluded, therefore, that the 2 : 6-oxide ring structure of the original osazone (VII) (*J.*, 1935, 1398) is retained, and that anhydride formation takes place between the hydrazide group on C_2 and one of the hydroxyl groups on C_4 and C_5; interaction between the :NH group on C_1 and a hydroxyl group is excluded because the product would then have three groups, *viz.*, two hydroxyls and the hydrazide residue, available for acetylation. Constitutions (XII) and (XIII) remain therefore for consideration, and the former is to be preferred for two reasons. First, the diacetate of (XIII) would be expected to yield the *d*-dianhydrohexosazone (XIV) which is isolated from *d*-galactosazone and *d*-glucosazone tetra-acetates on


(VII.)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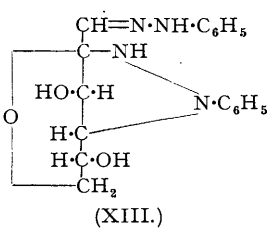
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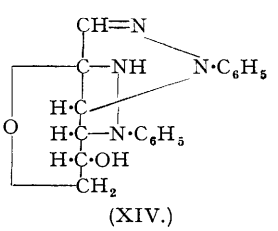
(XIV.)

deacetylation (*J.*, 1936, 1770; 1938, 1384); second, an inspection of models shows (XII), containing three six membered rings, to be less strained than (XIII).

Experimental.

3 : 6-*Anhydrogalactosazone and its Diacetate*.—Pure 3 : 6-anhydro-α-methylgalactoside (2·0 g.) prepared according to Haworth, Jackson, and Smith (*loc. cit.*) was hydrolysed at 15° with 0·1N sulphuric acid (25 c.c.) for 24 hours. The solution was then diluted with water and heated with sodium acetate (20 g.), phenylhydrazine hydrochloride (5 g.) and a little sodium bisulphite at 90° for 2 hours. The bright yellow osazone so obtained was collected, washed and dried (1·6 g.), m. p. 215°, $[\alpha]_D^{16°}$ +71° (c, 0·35, in methanol) (Found: C, 63·3; H, 6·0; N, 16·6. Calc. for $C_{18}H_{20}O_3N_4$: C, 63·5; H, 5·9; N, 16·5%). This product (1 g.) was acetylated with pyridine (6 c.c.) and acetic anhydride (4 c.c.) at 15° for 2 days, the mixture poured into water and crystallised from aqueous ethanol (0·9 g.), m. p. 74—76°, $[\alpha]_D^{17°}$ +64° (c, 0·5, in chloroform) (Found: C, 62·0; H, 5·8; N, 13·2; Ac, 21·0. $C_{22}H_{24}O_5N_4$ requires C, 62·3; H, 5·7; N, 13·2; Ac, 20·3%).

Diels' Anhydrogalactosazone and its Diacetate.—Pure *d*-galactosazone when treated according to Diels and Meyer (*loc. cit.*) gave an anhydrogalactosazone, m. p. 215° not depressed with the osazone prepared directly from 3 : 6-anhydrogalactose, $[\alpha]_D^{17°}$ +71° (c, 0·3, in methanol) (Found : N, 16·4%). The diacetate (Ac, 20·8%) had m. p. 74—76° not depressed with the diacetate described above, $[\alpha]_D^{16°}$ +64° (c, 0·4, in chloroform). The m. p. 86° recorded previously for this substance (*J.*, 1937, 1320) could not be reached.

Four attempts to condense 3 : 6-anhydrogalactosazone with acetone in the presence of copper sulphate (*ibid.*) failed; unchanged material and an uncrystallisable syrup (Found : $COMe_2$, 1·8%) resulted.

3 : 6-Anhydrogalactosazone (0·4 g.) in pyridine (4 c.c.) was treated with toluene-*p*-sulphonyl chloride (0·8 g.) at 15° for 3 days. On pouring into water the starting material was recovered unchanged (Found : S, 0·0%). Treatment with triphenylchloromethane (Muir and Percival, *loc. cit.*) gave a similar result.

A Second 3 : 6-*Anhydrogalaetosazone.—Deacetylation of* 3 : 6-*anhydrogalactosazone diacetate.* The acetate (0·4 g.) in acetone (50 c.c.) was kept for 3 hours with 0·1N sodium hydroxide solution (50 c.c.). The mixture was then acidified and the acetone allowed to evaporate. A small quantity (0·05 g.) of a crystalline *product* was obtained, m. p. 226°, depressed on mixing with **3 : 6**-anhydrogalactosazone; $[\alpha]_D^{15°}$ +44° (c, 0·3 in methanol) (Found : C, 63·2; H, 6·1; N, 16·5. $C_{18}H_{20}O_3N_4$ requires C, 63·5; H, 5·9; N, 16·5%). Acetylation gave a *diacetate*, m. p. 204°, $[\alpha]_D^{16°}$ −90° (c, 0·6 in chloroform) (Found : C, 62·3; H, 5·4; N, 13·4; Ac, 20·6%. $C_{22}H_{24}O_5N_4$ requires C, 62·3; H, 5·7; N, 13·2; Ac, 20·3%). The anhydrogalactosazone failed to react with toluene-*p*-sulphonyl chloride or triphenylchloromethane.

3 : 6-*Anhydroglucosazone and its Diacetate.*—Several preparations of the osazone were made as described previously (*J.*, 1945, 119) to give as the main product (A), m. p. 187°, $[\alpha]_D^{17°}$ −150° (*c*, 0·35, in methanol) (Found : N, 16·5. Calc. for $C_{18}H_{20}O_3N_4$: N, 16·5%), together with a smaller quantity of the osazone, m. p. 108° (B) (Found : N, 15·5. Calc. for $C_{18}H_{22}O_4N_4$: N, 15·6%).

These products were acetylated as before. (A) gave a *diacetate* in good yield : m. p. 190°, $[\alpha]_D^{14°}$ −20° (c, 0·1, in acetone), −49° (c, 0·6, in chloroform), (Found : C, 62·0; H, 5·8; N, 12·8; Ac, 20·5. $C_{22}H_{24}O_5N_4$ requires C, 62·3; H, 5·7; N, 13·2; Ac, 20·3%). (B) gave an acetate which was less easily crystallised than the acetate from (A) but which also yielded the diacetate, m. p. 190° not depressed on admixture with the acetate from (A). Before recrystallisation the acetate had $[\alpha]_D^{14°}$ −50° (c, 0·3, in chloroform) (Found : C, 62·1; H, 5·9; N, 13·1; Ac, 20·4%). It is clear that (B) is a hydrate of (A) and is not a hexosazone.

Dehydro-3 : 6-*anhydroglucosazone and its Diacetate.*—Crystalline 3 : 6-anhydroglucosazone diacetate (0·38 g.) was deacetylated as described previously (*J.*, 1935, 1398) to give a crude product (0·25 g.) which on recrystallisation gave a *compound* (0·08 g.), m. p. 232—233°, $[\alpha]_D^{16°}$ −76° (c, 0·3, in acetone) (Found : C, 63·9; H, 5·5; N, 16·6. $C_{18}H_{18}N_4O_3$ requires C, 63·9; H, 5·4; N, 16·6%).

The non-crystalline residue was reacetylated to give the starting material, m. p. 190°. This experiment was repeated twice in air with similar results, and once in a nitrogen atmosphere when no dehydroanhydro-osazone was obtained. Acetylation gave a crystalline *diacetate*, m. p. 191°, considerably depressed on admixture with 3 : 6-anhydroglucosazone diacetate, $[\alpha]_D^{20°}$ −200° (c, 0·3, in chloroform) (Found : C, 62·2; H, 5·5; N, 13·5. $C_{22}H_{22}O_5N_4$ requires C, 62·5; H, 5·3; N, 13·3%). The dehydroanhydroglucosazone was also obtained on deacetylating the amorphous acetate of (B).

Several attempts to condense 3 : 6-anhydroglucosazone with acetone failed; in all cases some starting material was recovered and the accompanying syrups contained only a trace (*ca.* 2%) of acetone.

Experiments to prepare the toluene-*p*-sulphonate and the triphenylmethyl ether of 3 : 6-anhydroglucosazone were unsuccessful. In one case the supposed toluene-*p*-sulphonate contained S, 0·8%, but acetylation gave the crystalline diacetate, m. p. 190°, in good yield.

Diels' Anhydroglucosazone.—The method of Diels and Meyer (*loc. cit.*) was used to prepare the anhydroglucosazone, m. p. 176—178° depressed on admixture with 3 : 6-anhydroglucosazone, $[\alpha]_D^{20°}$ −157° (c, 0·4, in methanol) (Found : C, 63·3; H, 6·0; N, 16·2%). Acetylation and crystallisation from aqueous ethanol gave a crystalline *diacetate*, m. p. 90°, $[\alpha]_D^{16°}$ −144° (c, 0·3, in chloroform) (Found : C, 62·0; H, 5·9; N, 13·3; Ac, 20·9. $C_{22}H_{24}O_5N_4$ requires C, 62·3; H, 5·7, N, 13·2; Ac, 20·3%). Deacetylation as described previously gave the original anhydroglucosazone in good yield, m. p. and mixed m. p. 176°.

*The Toluene-*p*-sulphonate.*—Diels' anhydroglucosazone (0·5 g.) in pyridine (5 c.c.) was allowed to react with toluene-*p*-sulphonyl chloride (0·5 g.) for 3 days. On pouring into water a *product* (0·52 g.) was obtained which could not be crystallised. $[\alpha]_D^{15°}$ −126° (c, 0·3, in chloroform) (Found : C, 60·5; H, 5·4; N, 11·7; S, 6·7. $C_{25}H_{26}N_4O_5S$ requires C, 60·7; H, 5·3; N, 11·3; S, 6·5%). This material (0·23 g.), on treatment with sodium iodide in acetone at 100° according to Oldham and Rutherford (*loc. cit.*) gave a trace (0·01 g.) of sodium toluene-*p*-sulphonate, but the reaction product was devoid of iodine. Attempts to prepare a triphenylmethyl ether were unsuccessful.

Treatment of the Diels anhydroglucosazone with acetone and copper sulphate for 24 hours gave unchanged material and a syrup ($COMe_2$, 1·9%). Three experiments for periods ranging from 1 to 3 days gave similar results.

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