

Chemistry. — “*On Disaccharins.*” (Preliminary communication).
By Prof A. F. HOLLEMAN and H. J. CHOUFOER.

(Communicated at the meeting of March 29, 1924).

Though the investigation of saccharin derivatives is already pretty extensive, there are still three directions in which further researches might be made, in order to obtain a better insight in the relation between structure and taste of these interesting compounds. ¹⁾

Researches in the third direction indicated loc. cit., i.e. into the taste of compounds containing the group CO—NH—SO, more than once, substituted at orthoplaces in the benzene nucleus, have been taken in hand by me (Ch.). As also POLLAK and LUSTIG ²⁾ have undertaken researches in this region, I feel obliged to make a provisional communication on the results already found by me.

My purpose was to prepare disaccharins which can be derived from the three xylenes; this rendered a renewed study of their di-sulphonic acids necessary.

Disaccharins from m-xylene.

Through WISCHIN'S ³⁾ investigations a disulpho-chloride, melting-point 129°, has become known. The corresponding di-sulphonic acid is formed by heating m-xylene with crystallized fuming sulphuric acid.

When I applied chloro-sulphonic acid for the sulphonation, I found that on treatment of m-xylene with a great excess, the disulpho chloride is immediately formed. On pouring out on ice, a pretty pure product arises, which is only contaminated by small quantities of an oily substance. The oil can be easily removed with ether, after which through recrystallisation from ligroin, ether, and chloroform, the substance can be obtained pure, melting-point 129°.

From the disulpho-chloride the diamide can be obtained with alcoholic ammonia in a fair yield. It is advisable to dissolve the disulpho chloride first in benzene, and to add the calculated quantity of alcoholic

¹⁾ Rec. **42**, 839 (1923).

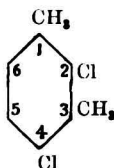
²⁾ A. **433**, 191 (1923).

³⁾ Ber. **23**, 3113 (1890).

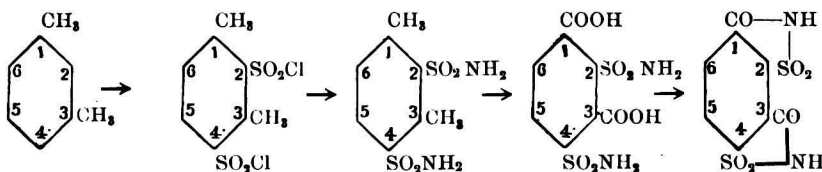
ammonia in drops amidst stirring. There is formed a white crystalline mass. By washing with a little water the NH_4Cl can be easily removed. Then the amide is recrystallized from much water. It appears in long, fine needles, melting-point 249° .

WISCHIN¹⁾ has already oxidized this diamide with KMnO_4 in aqueous solution. He states that he has obtained a diimide of the m.p. 225° . On repetition of this oxidation I observed that when the diamide is oxidized with KMnO_4 , and the solution is acidified, first unchanged diamide crystallizes out, and then a finely crystallized product m.p. 268° — 270° . According to analysis this agrees with a diimide, called *disaccharin* by us.

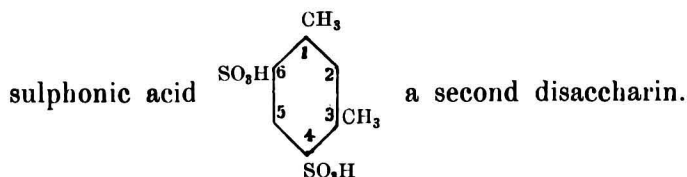
WISCHIN found that the disulpho chloride m.p. 129° on strong heating with PCl_5 passes into a dichloro-xylene of the structure:



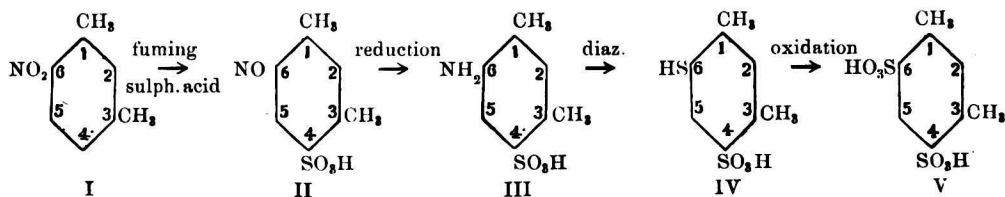
This induces us to represent the conversions described as follows:



It is easy to see that it must be possible to obtain from the



To prepare this substance the following plan was devised:



The nitroxytoluene was obtained from POULENC FRÈRES. With fuming sulphuric acid it is converted into the sulphonic acid (II) at the

¹⁾ Ber. **23**, 3113 (1890).

ordinary temperature. With BaCO_3 it is converted into the Ba-salt. This being sparingly soluble, the precipitation of BaSO_4 must be boiled out a many times. The Ba-salt is converted into the Na-salt with soda. This Na-salt crystallizes in fine needles. It is reduced by boiling with $(\text{NH}_4)_2\text{S}$. The free amido sulphonic acid (III) is sparingly soluble.

The most convenient way of bringing about the diazotation is by mixing the Na-salt of the sulphonic acid (III) with the equivalent quantity of Na-nitrite, and slowly adding drops of hydrochloric acid at 0° .

The diazonium solution obtained is added to a solution of sodium disulphide. The reaction can be tempered by the addition of some ice. Already at 5° there takes place a violent generation of nitrogen.

The solution now contains the Na-salt of IV, which by oxidation at low temperature with potassium permanganate passes into the Na-salt of the disulphonic acid V. This is purified by evaporation and recrystallisation, but is not yet free then from inorganic salts. Now the mass is treated with PCl_5 . On pouring out on ice the inorganic substances goes into solution and the sulpho-chloride is obtained pretty pure. It crystallizes very beautifully from chloroform, and melts at 128° . The yield is satisfactory.

These experiments were nearly completed when I became acquainted with the thesis for the doctorate of PFANNENSTILL¹⁾. It appeared from this that he had prepared the disulpho-chloride in a similar way. According to him the melting-point is 131° . He has sulphonised the xylidine. His method of diazotation²⁾ does not proceed so smoothly as mine (temp. $\pm 70^\circ$).

By recrystallization from chloroform I could bring the melting-point of my compound at 129° . PFANNENSTILL prepared the diamide by treatment with ammonia. It crystallized in small globules, m.p. 243° . With alcoholic ammonia I could convert the dichloride into the diamide, which crystallized from water in shiny needles, m.p. 248° . On oxidation with permanganate I obtained the unchanged product back, after having acidified the liquid. From the mother liquid I could isolate a hygroscopic nitrogen-containing product, of which the percentage of N is 7.8 (N-percentage of a disaccharin is 9.7).

Then appeared the before-mentioned paper by POLLAK and LUSTIG. By synthesis they too succeeded in preparing the 1,3-xylene-4,6-disulpho-chloride. They also showed that this disulpho chloride is

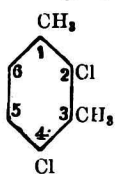
¹⁾ Diss. Lund. 1894.

²⁾ P. KLASON, Ofvers. af K. VET. Akad. förh. 1887.

identical with the disulpho-chloride, obtained by direct sulphonation from *m*-scylene.

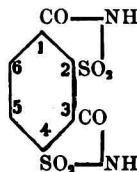
On comparison also my product appeared to be identical with it. On repetition of the oxidation of the diamide with larger quantities, I now could isolate the disaccharin, m.p. 268° by the side of the unchanged product. It is now evident that on direct sulphonation of *m*-xylene, 1,3-xylene-4,6-disulphonic acid is formed, and that the saccharin prepared from it has the corresponding structure. The melting-point of this substance is 268°—270°; its taste is acid and bitter.

WISCHIN has shown that by heating 1,3-xylene-4,6-disulpho-chloride

with PCl_5 , the compound is  formed. We must there-

fore, assume a shifting of groups to have taken place. Such an assumption is always more or less arbitrary.

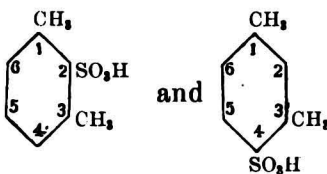
Now the saccharin



is still to be prepared from *m*-xylene.

This comes chiefly to the same thing as the preparation of 1,3-xylene-2,4-disulphonic-acid.

The two mono-sulphonic acids



has long been known.

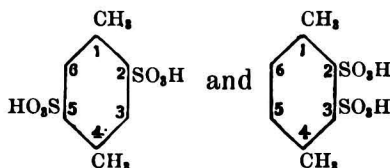
PFANNENSTILL has shown that on further sulphonation 4-sulphonic acid produces 4,6-disulphonic acid.

He calls this 2,4-disulphonic acid, in connection with WISCHIN's experiments. The 2-sulphonic acid yields chiefly 4,6-disulphonic acid on continued sulphonation, and as bye-product a disulphonic acid, the chloride of which is oily. In this sulphonation there has, therefore, again taken place a shifting of groups.

To all probability the oily disulpho chloride is the 2,4-derivative so that it must be possible to prepare the second disaccharin from it. The amide has already been prepared by me; it melts at $\pm 220^\circ$.

Disaccharins from p-xylene.

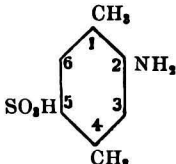
For the preparation of these saccharins are required the sulphonic acids:



It has been found by JESSE HOLMES¹⁾ that on direct sulphonation of *p*-xylene 1,4-xylene-2,6-disulphonic acid is formed. The di-amide prepared from this cannot be oxidized to a di-imide with KMnO_4 .

PFANNENSTILL has found that on sulphonation with SO_2HCl there is formed besides 1,4-xylene-2,6-disulphochloride, m.p. 75° , a small quantity of another disulpho-chloride, m.p. 160° . These experiments have also been made by POLLACK and LUSTIG, who were evidently not acquainted with PFANNENSTILL's work.

For the preparation of 1,4-xylene-2,5-disulphonic acid I have started from *p*-xylene. This was nitrated. The nitro-compound was reduced with iron-filings, and the xylidine was converted into the sulphonic acid with fuming sulphuric acid. This sulphonic acid has

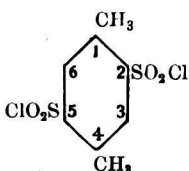
the structure  as *p*-xyloquinone is formed on oxidation with chromic acid.

The Na-salt of the amido sulphonic acid is mixed with the quantity of Na-nitrite calculated and while it is being cooled, drops of hydrochloric acid are added. The sparingly soluble diazonium hydroxide precipitates for the greater part.

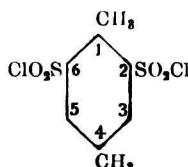
In the meantime a solution of sodium disulphide is prepared, which is cooled by ice being thrown into it. Now the diazonium hydroxide is added. It goes into solution and gives an intensive colour to the liquid. At once a gradual generation of nitrogen sets in. Finally it is heated on the waterbath, till the nitrogen generation stops. Then the solution has lost its intensive colour.

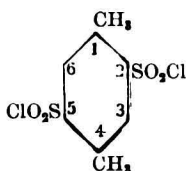
¹⁾ Am. 13, 371 (1891).

Now permanganate solution is added while the cooling is continued, till it is no longer immediately decolorized. The liquid is entirely evaporated, and the salt mass is dried and powdered. This is shaken with its own weight of PCl_5 . At once a violent generation of heat sets in. When the reaction has stopped, the substance is heated to 140° , at which temperature POCl_3 goes over. Now the product is placed on ice. A solid mass of a somewhat brownish colour separates, which is filtered off. A little ether almost entirely removes the brown colour. The disulpho chloride, of which the following structure was

ascertained by this synthesis  proved to be identical

with the product of the direct sulphonation of p-xylene.

Hence in the sulphonation of p-xylene is formed  as

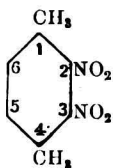
main product, m.p. 75° , and  as by-product, m.p. 162° .

In the usual way the disulphamide is obtained from the disulpho chloride. The disulphamide is insoluble, even in boiling water, but can be purified by solution in lye, and subsequent precipitation by means of hydrochloric acid; m.p. $\pm 310^\circ$.

For the preparation of disaccharin the diamide is stirred up in water, and oxidized with KMnO_4 on a waterbath while heated. After the oxidation the manganese dioxide is filtered off, and the liquid partly evaporated. On acidification with HCl a white product separates slowly. The disaccharin can be separated from the unchanged diamide by recrystallisation from water. M.p. $\pm 320^\circ$. The yield is satisfactory. Also the analysis points to a disaccharin. The taste is bitter.

The second disulphonic acid which must yield a disaccharin, is evidently, not formed on direct sulphonation of p-xylene.

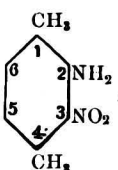
As starting-point for the synthesis of this compound I have chosen



which is formed on strong nitration of *p*-xylene by the

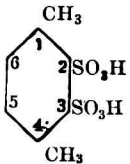
side of 2,5-dinitro-1,4-xylene. The complete separation of these isomers cannot be accomplished, because of the formation of a compound. Small quantities can, however, be separated.

On partial reduction with $(\text{NH}_4)_2\text{S}$ two nitro-xylydines are formed, one of which is very sparingly soluble in acid. This indicates the

structure , as in this compound the amido-group is very

greatly under the influence of the nitro-group.

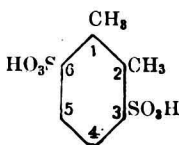
Actually the pure 2,3-dinitro-compound only yields xylydine, which is not easily soluble in acid.

I hope that I shall succeed in preparing the acid  by sub

stitution from this compound.

The disaccharin from o-xylene.

The required sulphonic acid is



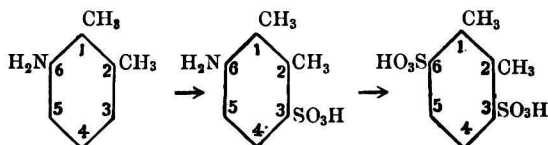
The xylydine  of POULENC FRÈRES was taken as starting-

point.

It is sulphonised with fuming sulphuric acid. First the sulphuric acid salt is formed, which slowly dissolves in the acid. The solution is poured on water and ice. A thick pulpy mass is formed. The precipitate is filtered off and washed, till all the sulphuric acid has been removed. The amido sulphonic acid thus obtained is converted to the Na-salt; from the mother

liquor still more of this salt can be obtained by the leadmethod. It is easily soluble and crystallizes in leaflets. By diazotation with Na_2S_2 sulphur is introduced. Already at -5° a violent generation of nitrogen sets in. The Na-salt of the sulphonic acid and the sulpho chloride are obtained in the usual way. The latter is liquid.

The amido group being strongly para-directing, the above conversions may be represented thus:



I hope to prove the structure further by melting with KOH , the corresponding phenol (m.p. 221°) being known.

A satisfactory yield of diamide can only be obtained from disulpho chloride when it is dissolved in benzene, and gaseous NH_3 is introduced. The diamide can be recrystallized from alcohol. Mp. 251° .

On oxidation with KMnO_4 I obtained, after the liquid was acidified, a first crystallisation that melts at 275° — 280° . This substance is probably the disaccharin. A preliminary micro-analysis is in agreement with this assumption. By means of a mixing-experiment I have shown that diamide and so-called disaccharin are different. The taste is bitter.

Amsterdam }
The Hague } March 1924.