Note

The stereoselectivity of anhydro- and dehydro-osazone formation

H. EL KHADEM

Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan 49931 (U. S. A.)

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Recent studies[1] of the absolute configuration of the 3,6-anhydro-osazones and dehydro-osazones revealed that, during their formation by dehydration and oxidation of osazones, the first asymmetric center (C-3) after the two bearing a hydrazone group invariably assumes the same configuration in the Fischer projection formula as the next carbon atom (C-4), irrespective of the configuration at C-3 in the starting osazone.

This stereoselectivity is not restricted to anhydro- and dehydro-osazones, but also applies to hydroxyalkyl hetero-aromatic ring systems[2], such as saccharide triazoles. An attempt will be made here to explain the stereospecificity of the reaction leading to the formation of anhydro-osazones, in the light of a recently[3] suggested mechanism of formation of these compounds which can be extended to triazoles and other hetero-aromatic systems undergoing anhydro-ring formation. The formation of dehydro-osazones will then be shown to follow a closely related pathway.

DISCUSSION

Any attempt to explain the stereospecificity of the cyclization of anhydro- and dehydro-osazones and anhydro-triazoles must take into consideration the following facts.

1. The inversion of configuration takes place with one 3-epimer only; the other undergoes cyclization without inversion, denoting that the reaction is not a simple inversion of the SN2 type, wherein both isomers undergo inversion.

2. Whenever delicate analytical techniques were used to investigate the reaction products, a small proportion of the second, 3-epimeric, cyclic derivative was detected[4], suggesting that, at one stage, a racemization must have occurred, probably through formation of a double bond, followed by regeneration of the asymmetric center to yield a major, sterically favored 3-epimer and a small proportion of the less-favored one.

3. When inversion of configuration occurs, it invariably takes place at C-3, contiguous to C-2 (bearing a hydrazone group or triazole ring), indicating that a double bond is formed between C-2 and C-3 at one stage of the reaction.

4. The aforementioned rule[1] of stereoselectivity correlates the configurations at C-3 and C-4 in anhydro- and dehydro-osazones depicted as Fischer projection formulas. However, a closer study of the models reveals that two situations actually exist.

a. For 3,6-anhydro-osazones (and also for 3,6-anhydro-triazoles, which were found to obey the same rule), the O-3 is the ring-oxygen atom, and a change in configuration at C-3 results in assumption by the two hydrazone groups (or the triazole ring) of a position above or below the plane of the ring. Study of the structure of major isomers of 3,6-anhydro-osazones belonging to the hexose and heptose series (see Fig. 1) revealed that, invariably, the two hydrazone groups assume a posi-

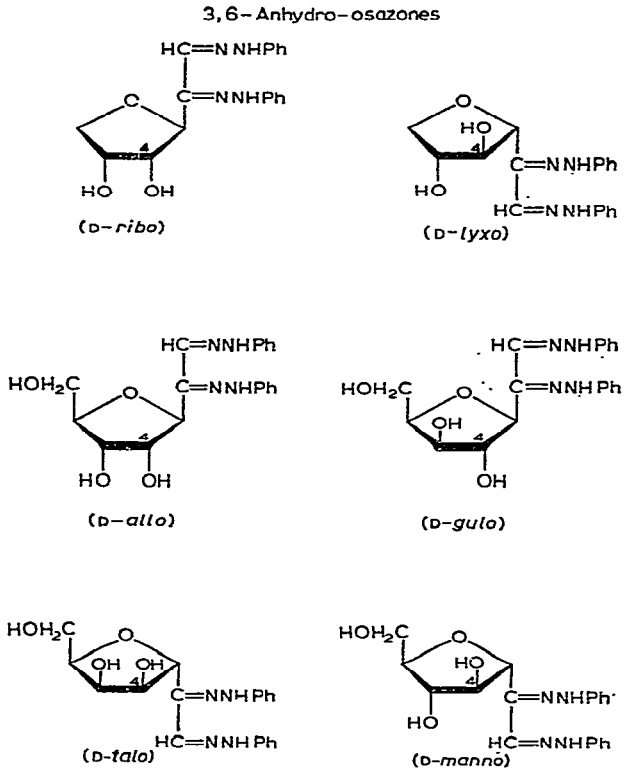
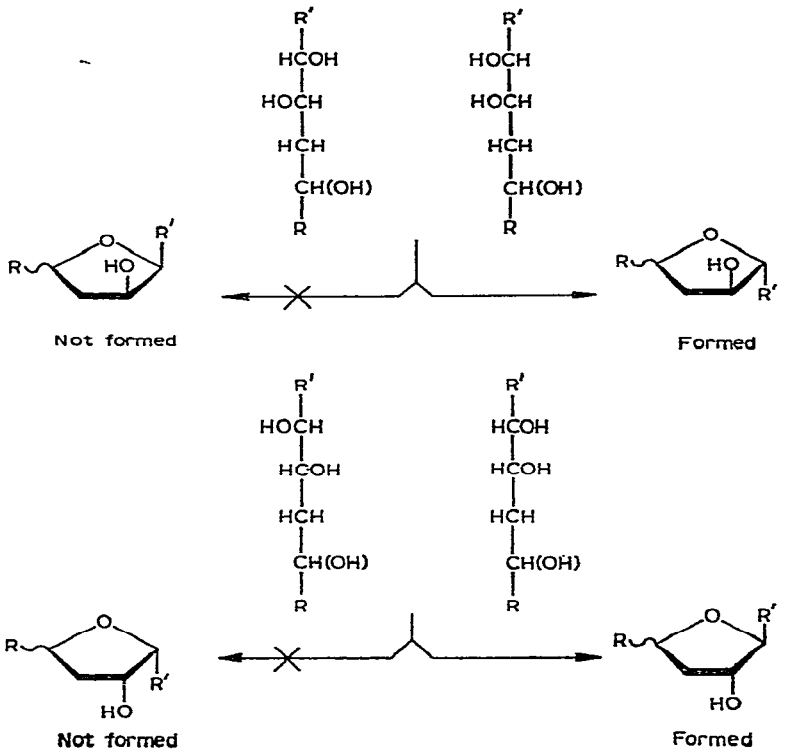


Fig. 1. Structures of sterically favored forms of phenylosazones of hexuloses and heptuloses.

tion opposite that of the 4-hydroxyl group; *i.e.*, if the 4-hydroxyl group is below the plane of the ring, the two hydrazone groups will lie above the ring, and *vice versa*, clearly suggesting that a steric factor is involved in this stereospecificity.

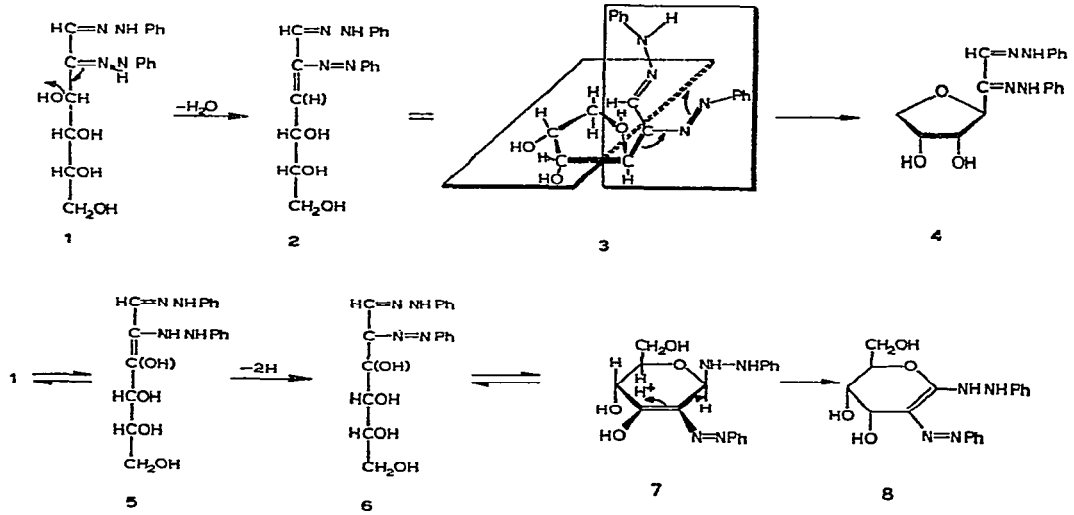
For 3,6-anhydro-triazoles, a review of the configuration of the known 3,6-anhydro-phenylosotriazoles[5] revealed that the triazole ring (R') also invariably assumes a position *trans* to the 4-hydroxyl group.

b. A different situation exists with dehydro-osazones; here, the preponderant isomers have the 3- and 4-hydroxyl groups on the *same* side of the dihydropyran ring.



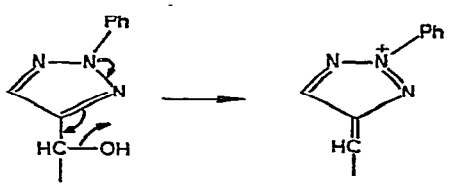
It is now suggested that the stereoselectivity of formation both of 3,6-anhydro-osazones and dehydro-osazones involves racemization through the formation of a double bond between the carbon atom bearing the hydrazone residue (C-2) and the contiguous carbon atom (C-3). Although such compounds have not yet actually been isolated from osazone reactions, several 2-ene intermediates have been shown to be formed in the course of osazone reactions[3]. Acetates of phenylhydrazones are also known to yield similar derivatives, the 1-phenylazo-1-enes[6], on treatment with bases. Examples of 2-ene intermediates in osazone reactions were provided by Simon and co-workers[3], who showed that, in acidic or basic media, osazones readily rearrange to 2-phenylazo-2-ene derivatives (**2**) by elimination of the 3-hydroxyl group, and to 2-(phenylhydrazino)-2-en-3-ols (**5**) by a prototropic rearrangement. They showed that formation of 3,6-anhydrohexulose phenylosazones and 3-alkoxypentulose phenylosazones, obtained by interacting hexulose and pentulose phenylosazones with alcoholic sulfuric acid, actually proceeds *via* a 2-phenylazo-2-ene intermediate (**2**), and that 2-(phenylhydrazino)-2-en-3-ol intermediates are involved in the elimination of aniline from phenylosazones in the presence of an acid or base, as well as during the formation of azopyrazoles[7]. The latter intermediates are probably also responsible for dehydro-osazone formation.

The suggested mechanism for the stereospecific conversion of osazones into 3,6-anhydro-osazones starts with the same 2-phenylazo-2-ene intermediate (**2**)



suggested by Simon and co-workers[3], which then undergoes 3,6-anhydro ring-formation by oxygen attack on C-3. A study of models reveals that an oxygen attack on the sterically unfavorable rotamer (having the two bulky hydrazone groups on the same side as C-4) would lead to the minor product; whereas, the sterically favored rotamer (3), having the hydrazone groups *trans* to the 4-hydroxyl group, would yield the major product.

For the formation of 3,6-anhydro-osotriazoles, the mechanism is more or less the same; here, racemization occurs when N-2 in the triazole donates an unbonded electron to N-1, causing migration of the double bond to C-1 of the alkyl chain and subsequent loss of OH^-. This would be followed by attack by O-6 on the rotamer



having the triazole ring on the opposite side of the 4-hydroxyl group, in exactly the same way as with 3, thus giving rise to the epimeric triazole. This type of cyclization probably occurs with other nitrogen hetero-aromatic ring-systems linked to a hydroxyalkyl chain, provided that the heterocyclic moiety is bulky enough to favor one rotamer.

For the formation of dehydro-osazones, it is suggested that the reaction proceeds through a 2-(phenylhydrazono)-2-en-3-ol, similar to that proposed by Simon *et al.*[3] to explain the loss of aniline from osazones; this intermediate (5) would be quite susceptible to oxidation, giving the 2-phenylazo-2-en-3-ol (6). Cyclization of the

latter would then afford intermediate **7**, which could be protonated either from above or below the ring, depending on the position of the 4-hydroxyl group. Protonation from the sterically least-hindered position (the side opposite the 4-hydroxyl group) would afford the preponderant, 3-epimeric dehydro-osazone.

Understanding of the mechanism of cyclization of the aforementioned compounds should prove useful in planning the synthesis of *C*-nucleoside analogs by cyclization of a hetero-aromatic ring linked to an acyclic saccharide residue. This method has not yet been extensively used, because there was uncertainty regarding the configuration of the products.

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