# The Reactivity of 1,2-Diaminosugars in the Osazone and Quinoxaline Formation in the Sugar Series

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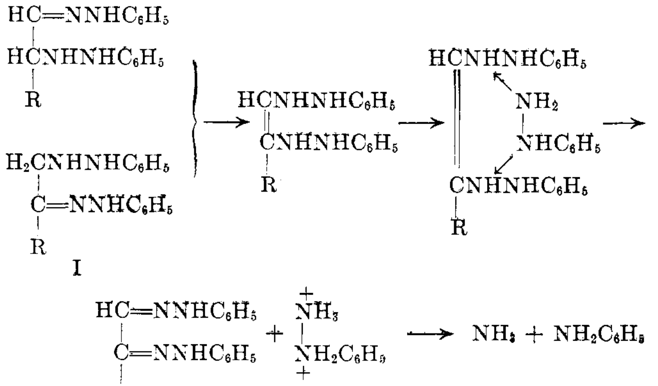
It has been reported elsewhere[1] that *N*-benzyl-(1-deoxy-1-*p*-toluidino)-D-fructosylamine is cleaved by molecular oxygen to give *N*-benzyl-D-arabinonamide while *N*-cyclohexyl-(2-cyclohexylamino-2-deoxy)-D-glucosylamine yields under similar mild conditions *N,N'*-bis(cyclohexyl)oxaldiamide, dicyclohexyliminoglyoxal, and cyclohexylammonium D-arabinonate as the cleavage products. It has been shown that the 1,2-diaminosugars are first rearranged into the enediamine structures which have powerful reducing abilities and that one of the primary oxidation products of the enediamine from the latter diaminosugar is 1,2-dicyclohexylimino-D-glucosone. Literature reporting the high reducing ability of enediamino compounds and their ready conversion into 1,2-diiminodiketo compounds by the action of atmospheric oxygen has also been reviewed.

Because the formation of osazones and quinoxalines in the sugar series involves the transformation of 1,2-diaminosugars into 1,2-diimino-osones, it appears that the above findings will help to elucidate the reaction mechanisms.

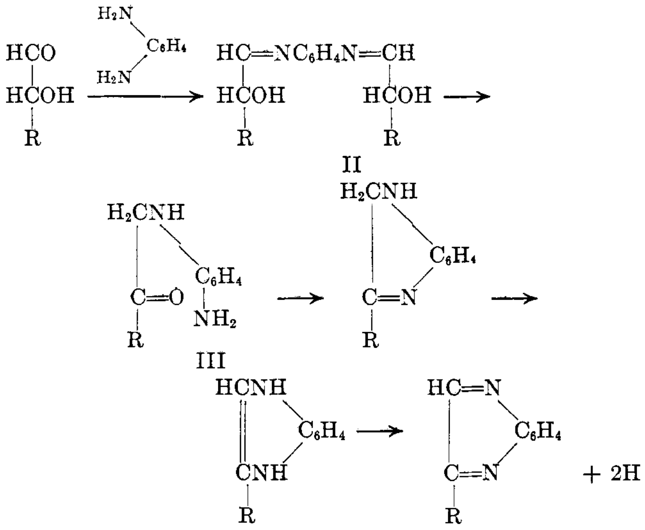
Among a number of the theories advanced for explaining the mechanism of the osazone formation,[2] the most widely accepted ones[3] are apparently the mechanisms by Weygand[4] and by Bloink and Pausacker.[5] In both mechanisms a 1,2-diaminosugar (I) is postulated as the key intermediate. The mechanism of the oxidation of this diaminosugar to diimino-osone differs between the two schemes and remains to be clarified.

Based upon the new evidence[1] concerning the 1,2-diamine-enediamine rearrangement and the powerful reducing ability of the rearrangement product, the following scheme could represent the last step in the formation of osazones.



(R: the sugar residue below C-3)

Formation of 2-substituted quinoxaline by the reaction of a reducing sugar and *o*-phenylenediamine has been shown to follow a mechanism similar to that of the osazone formation.[6] From the present knowledge on the reactivity of the 1,2-diaminosugars, the mechanism of the last step of the quinoxaline formation may be shown as follows:[7]



(R: the sugar residue below C-3)

The hydrogen acceptor in this reaction is atmospheric oxygen under ordinary reaction conditions, but hydrazine is a better acceptor since addition of hydrazine has been shown to improve the yield of the quinoxaline derivative.[6,8] To indicate the different ability as the hydrogen acceptor between molecular oxygen and hydrazine, a set of experiments was conducted with *N,N'*-di-D-glucosyl-3,4-diaminotoluene. In contrast to *o*-phenylenediamine, 3,4-diaminotoluene does not give the quinoxaline derivative in the reaction with D-glucose.[9] It was thought therefore that *N,N'*-di-D-glucosyl-3,4-diaminotoluene, the first intermediate (corresponding to II) in the reaction of the diaminotoluene and D-glucose, would be a good starting material to show the effect of hydrogen acceptors more distinctly in the quinoxaline formation. When *N,N'*-di-D-glucosyl-3,4-diaminotoluene was refluxed in 10% acetic acid for thirty minutes, the yield of the formed quinoxaline derivative was merely trace under an ordinary atmosphere, 7.8% under passing of oxygen through the solution and 18.2% when an equimolecular amount of hydrazine was added.

## Experimental

***N,N'*-Di-D-glucosyl-3,4-diaminotoluene.**—A mixture of 36 g. of D-glucose, 12 g. of 3,4-diaminotoluene, 0.2 g. of ammonium chloride, and 300 ml. of methanol was refluxed for 30 min. Sepa-

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[1] S. Kitaoka and K. Onodera, *Agr. Biol. Chem.*, **26**, 572 (1962).

[2] E. G. V. Percival, *Advan. Carbohydrate Chem.*, **3**, 23 (1948).

[3] W. Pigman, "The Carbohydrates," W. Pigman, ed., Academic Press Inc., New York, N. Y., 1957, p. 456.

[4] F. Weygand, *Ber.*, **73**, 1284 (1940); F. Weygand and M. Reckhaus, *ibid.*, **82**, 438 (1949); F. Weygand, H. Simon, and J. F. Klebe, *ibid.*, **91**, 1567 (1958); H. Simon, K.-D. Keil, and F. Weygand, *ibid.*, **95**, 17 (1962).

[5] G. J. Bloink and K. H. Pausacker, *J. Chem. Soc.*, 661 (1952).

[6] F. Weygand and A. Bergmann, *Ber.*, **80**, 255 (1947).

[7] Occurrence of the 1-amino-1-deoxyketose intermediate (III) in the quinoxaline formation has been postulated by Weygand and Bergmann (ref. 6). Since the only condensation product ever isolated of a reducing sugar and *o*-phenylenediamine is *N,N'*-diglycosyl-*o*-phenylenediamine (II), one glycosyl residue must be cleaved off at the formation of III. The reaction mechanism of this step is not clear.

[8] H. Ohle and J. J. Kruyff, *Ber.*, **77**, 507 (1944).

[9] P. Griess and G. Harrow, *ibid.*, **20**, 2205 (1887).

ration of the crystalline product was prompt, and, after cooling, the crude yield was 33.8 g. (70.4%). It was recrystallized from a large volume of aqueous methanol; m.p. 142–143°, $[\alpha]^{16}_{D}$ −41° (*c* 0.5, pyridine, 24 hr.).

*Anal.* Calcd. for $C_{19}H_{30}N_2O_{10}\cdot 3H_2O$: C, 45.59; H, 7.25; N, 5.60. Found: C, 45.04; H, 7.16; N, 5.68.

**2-D-*arabino*-Tetrahydroxybutyl-6-methylquinoxaline.**—An amount of 4.5 g. of *N,N'*-di-D-glucosyl-3,4-diaminotoluene was heated to boiling in 50 ml. of 10% acetic acid for 30 min. Under an ordinary atmosphere no separable amount of the crystalline product was obtained, but, under vigorous passing of oxygen through the solution, this quinoxaline derivative was obtained in the yield of 0.35 g. (7.8%) after cooling. When the equimolecular amount of hydrazine was added to the reaction system under an ordinary atmosphere, the yield was 0.82 g. (18.2%). This compound had m.p. 177–178° and $[\alpha]^{16}_{D}$ −200° (*c* 0.8, pyridine).

*Anal.* Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10; N, 10.60. Found: C, 58.87; H, 6.33; N, 10.61.

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## Dimethylamides from Alkali Carboxylates and Dimethylcarbamoyl Chloride

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Dimethylamides of carboxylic acids have become increasingly interesting in recent years because certain ones are good solvents for polymers composed mainly of acrylonitrile[1,2] and because they are excellent reaction solvents, particularly for nucleophilic displacements.[3] Ordinarily they may be prepared by almost any of the conventional means for synthesis of amides in general, including thermal reaction between the appropriate acid and dimethylamine, or reaction between dimethylamine and an acid chloride, anhydride, or ester.

Recently in our laboratories it became necessary to convert a small amount of the sodium salt of an acid into the corresponding dimethylamide as quantitatively as possible, yet with a high degree of product purity. While one of the preparative methods mentioned above might have been used, it appeared that each one offered some points of inconvenience and possible loss. A study of the literature did not suggest any more promising approaches until attention was drawn to the reaction between carboxylic acids and isocyanates to form monoalkylamides.[4] This reaction has been demonstrated[4b] to proceed through the intermediate formation of a relatively unstable mixed carboxylic–carbamic anhydride, RCOOCONHR'. Because a similar mixed anhydride should result from the action of a dialkylcarbamoyl chloride on a salt of a carboxylic acid, it seemed likely that such a reaction would be useful in preparing dialkylamides.

The mixed anhydrides from isocyanates and carboxylic acids are capable of decomposing by either of the routes shown below.[4c,d,e]

$$\mathrm{RCOOCONHR'} \longrightarrow \mathrm{RCONHR'} + \mathrm{CO_2} \tag{1}$$

$$\mathrm{2RCOOCONHR'} \longrightarrow \mathrm{(RCO)_2O} + \mathrm{(R'NH)_2CO} + \mathrm{CO_2)} \tag{2}$$

Fry[4c] demonstrated that all of the carbon dioxide formed in these reactions arose from the isocyanate used, and indicated further that the acid anhydride and dialkylurea formed in reaction 2 would interact at somewhat higher temperatures to form additional quantities of monoalkylamide as indicated in equation 3.

$$\mathrm{(RCO)_2O} + \mathrm{(R'NH)_2CO} \longrightarrow \mathrm{2RCONHR'} + \mathrm{CO_2} \tag{3}$$

These facts suggested that this reaction was potentially capable of giving high yields of monoalkylamides from carboxylic acids, and that dialkylamides might by synthesized equally well by the action of dialkylcarbamoyl chlorides on salts of carboxylic acids (equation 4).

$$\begin{aligned}\mathrm{RCOONa} + \mathrm{R_2'NCOCl} &\longrightarrow \mathrm{NaCl} + \mathrm{RCOOCONR_2'}\\ \mathrm{RCOOCONR_2'} &\longrightarrow \mathrm{CO_2} + \mathrm{RCONR_2'}\end{aligned} \tag{4}$$

Support for this conclusion was obtained from the work of von Braun,[5] who obtained dimethylbenzamide almost quantitatively from the spontaneous decomposition of benzoyl dimethyldithiocarbamate. Somewhat

$$\mathrm{(CH_3)_2NCSSCOC_6H_5} \longrightarrow \mathrm{CS_2} + \mathrm{C_6H_5CON(CH_3)_2} \tag{5}$$

similarly, Herzog and Hancu[6] prepared the diphenylamides of benzoic and cinnamic acids by the action of diphenylcarbamoyl chloride on the appropriate acid in excess pyridine at 100°. Presumably this procedure involves a mixed anhydride as an intermediate.

$$\begin{aligned}&\mathrm{C_6H_5COOH} + \mathrm{(C_6H_5)_2NCOCl} + \mathrm{C_5H_5N} \longrightarrow\\ &\qquad \mathrm{C_6H_5COOCON(C_6H_5)_2} + \mathrm{C_5H_5N\cdot HCl}\\ &\mathrm{C_6H_5COOCON(C_6H_5)_2} \longrightarrow \mathrm{CO_2} + \mathrm{C_6H_5CON(C_6H_5)_2}\end{aligned} \tag{6}$$

At the conclusion of the work described here, further search of the literature revealed that the reaction between salts of carboxylic acids and dialkylcarbamoyl chlorides is the subject of a patent.[7] Because the results reported here give some additional insight as to the general utility of the reaction, it is felt that they may be of value.

A synthesis of dimethylacetamide from potassium acetate and dimethylcarbamoyl chloride gave a 96.5% yield of product having the correct refractive index and containing less than 0.01% residual chlorine. Similarly, repetition of this experiment with labeled sodium acetate on two occasions gave yields of 94.2 and 95.8%, with isotopic conversions of 95.88 and 97.1%, respectively.

Other experiments were then performed to determine the generality of this reaction. Dimethylpropionamide with the correct refractive index was obtained in 97% yield. Sodium palmitate gave an 87% yield of dimethylpalmitamide. Sodium carbonate was converted to tetramethylurea in 96.5% yield; while the refractive index has not been previously reported, the product had the proper density and boiling point. The technique is not suitable for the preparation of dimethylformamide;

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(1) G. H. Latham (to E. I. du Pont de Nemours & Co., Inc.), U.S. Patent 2,404,714 (July 23, 1946).

(2) G. F. D'Alelio (to Industrial Rayon Corp.), U.S. Patent 2,531,407 (November 28, 1950).

(3) H. E. Zaugg, B. W. Horrom, and S. Borgwardt, *J. Am. Chem. Soc.*, **82**, 2895 (1960).

(4) (a) C. Naegeli and A. Tyabji, *Helv. Chem. Acta*, **17**, 931 (1934); (b) W. Dieckmann and F. Breest, *Ber.*, **39**, 3052 (1906); (c) A. Fry, *J. Am. Chem. Soc.*, **75**, 2686 (1953); (d) J. H. Saunders and R. J. Slocombe, *Chem. Rev.*, **43**, 210 (1948); (e) R. G. Arnold, J. A. Nelson, and J. J. Verbanc, *ibid.*, **57**, 52 (1957).

(5) J. von Braun, *Ber.*, **36**, 3525 (1903).

(6) J. Herzog and V. Hancu, *ibid.*, **41**, 636 (1908).

(7) E. Stein and O. Bayer (to Farbenfabriken Bayer A.-G.), West German Patent 875,807 (May 7, 1953).