

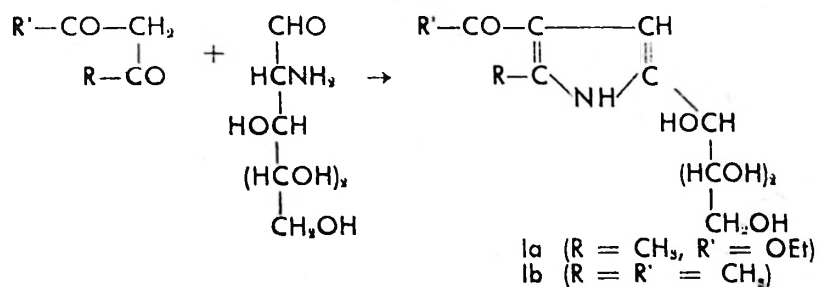
Cátedra de Química Orgánica  
 Universidad de Sevilla and Instituto "Alonso Barba"  
 Consejo Superior de Investigaciones Científicas  
 Sevilla (Spain)

## Reaction of glycosylamines with beta-dicarbonyl-compounds \*

by  
 A. Gómez-Sánchez, F. García-González and J. Gasch-Gómez

(Recibido para publicar el 10 de noviembre de 1958)

D-Glucosamine reacts with beta-dicarbonyl-compounds to give pyrrole derivatives of type I [H. PAULY and E. LUDWIG, Hoppe-Seyler's, Z. physiol. Chem., 121, 170 (1922), F. GARCÍA-GONZÁLEZ, Anales fís. y quím., 32, 815 (1934), F. GARCÍA GONZÁLEZ and R. TRUJILLO, ibid., 33, 566 (1935). For a review see F. GARCÍA GONZÁLEZ, Advances in Carbohydrate Chem., 11, 97 (1956)] :



I. A. ELSON and W. T. MORGAN [Biochem. J., 27, 1824 (1933)] used this reaction to develop a colorimetric method for the estimation of 2-amino-hexoses. It was demonstrated afterwards [B. S. SCHLOSS, Analytical Chem., 23, 1321 (1951)] that, in the conditions prescribed in the analytical method, the reaction is more complex, and that pyrrole derivatives simpler than I, for instance 2-methylpyrrole and 2-methyl-3-acetylpyr-

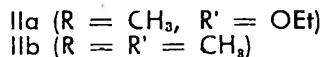
\* Communication to the 4th International Congress of Biochemistry, Wien, September, 1958.

role [J. W. CORNFORTH and M. E. FIRTH, J. Chem. Soc., 1091 (1958)], contribute as chromogens. It is also of interest that reducing sugars, and particularly ketoses, in the presence of ammonia, amines and aminoacids, interfere in the colour reaction [H. N. HOROWITZ, M. IKAWA and M. FLING, Arch. Biochem., 25, 227 (1950)]. The mechanism of this interference has not been elucidated, it might be attributed to the reaction of the sugar with the amino-compound to give a glycosylamine that in further steps could be transformed, either by the catalytic action of the beta-dicarbonyl-compound (acetylacetone in the case of the ELSON-MORGAN estimation method) or by reacting with it, in heterocyclic compounds capable of giving the EHRLICH colour test. This idea is supported by the observation of ELSON and MORGAN that D-glucosylamine gives in the conditions of the estimation method a colouration that they could not distinguish from that produced by D-glucosamine.

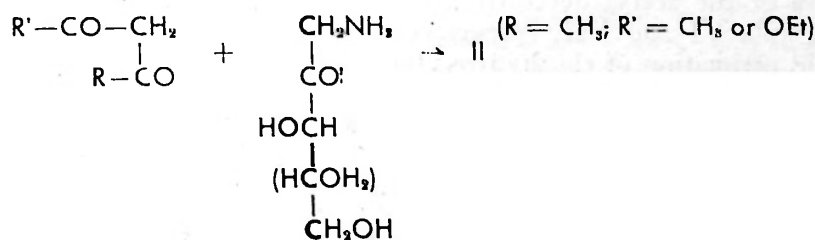
In this paper it is shown that glycosylamines and beta-dicarbonyl-compounds react to give pyrrole compounds. An alcoholic solution of D-glucosylamine and acetoacetic ester containing catalytic amounts of piperidine gives, after standing at room temperature or heating for a shorter time, a positive reaction to the EHRLICH reagent. Chromatographic analysis of the reaction mixture showed the presence of at least three components positive to the EHRLICH and potassium permanganate reagents, apparently one of them in higher concentration than the others. This compound was separated in a cellulose powder column and obtained in crystalline state. Structure IIa is attributed to it according to its analytical data and the following facts:

It gives a positive reaction with the EHRLICH reagent in the cold, in accordance with its pyrrolic nature and the presence of a free alpha position.

Its ultraviolet absorption spectrum shows maxima at 235 mμ ( $\epsilon$ , 7,796) and 263 mμ ( $\epsilon$ , 6,571), and minima at 221 mμ ( $\epsilon$ , 6,653) and 251 mμ ( $\epsilon$ , 5,918). This absorption corresponds very closely to that of an ester of a 3-pyrrolicarboxylic acid. For instance, the simplest compound similar to IIa, ethyl 2,4-dimethyl-3-pyrrolicarboxylate (III), has the maxima at 232 mμ ( $\epsilon$ , 8,840) and 259 mμ ( $\epsilon$ , 5,030), and the minima at 220 mμ ( $\epsilon$ , 7,100) and 250 mμ ( $\epsilon$ , 4,670). The infrared spectrum of the compound shows bands corresponding to the OH, NH, and EtOCO groups, and, on the other hand, has the same general pattern as the spectrum of compound Ia, the isomer of IIa having the polyhydroxylic chain in alpha position.

[illegible]

D-glucosylamine and acetylacetone react to give a complex mixture of compounds positive to the EHRLICH reagent, which could not be resolved. The main component was, however, chromatographically identical to the compound IIb obtained from l-amino-l-deoxy-D-fructose and acetylacetone.



D-Mannosylamine and acetoacetic ester react to give the same compound IIa obtained from D-glucosylamine. There is no difference either between D-mannosylamine and D-glucosylamine in their reaction with acetylacetone.

A syrup obtained from D-fructose and ammonia (and supposed to contain D-fructosylamine) reacts with acetoacetic ester to give compound Ia, previously obtained by PAULY and LUDWIG from D-glucosamine and acetoacetic ester. Acetylacetone and the same syrupy D-fructosylamine react giving compound Ib, which may also be obtained from D-glucosamine and acetylacetone.

N-aryl-D-glucosylamines behave similarly to their parent compound in their reaction with beta-dicarbonyl-compounds, the N-aryl-substituted derivatives of compounds II being obtained as is indicated in Figure 2. These compounds may be also obtained from the suitable l-arylamino-1-deoxy-D-fructose and acetoacetic ester or acetylacetone.

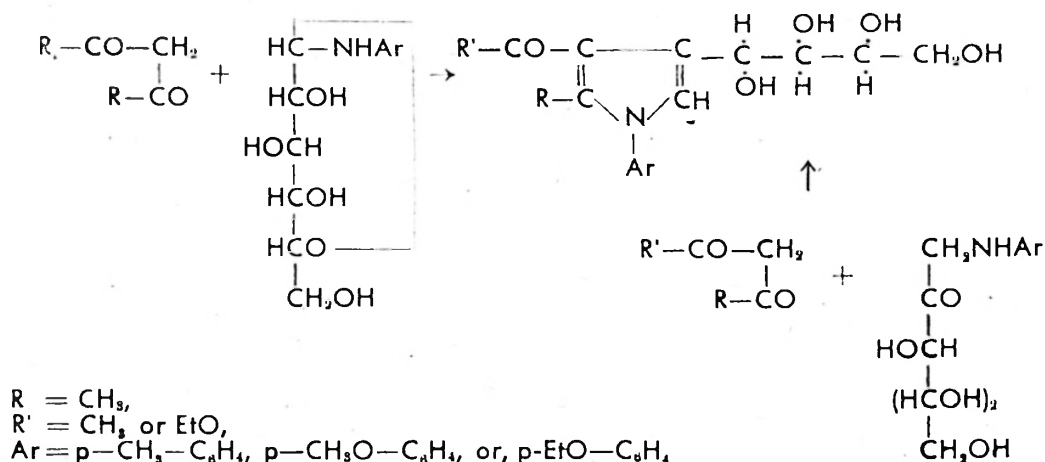
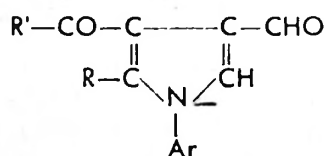
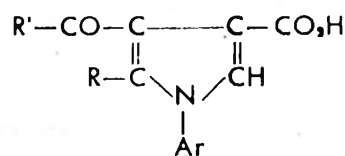


Figure 2

As previously, these structures are based on the preparation of the acetyl derivatives and the aldehydes and acids of formula VI and VII, respectively, as well as on the periodic acid estimation of the hydroxylic chain.



VI



VII

There is not evidence about the mechanism of this reaction, but very likely it takes place in two steps: in the first the glycosylamine undergoes an AMADORI rearrangement to the corresponding l-amino-1-deoxyketose (or 2-amino-2-deoxyaldose in the

case of D-fructosylamine), and in the second one the aminosugar formed reacts with the beta-dicarbonyl-compound according to a Knorr-type reaction to yield the pyrrole compound (Figure 3).

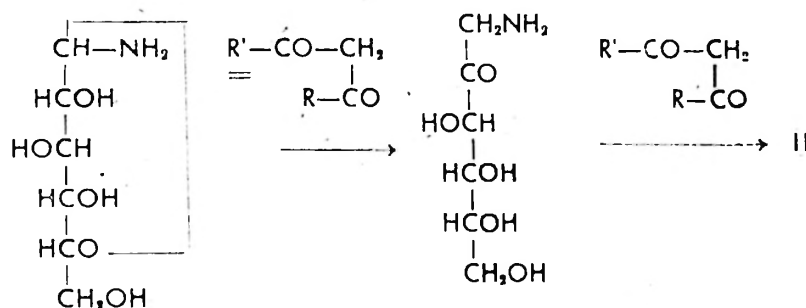


Figure 3

That is supported by the observation of J. E. HODGE and C. E. RIST [J. Am. Chem. Soc., 74, 1494 (1952); 75, 316 (1953)] that compounds containing methylenic active groups can act as catalysts in the AMADORI rearrangement, and by the fact that in the reaction of N-aryl-D-glucosylamines with acetoacetic ester or acetylacetone, the 1-arylamino-1-deoxy-D-fructoses produced in the AMADORI rearrangement may be isolated in addition to the pyrrole derivatives. K. HEYNS and coworkers [Chem. Ber., 86, 1453 (1953), 90, 2039 (1957)] have shown that D-fructosylamine and other ketosylamines are liable to undergo an AMADORI-type rearrangement. There is no antecedent, as far as the authors are aware, that D-glucosylamine itself may be rearranged to 1-amino-1-deoxy-D-fructose, and the results presented in this paper are the first, indirect, data that it in fact may happen. The possibility of the second step, that is to say the condensation of aminosugars and beta-dicarbonyl-compounds, has been shown by the experiments of PAULY and LUDWIG (loc. cit.) with D-glucosamine, and by the experiments reported in this paper of direct syntheses of the pyrrole compounds II from 1-amino-ketoses. This reaction is, therefore, common to both aldosa-mines and ketosamines.

