Frankland, and of Kolbe, 1849–1850. The former claimed to have isolated the radicals—*methyl, ethyl, etc.*—by the action of zinc upon the corresponding iodides, while Kolbe obtained the same radicals by the hydrolysis of the sodium salts of acetic, propionic and such acids. In vain did Gerhard and Laurent insist that the molecular formulas of all these so-called free radicals must be doubled, in accordance with Avogadro's hypothesis. The existence of free radicals was generally accepted as late as 1865, fifty years after Gay Lussac's introduction of this idea into chemistry. Even Kekulé for a time considered Frankland's "methyl" as distinct from ethane. But in 1864 Schorlemmer showed by experimental evidence that Frankland's and Kolbe's methyl and ethyl were nothing else than ethane and butane. From that time on, the question relative to the existence of free radicals was never seriously raised until the discovery of triphenylmethyl.

How parallel these two periods in the history of chemistry are! Now, as then, a methyl was prepared by the abstraction of halogen from the corresponding alkyl-halide. Now, as then, it was found that the molecular weight of the product must be doubled. But now, unlike as in the period of fifty years ago, it was possible to show, by physical and chemical evidence, that the product which results from the coupling of the radicals is at best unstable. It was possible to show that it does not retain its individuality, but tends to break down again and is in equilibrium with the truly free radicals. And so we find ourselves obliged to reintroduce the conception of free radicals, and also to introduce the supplementary notion of organic substances existing under certain conditions in a state of actual dissociation.

What the future holds in regard to this new revival of the much disputed question is difficult to foretell. As a working hypothesis it has fully justified its existence, it has opened a new branch of organic chemistry.

ANN ARBOR, MICH.

SYNTHESIS OF DEPSIDES, LICHEN-SUBSTANCES AND TANNINS.

BY EMIL FISCHER.[1]

Received April 30, 1914.

Gentlemen:

The substances mentioned in the title are ester-like derivatives of the phenol carbonic acids, to which belongs gallic acid, so widely distributed in the plant kingdom and discovered in 1786 by C. W. Scheele, as well

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[1] Address delivered before the Naturforscher-Versammlung, Vienna, Sept. 23, 1913; and published in *Ber.*, 46, 3253–89 (1913). Translated by Frank Rose Elder, Columbia University, and published here through the courtesy and with the consent of Excellent Fischer and of the editors of the *Berichte.*

as the famous remedy salicylic acid, and which, therefore, are interesting, not alone to chemists, but also to the plant physiologists and the medical profession. Their study occupies a large space in the history of the aromatic group, and it gives me pleasure to refer to the fact that, at no place, so much has been worked out concerning these substances as right here in Vienna. It suffices to recall the investigations of F. Rochleder, H. Hlasiwetz, L. Barth and recently of J. Herzig and his students.

These phenol carbonic acids possess, among other properties, the ability to form ester-like anhydrides with one another, in such a manner that the carboxyl of the first molecule unites with the phenol group of the second. As the simplest example, I would cite the first anhydride of hydroxybenzoic acid:

$$HO.C_6H_4.CO.O.C_6H_4.COOH$$

By similar coupling of a third molecule of hydroxybenzoic acid the following system results:

$$HO.C_6H_4.CO.O.C_6H_4.CO.O.C_6H_4.COOH$$

Such ester-like anhydrides, Freudenberg and I have named[1] "depsides." The word is derived from the Greek δε'ψειν (to tan), because many of these substances show resemblances to the tannins. According to the number of phenol carbonic acids which are coupled together, one distinguishes didepsides, tridepsides, tetradepsides. Thus the nomenclature is formulated as in the case of the polysaccharides and polypeptides. Such depsides are nowise new, for the two substances just mentioned above, the di- and tridepsides of *p*-hydroxybenzoic acid, were obtained by Klepl in 1883[2] by simply heating *p*-hydroxybenzoic acid. But his simple procedure is not applicable to most of the other phenol carbonic acids, as they cannot stand the necessarily high temperature. Still older are the exhaustive investigations of Schiff,[3] on the formation of similar substances from the phenol carbonic acids by dehydrating agents.

By treatment of gallic acid with phosphorus oxychloride, Ch. Gerhardt,[4] in 1853, prepared the amorphous anhydride of salicylic acid from sodium salicylate, obtaining an amorphous product which showed the tannin reactions, and which he considered to be digallic acid, $C_{14}H_{10}O_9$. Prior to this, J. Löwe[5] had observed that gallic acid, when heated with arsenic acid, was changed into a tannin-like body. On repetition of the experiment, Schiff came to the conclusion that this product was also digallic acid. Later he and his students applied the anhydrization by

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[1] *Ann.*, **372**, 35 (1910).

[2] *J. prakt. Chem.*, [2] **28**, 208.

[3] *Ber.*, **4**, 232, 967 (1871); *Ann.*, **170**, 43 (1873); **163**, 218, 219 (1872); **172**, 356 (1874); *Ber.*, **15**, 2588 (1882); *Gazz. chim. ital.*, **17**, 552 (1887); *Ann.*, **252**, 87 (1889).

[4] *Ann.*, **87**, 159.

[5] *J.*, **1868**, 559.

phosphorus oxychloride to a whole series of other phenol carbonic acids, protocatechuic acid, salicylic acid, *m*-hydroxybenzoic acid, cresotinic acid, phloretic acid and pyrogallol carbonic acid. According to the conditions, didepsides or complicated anhydrides resulted.

Unfortunately, the majority of depsides described by Schiff are amorphous, and, therefore, have not withstood criticism concerning their individuality and composition. In particular, his view that the amorphous digallic acid is identical with tannin cannot be maintained.[1] This will be returned to later.

However, the procedure of Schiff, repeated in other hands, has led to sharply defined didepsides. Thus, in a patent of the firm of C. F. Böhringer and Son[2] is cited a useful process for preparing disalicylic acid with phosphorus oxychloride and I, together with Freudenberg, have shown that by the same treatment of *p*-hydroxybenzoic acid, under certain conditions, the didepside of the acid discovered by Klepl[3] is obtained in excellent yield.

Besides the depsides, which are true acids, the phenol carbonic acids also may form neutral anhydrides. To this class belongs the *p*-hydroxybenzoide $(C_7H_4O_2)_x$, of Klepl; then the different salicylides, cresotides, phloretides and probably also the tetra-*p*-hydroxybenzoide[4] of Schiff. These, however, cannot be further considered here.

The inducement to take up the synthesis of the depsides was presented by the following observation in the synthesis of polypeptides of tyrosine:

For the preparation of glycyltyrosylglycine, a chloride of chloroacetyl tyrosine was necessary. Since the free phenol group appears to hinder the action of phosphorus chloride, I thought of the scheme of protecting the latter by introducing a group which subsequently could be easily removed, and chose for this purpose the carbomethoxy group.[5] The application of this process to the common phenol carbonic acids is the starting point for all the products which I will take up today. I have, in this investigation, enjoyed the valuable assistance of different young professional colleagues, whose share is evident from the titles of the single publications, and of these I will mention particularly Mr. Karl Freudenberg.

Carbomethoxylation of the Phenolcarbonic Acids.

Carboalkoxy derivatives of the common phenols have been long known. However, with a single exception,[6] which I will later mention particularly, these derivatives of their carbonic acids were lacking. It is now known

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[1] Freda, *Gazz. chim. ital.*, **8**, 9, 363 (1878); **9**, 327 (1879); Bignelli, *Chem. Zentr.*, **1909**, II, 1861–3; **1910**, II, 23; cf. further the later history of the tannins.

[2] D. R. P., 211,403; cf. *Chem. Zentr.*, **1909**, II, 319, 1285.

[3] *Ann.*, **372**, 45 (1910).

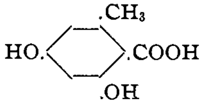
[4] *Ber.*, **15**, 2588 (1882).

[5] *Ibid.*, **41**, 2860 (1908).

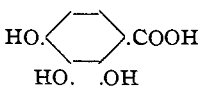
[6] Carboethoxy-salicylic acid of F. Hofmann.

that such substances result easily by the action of chlorocarbonic alkyl ester and alkali on phenol carbonic acids in cold aqueous solution.[1]

The course of the reaction is particularly smooth, if the phenol group is in the *meta* or *para* position to the carboxyl and, the accumulation of hydroxyl groups is no obstacle; for protocatechuic acid and gallic acid can be completely carbomethoxylated with slightly more than the theoretical quantity of chlorocarbonic methyl ester. The behavior is somewhat otherwise if a hydroxyl stands next to a carboxyl. Sometimes the complete carbomethoxylation succeeds in aqueous alkaline solution with an excess of chlorocarbonic methyl ester, as the case of orsellinic acid[2] and pyrogallolcarbonic acid,[3] demonstrates.

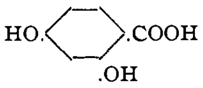


Orsellinic acid.



Pyrogallolcarbonic acid.

In other cases, under the same conditions, the ortho hydroxyl remains incompletely carbomethoxylated, even if a large excess of the reagent is employed. The case of β-resorcylic acid has been more minutely investigated.[4]



Salicylic acid behaves similarly. The complete carbomethoxylation of this latter acid can be attained by treatment with chlorocarbonic methyl ester in presence of dimethyl aniline in an indifferent solvent, for example, benzene. The process was first used by Fritz Hofmann for the preparation of carboethoxy salicylic acid, but has only been described in an American patent (No. 1,639,174 of Dec. 12, 1899), which has been recorded neither in the scientific nor in the collected chemical patent literature. I learned of it only by chance, in a private communication from Mr. A. Einhorn, just at a time when I was occupied in working out such a method myself. We have since applied the process with success, not alone to salicylic acid,[5] but also to some other *o*-phenolcarbonic acids, such as the just mentioned β-resorcylic acid,[6] and the isomeric gentisic acid[7] (hydroquinone carbonic acid). Even with phloroglucine carbonic acid,[8] which in aqueous alkaline solution takes on only one carbomethoxy group, the

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[1] E. Fischer, *Ber.*, **41**, 2875 (1908).

[2] E. Fischer and K. Hoesch, *Ann.*, **391**, 366 (1912).

[3] E. Fischer and M. Rapaport, *Ber.*, **46**, 2389 (1913).

[4] E. Fischer and K. Freudenberg, *Ann.*, **384**, 234 (1911).

[5] *Ber.*, **42**, 218 (1909).

[6] *Ibid.*, **42**, 225 (1909).

[7] *Ibid.*, **42**, 223 (1909).

[8] *Ann.*, **371**, 306 (1910).

process succeeds if one uses a large excess of chlorocarbonic methyl ester and dimethyl aniline. However, the carboxyl group is also affected, and it forms an indifferent product, probably of anhydride-like nature. This, however, can be destroyed (as I, in conjunction with H. Strauss, have shown), by bicarbonate in acetone solution, without splitting off the carbomethoxy group. By this artifice, which is also applicable in other cases, the preparation of tricarbomethoxy phloroglucine carbonic acid,[1] succeeded without difficulty and thus it appears that the method is sufficiently complete to be available for all phenol carbonic acids.

It is remarkable that the difficulty encountered with the *ortho* phenol group disappears, if the carboxyl is not directly attached to the benzene nucleus; for *o*-coumaric acid (*o*-hydroxy cinnamic acid) can be very easily carbomethoxylated in aqueous alkaline solution. So far, the following acids have been completely carbomethoxylated:

(*a*) In aqueous alkaline solution:
    p-Hydroxybenzoic acid (*Ber.*, **41**, 2877 (1908))
    m-Hydroxybenzoic acid (will be published later)
    Vanillic acid (*Ann.*, **372**, 47 (1910))
    o-Coumaric acid (*Ber.*, **42**, 226 (1909))
    Phloretic acid (will be published later)
    Caffeic acid (will be published later)
    Ferulic acid (*Ann.*, **391**, 357 (1912))
    Protocatechuic acid (*Ber.*, **41**, 2881 (1908))
    α-Resorcylic acid (*Ber.*, **46**, 1145 (1913))
    Orsellinic acid (*Ann.*, **391**, 366 (1912))
    Gallic acid (*Ber.*, **41**, 2882 (1908))
    Pyrogallolcarbonic acid (*Ber.*. **46**, 2390 (1913))
    Syringic acid (will be published later)

(*b*) According to the process of F. Hofmann:
    Salicylic acid (*Ber.*, **42**, 218 (1909))
    α- and β-Hydroxynaphthoic acids (*Ann.*, **391**, 352, 355 (1912))
    β-Resorcylic acid (*Ber.*, **42**, 225 (1909))
    Gentisic acid (*Ber.*, **42**, 223 (1909))
    Phloroglucinecarbonic acid (*Ber.*, **46**, 2400 (1913))

With the polyphenol carbonic acids, there is naturally the possibility of partial carbomethoxylation. They are governed by the orienting influence which the carboxyl exercises on the entrance of the carbomethoxy group. On this point the following data have, so far, been gathered:

In the *o*-, *p*-dihydroxybenzoic acid, the carbomethoxy group enters preferably in the *p*-position; and, if one decreases the quantity of chlorocarbonic ester to one mol, with gentisic acid,[2] β-resorcylic acid and orsellinic acid,[3] the *p*-monocarbomethoxy compound can be isolated in moderately pure condition.

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[1] E. Fischer and H. Strauss, *Ber.*, **46**, 2400 (1913).

[2] *Ber.*, **42**, 222, 224 (1909).

[3] E. Fischer and K. Hoesch, *Ann.*, **391**, 364 (1912).

It is otherwise with gallic acid; for here the first carbomethoxy group enters preferably in the *m*-position,[1] perhaps because the *p*-hydroxyl is protected from reaction by the two other neighboring hydroxyls. Partial carbomethoxylation succeeds easily with phloroglucinecarbonic acid; for in aqueous alkaline solution it takes on only one carbomethoxy group, and that happens most probably in the para position.[2]

The change from carbomethoxy compounds ,back to phenolcarbonic acids is accomplished with extraordinary ease by excess of cold aqueous alkali. Aqueous N ammonia acts similarly, though somewhat more slowly; but the carbomethoxy group is then split off mostly as urethane and not as carbonate. Neutral alkali carbonate also acts in the cold, but more slowly; while bicarbonate is rather indifferent, and thus, in most cases, serves to dissolve the acids. Only a few difficultly soluble alkali salts were encountered.

By insufficient quantity of alkali, partial elimination of the carbomethoxy groups results. Thus there was obtained from the dicarbomethoxyprotocatechuic acid, the *m*-monocarbomethoxy compound;[3] and from the tricarbomethoxygallic acid, the 3,5-dicarbomethoxy compound.[4] In both cases, preferably the *p*-carbomethoxy group was split off.

These partially carbomethoxylated substances have played a role in the synthesis of didepsides which will be spoken of later.

Furthermore, they can be methylated by diazomethane, whereby the carboxyl is esterified and all the free phenol groups methylated. These esters then yield, by double saponification, the corresponding partially methylated phenolcarbonic acids. In such a way, the structure of the monocarbomethoxyprotocatechuic acid,[5] and of the 3,5-dicarbomethoxygallic acid,[6] was determined.

The same process is also adapted to the practical preparation of such partially methylated substances as are difficult to prepare in other ways. In this manner, the *o*-methyl ethers of gentisic acid,[7] β-resorcylic acid[7] and orsellinic acid[8] were prepared; as well as the *o,o*-dimethyl ether of phloroglucinecarbonic acid,[7] the *p*-methyl ether[7] and the *m,p*-dimethyl ether of gallic acid.[9]

It is worth noticing that with the above-mentioned esters of carbo-

[1] E. Fischer and K. Freudenberg, *Ber.*, **45**, 2716 (1912).

[2] *Ann.*, **371**, 306 (1910).

[3] E. Fischer and K. Freudenberg, *Ibid.*, **384**, 235 (1911).

[4] E. Fischer, *Ber.*. **41**, 2885 (1908); further, E. Fischer and K. Freudenberg, *Ann.*, **384**, 240 (1911); cf. E. Fischer and O. Pfeffer, *Ibid.*, **389**, 211–4 (1912).

[5] E. Fischer and K. Freudenberg, *Ibid.*, **384**, 236 (1911).

[6] E. Fischer and O. Pfeffer, *Ibid.*, **389**, 199 (1912).

[7] *Ibid.*, **389**, 199 ff. (1912).

[8] E. Fischer and K. Hoesch, *Ibid.*, **391**, 372 (1912).

[9] E. Fischer and K. Freudenberg, *Ber.*. **45**, 2717 (1912).

methoxylated phenolcarbonic acids, the ester group is removed more easily by cold concentrated sulfuric acid, the carbomethoxy group on the other hand more easily by cold alkali.

Chlorides of the Carbomethoxyphenolcarbonic Acids.

These result from the action of phosphorus pentachloride on the acids, are usually crystalline, and show the important reactions of benzoyl chloride. Since, further, the carbomethoxy group can be subsequently easily removed, they have been valuable materials for synthesis.

It would naturally be still simpler to use in their place the chlorides of the phenolcarbonic acids themselves, but their preparation involves difficulties. In the action of phosphorus pentachloride it is well known that, besides the carboxyl, the phenol group is attacked, as R. Anschütz has shown in many cases. Only when the hydroxyl is crowded in between a neighboring carboxyl and a second *o*-substituent, is it removed from the action of phosphorus chloride and thus permits the preparation of the simple acid chloride.[1]

The chlorides of the phenolcarbonic acids can, as a rule, be prepared, directly according to the method of H. Meyer,[2] by heating with thionyl chloride; but the products are with few exceptions oils, whose individuality appears doubtful to me, and from which the discoverer, aside from the esters, has prepared no other derivatives of the phenolcarbonic acids. Thus they cannot be compared in regard to usefulness, with the well behaved and relatively stable chlorides of the carbomethoxy phenolcarbonic acids. The process of Meyer has recently been improved by Kopetschni and Karzag, in that, in the place of the free acid, the alkali salt is treated with thionyl chloride. In this way they succeeded in obtaining a crystalline salicylic acid chloride.[3]

Finally, the chlorides of the completely methylated or acetylated phenolcarbonic acids have been long known. They are sufficiently stable to be of service in synthesis. But, the later removal of the methyl or acetyl group demands energetic treatment with acids or alkalies, and is thus excluded for all products which, by this treatment, undergo further change, for example, with the ester-like derivatives of the phenolcarbonic acids.

The chlorides of all the above-mentioned carbomethoxylated phenolcarbonic acids have been prepared by use of phosphorus pentachloride, either by gentle heating, or, in the case of sensitive substances, by shaking the acid and pentachloride with dry chloroform. If the chloride crystallizes with difficulty, it is advisable to remove the phosphorus oxychloride by dilution of the chloroform solution and by long, very gentle, heating of the residue in a high vacuum.

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[1] Anschütz, *Ber.*. **30**, 221 (1897).

[2] *Monatsh.*, **22**, 415 (1901).

[3] *Chem. Zentr.*, **1913**, II, 728.

Most of the chlorides were obtained crystalline, only the tricarbomethoxy phloroglucinecarbonic acid, carbomethoxysalicylic acid, and carbomethoxyphloretic acid have so far remained as oils. The last two, however, can be sufficiently purified by distillation in a high vacuum.

These chlorides have been used, so far, for the following syntheses:

1. With alcohols they immediately form esters, which, by subsequent saponification with alkali, are changed into the ester of the free phenolcarbonic acid. An example is the preparation of ethyl gallate.[1] The method, naturally, has here no practical significance, because the esterification of the phenolcarbonic acids with the monohydric alcohols is attained much more conveniently by older methods. On the other hand the process acquires great importance in its application to the polyhydric alcohols and especially in the sugar series. This will be fully considered later.

2. The chlorides act energetically on the esters of amino acids and can be coupled with amino acids in aqueous alkaline solution. By subsequent splitting off of the carbomethoxy group there results finally the derivative of the phenolcarbonic acid. As an example, the synthesis of *p*-hydroxyhippuric acid (*p*-hydroxybenzuric acid)[2] may serve. It is accomplished according to the following equations:

$$CH_3CO_2.O.C_6H_4.CO.Cl + 2NH_2.CH_2.CO_2C_2H_5 =$$
$$CH_3CO_2.OC_6H_4.CO.NH.CH_2.CO_2C_2H_5 + HCl.NH_2.CH_2.CO_2C_2H_5$$
$$CH_3CO_2.O.C_6H_4.CO.NH.CH_2CO_2C_2H_5 + 3NaOH =$$
$$HO.C_6H_4.CO.NH.CH_2COONa + Na_2CO_3 + C_2H_6O + CH_4O$$

Similarly, the isomeric salicyluric acid was prepared.[3] The process appears, to me, to be much better than the one used somewhat earlier by Bondi[4] for the preparation of salicyluric acid from glycocoll and salicylic acid azide. Finally, there is still to be mentioned the synthesis of 3,4-dihydroxyhippuric acid from the chloride of the dicarbomethoxyprotocatechuic acid and glycocoll ester,[5] as well as of vanilloylglycine from the chloride of carbomethoxyvanillic acid.[6] I do not doubt that this method is sufficient for the preparation of numerous combinations of this sort.

3. Under the influence of aluminium chloride, the chlorides unite easily with benzene, and on subsequent splitting off of the carbomethoxy group, there results the unsymmetrical hydroxy derivatives of benzophenone. For *p*-hydroxybenzophenone,[7] the synthesis runs according to the following equations:

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[1] *Ber.*, **42**, 1022 (1909).
[2] *Ibid.*, **41**, 2880 (1908).
[3] *Ibid.*, **42**, 219 (1909).
[4] *Z. physiol. chem.*, **52**, 170 (1907).
[5] T. Kametaka, *Ber.*, **42**, 1482 (1909).
[6] E. Fischer and K. Freudenberg, *Ann.*, **372**, 66 (1910).
[7] *Ber.*, **42**, 1017 (1909).

$$CH_3CO_2.O.C_6H_4.CO.Cl + C_6H_6 = CH_3CO_2.O.C_6H_4.CO.C_6H_5 + HCl$$

$$CH_3CO_2.O.C_6H_4.CO.C_6H_5 + 3NaOH = Na_2CO_3 + CH_3OH + H_2O + NaO.C_6H_4.CO.C_6H_5.$$

In this manner, there was prepared from α-resorcylic acid the 3,5-dihydroxybenzophenone,[1] from gallic acid the 3,4,5-trihydroxybenzophenone,[2] and from β-resorcylic acid the already known 2,4-dihydroxybenzophenone.[3] Finally, pyrogallolcarbonic acid gave the isomeric, 2,3,4-trihydroxybenzophenone,[4] which is identical with the mordant dyestuff known under the name of alizarin yellow A, and thus its structure is established beyond doubt.

4. The chlorides can be coupled with the free phenolcarbonic acids and, by subsequent splitting off of the carbomethoxy group, didepsides obtained. By repetition of the operation, tri- and tetradepsides were prepared. The process is susceptible of many variations, as the following sections will show.

The applicability of the chlorides for synthesis is certainly not exhausted by these reactions. One can hope that they will be useful in most cases where benzoyl chloride and its derivatives have already proven themselves of service, and where it is desired to regain the phenol group by very mild hydrolysis. Thus, I believe without hesitation, that the chloride of carbomethoxy ferulic acid can be recommended for the experiment on the building up of curcumin, just as V. Lampe and J. Milobedzka[5] have succeeded in preparing the similar dicinnamoylmethane.

Didepsides.

Their history has been so adequately treated before that I must here content myself by describing only the new method. *p*-Hydroxybenzoic acid serves for the simplest case of the synthesis. The chloride of its carbomethoxy derivative unites with *p*-hydroxybenzoic acid in cold, aqueous alkaline solution, according to the following equations, and there results the alkali salt of carbomethoxy-*p*-hydroxybenzoyl-*p*-hydroxybenzoic acid:[6]

$$CH_3CO_2.O.C_6H_4.CO.Cl + NaO.C_6H_4.COONa = NaCl + CH_3CO_2.O.C_6H_4.CO.O.C_6H_4.CO_2Na$$

On account of its slight solubility, it separates from its aqueous solution as the crystalline salt, but can be easily changed to the free acid by cold hydrochloric acid. In most other cases, the alkali salts are easily soluble

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[1] E. Fischer and H. O. L. Fischer, *Ber.*, **46**, 1147 (1913).

[2] *Ibid.*, **42**, 1018 (1909).

[3] *Ann.*, **371**, 317 (1910).

[4] E. Fischer and M. Rapaport, *Ber.*, **46**, 2393 (1913).

[5] *Ber.*, **46**, 2235 (1913).

[6] *Ibid.*, **42**, 216 (1909).

in water and the resulting aqueous liquid is precipitated directly by mineral acid.

Since the chlorides used are ordinarily solid and in this form react too slowly, I, at first, used ethereal solutions for this coupling; later, acetone solution[1] was shown to be preferable in the majority of cases, and many couplings can be carried out satisfactorily only by use of this expedient. The ordinary procedure is as follows: The phenolcarbonic acid to be coupled is dissolved in the calculated quantity of N or 2 N alkali, some acetone added, the whole cooled to a low temperature and to this solution is added, in several alternate portions, another 1.1 mol of 2 N alkali and a solution of the chloride in dry acetone, the mixture being well stirred. The coupling takes place very quickly and completely even at low temperature. In most cases, the difficultly soluble coupled product can be precipitated by acidification and dilution with water. In other cases, the acetone is distilled off at low pressure, or the liquid is extracted with ether directly after acidification and dilution.

Instead of the alkali, dimethyl aniline can be used as the base, and the coupling can be carried out with exclusion of water. An example of this sort is found in the preparation of carbomethoxy-β-hydroxynaphthoyl-β-hydroxynaphthoic acid[2] from β-hydroxynaphthoic acid and the chloride of its carbomethoxy derivative. The coupling is effected by dimethyl aniline in benzene solution.

Finally, as a curiosity, may be mentioned the coupling of carbomethoxyferuloylchloride with *p*-hydroxybenzoic acid by several hours' heating of its solution in acetylene tetrachloride at 110°. The reaction is completed with evolution of hydrochloric acid gas.[3]

The general process, naturally, can also serve for the preparation of mixed forms and it may be mentioned historically that the first coupling of this sort was carried out with *p*-hydroxybenzoic acid, and the chloride of tricarbomethoxygallic acid, whereby the tricarbomethoxygalloyl-*p*-hydroxybenzoic acid resulted.[4]

If the phenolcarbonic acid contains only one hydroxyl group, the course of the reaction is simple. The behavior is naturally more complicated when 2 or 3 hydroxyl groups are present; for not only can isomeric carbomethoxylated didepsides result, but also complicated products, such as derivatives of tri- or tetradepsides. In most investigations which have been carried out in this direction, the product was a mixture whose resolution into its constituents presented difficulty. Only one example was worked out satisfactorily with definite results. This is the coupling of

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[1] E. Fischer and K. Hoesch. *Ann.*, **391**, 348 (1912).

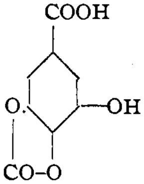
[2] *Ibid.*, **391**, 355 (1912).

[3] *Ibid.*, **391**, 359 (1912).

[4] *Ber.*, **41**, 2888 (1908).

the dicarbomethoxyorsellinic chloride with orsellinic acid,[1] which was necessary for the synthesis of lecanoric acid.

In other cases, it has been preferable to protect a part of the phenol groups of the phenolcarbonic acids to be coupled, by carbomethoxy groups. As an example, the synthesis of digallic acid serves. Here the chloride of tricarbomethoxygallic acid was coupled, not with free gallic acid, but, with its dicarbomethoxy derivative in alkaline solution,[2] and if, instead of the dicarbomethoxy compound, the carbonylogallic acid[3]



which contained a free hydroxyl in the *m*-position,[4] was used, still better results were obtained.

Another example is the coupling of dicarbomethoxyprotocatechuic acid chloride with monocarbomethoxyprotocatechuic acid in alkaline solution to give diprotocatechuic acid.[5]

According to the former process, in the coupling of a chloride to an *o*-phenol group in alkaline solution, a certain deviation which noticeably decreased the yield was observed, and thus, in many cases, it was impossible to isolate the product. Hence, another modification besides the use of dimethyl aniline was sought.

A satisfactory result was obtained when, instead of the phenolcarbonic acid, the aldehyde was used. The best example of this is furnished by the synthesis of *o*-diorsellinic acid,[6] for which the chloride of dicarbomethoxyorsellinic acid was brought together with *p*-monocarbomethoxyorcyl aldehyde in alkaline solution. The coupled product results in good yield and can be changed easily into tricarbomethoxy-*o*-diorsellinic acid by oxidation with permanganate. I am convinced that equally good results would be obtained with salicylic acid and similar substances.

For the preparation of *o*-didepsides the treatment of *o*-phenolcarbonic acids with phosphorus pentachloride and dimethyl aniline also serves, as is proven by the synthesis of disalicylic acid according to the patent of Böhringer and Son. We have applied the process with success to the monocarbomethoxy derivatives of gentisic acid and *β*-resorcylic acid,

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[1] E. Fischer and H. O. L. Fischer, *Ber.*, **46**, 1138 (1913).

[2] E. Fischer, *Ibid.*, **41**, 2890 (1908); E. Fischer and K. Freudenberg, *Ann.*, **384**, 242 (1911).

[3] E. Fischer and K. Freudenberg, *Ber.*, **46**, 1120 (1913).

[4] *Ibid.*, **46**, 1124 (1913).

[5] E. Fischer and K. Freudenberg, *Ann.*, **384**, 238 (1911).

[6] E. Fischer and H. O. L. Fischer, *Sitzungsber. d. Berliner Akad.*, **1913**, 507.

which contain the carbomethoxy group in the *p*-position. In both cases, the coupled product, *i. e.*, the dicarbomethoxy compound of the didepside, could be obtained crystalline.[1]

The carbomethoxy derivatives of the didepsides are as a rule crystalline substances. An exception is the amorphous derivative of digallic acid, which, so far, has resisted all attempts to crystallize it. Also, in other cases (for example with protocatechuic acid), we have given up the isolation of the carbomethoxy derivative, since the didepside itself is more easily purified. The carbomethoxy compounds are true acids and thus decompose alkali bicarbonate and, in general, are easily soluble in dilute potassium bicarbonate solution. This property can be used to advantage as a test of purity and also for separation from other indifferent substances.

The formation of the carbomethoxy didepsides often occurs with nearly theoretical yield. In other cases, this is lowered by side reactions. If the coupling takes place in aqueous alkaline solution, a large part of the chloride can be recovered as the corresponding acid. If the coupling takes place in alkaline acetone solution or in benzene solution with dimethyl aniline, there is obtained a varying quantity of indifferent substances of the nature of acid anhydrides. Their separation is carried out, as above mentioned, by treatment of the crude product with a dilute solution of potassium bicarbonate. Thus it is preferable to dissolve the crude product in a little acetone and then mix with the bicarbonate solution. The carbomethoxydidepside is then later precipitated from the aqueous solution of its potassium salt by mineral acid.

Elimination of the Carbomethoxy Group.

As already mentioned, this can be carried out by cold dilute alkali or by aqueous ammonia. In the first case the alkali carbonate results, in the second, a large part of the carbomethoxy group is split off as urethane.[2] If the depside union is strong enough to resist the action of the alkali for hours then this procedure is best. For this purpose, the carbomethoxy derivative is dissolved in enough *N* alkali to neutralize the carboxy group, and to eliminate the carbomethoxy group a further 2 mols of sodium hydroxide are added. This operation is best carried out at 20° and the reaction is generally ended in $^1/_2$ to $^3/_4$ hour. Only in the preparation of lecanoric acid from its carbomethoxy derivative was the alkali allowed to act for 2 hours, as lecanoric acid itself is very stable towards cold alkali; while with most didepsides, 24 hours' standing with 3 mols excess of *N* sodium hydroxide completely, or largely, splits the compounds into its components.

On account of this sensitiveness towards alkali, aqueous ammonia was used in the majority of cases for splitting the carbomethoxy derivative.

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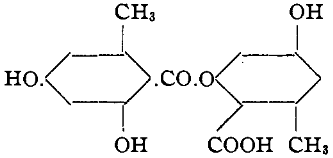
[1] E. Fischer and K. Freudenberg, *Ann.*, **384**, 225 (1911).

[2] *Ber.*, **41**, 2885 (1908).

Here, also, the action takes place best at 20° and N or $N/2$ solution in large excess was used. Since some of the ammonium salts of the carbomethoxy didepsides are rather insoluble in water, it is preferable, in such cases, to use acetone or pyridine as solvent.

The didepsides so far investigated are crystalline substances, difficultly soluble in cold water, which melt with decomposition, react acid and dissolve in bicarbonate solution. On account of the free hydroxyl group, they give colorations with ferric chloride which are suggestive of those produced by the free phenolcarbonic acids. If, for example, the phenol group is next to a carboxyl then, similarly to salicylic acid, a strong red to blue-violet coloration is observed. This color may not appear, however, if an hydroxyl is next to a depside union, for *p*-diorsellinic acid gives no real purple coloration.



All depsides are split into their components by excess of dilute alkali at room temperature, the reaction velocities differing very greatly.

By diazomethane, the depsides are totally methylated. Esterification of the carboxyl group takes place first and then methylation of the free phenol groups; the hydroxyl next to a carboxyl is attacked most slowly. The resulting, totally methylated, esters are beautifully crystalline substances which melt lower than the depsides and without decomposition. They thus serve very well as a means of characterization and identification of the depsides. As examples, I would cite the products which will be discussed later, namely, the methyl ester of trimethyl-*p*-diorsellinic acid from lecanoric and evernic acids and the pentamethyl-*m*-digallic acid from *m*-digallic acid.[1] If the depsides contain several adjacent phenol groups, as in gallic acid or pyrogallol carbonic acid, they are very sensitive to oxygen in alkaline solution, which deserves attention during their preparation.

The didepsides of gallic, protocatechuic, gentisic and β-resorcylic acids are precipitated by dilute glue solution and give precipitates with quinine acetate or by high dilution. They differ in this respect from the corresponding phenolcarbonic acids and approach the tannins.

Tridepsides.[2]

From monophenol carbonic acids, the theory only admits of the following type of tridepside:

$$HO.C_6H_4.CO.O.C_6H_4.CO.O.C_6H_4.COOH$$

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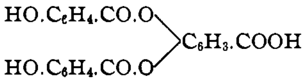
[1] E. Fischer and K. Freudenberg, *Ber.*, **46**, 1127 (1913).

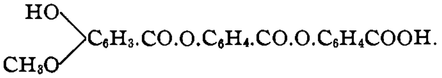
[2] E. Fischer and K. Freudenberg, *Ann.*, **372**, 32 (1910).

If however, a di- or triphenolcarbonic acid is considered, then the following type is possible:



$$\left.\begin{matrix} HO.C_6H_4.CO.O \\ HO.C_6H_4.CO.O \end{matrix}\right\rangle C_6H_3.COOH$$

Compounds of the second type have not been fully investigated so far. Perhaps to this class belongs a substance which Freudenberg and I[1] obtained as a by-product after saponification subsequent to the action of tricarbomethoxygalloyl chloride on gallic acid in alkaline solution. Our feeling that it is a bisgalloylgallic acid still lacks proof, however, and thus the exact description of our investigation has been delayed. Of the compounds of the first type, two examples are known, the di-*p*-hydroxybenzoyl-*p*-hydroxybenzoic acid, and the mixed form vanilloyl-*p*-hydroxybenzoyl-*p*-hydroxybenzoic acid,



$$\left.\begin{matrix} HO \\ CH_3O \end{matrix}\right\rangle C_6H_3.CO.O.C_6H_4.CO.O.C_6H_4COOH.$$

The first was obtained by Klepl, along with the didepside, by heating *p*-hydroxybenzoic acid. Freudenberg and I prepared it in beautifully crystalline and apparently pure condition by the new method in the following way:

p-Carboethoxybenzoyl chloride was coupled with *p*-hydroxybenzoyl-*p*-hydroxybenzoic acid in alkaline solution. To split off the carboethoxy group, the product was dissolved in a mixture of acetone and pyridine and ammonia was then added. The tridepside could be obtained in moderately long needles by recrystallization from acetone, while Klepl has described it as a scarcely crystalline powder. In spite of this, we believe that his preparation is identical with our tridepside. The same product could undoubtedly be obtained in a third way, namely by coupling *p*-hydroxybenzoic acid with the chloride of carbomethoxy-*p*-hydroxybenzoyl-*p*-hydroxybenzoic acid.

The second mixed tridepside was prepared in an analogous way from carbomethoxyvanilloyl chloride and *p*-hydroxybenzoyl-*p*-hydroxybenzoic acid.

The two tridepsides melt above 200°, are practically insoluble in water and difficultly soluble in most organic solvents. With ferric chloride they give colorations in alcohol solution similar to that of *p*-hydroxybenzoic acid.

Tetradepsides.[2]

Here also two forms are known, the tri-*p*-hydroxybenzoyl-*p*-hydroxybenzoic acid,

$$HO.C_6H_4.CO.O.C_6H_4.CO.O.C_6H_4.CO.O.C_6H_4.COOH,$$

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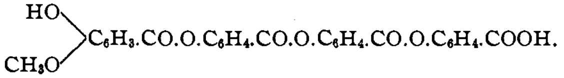
[1] *Ber.*, **45**, 2712 (1912).

[2] E. Fischer and K. Freudenberg, *Ann.*, **372**, 32 (1910).

and vanilloyl-di-*p*-hydroxybenzoyl-*p*-hydroxybenzoic acid,



$$\begin{matrix}HO\\CH_3O\end{matrix}\!\!>C_6H_3.CO.O.C_6H_4.CO.O.C_6H_4.CO.O.C_6H_4.COOH.$$

The first was prepared from carboethoxy-*p*-hydroxybenzoyl-*p*-hydroxybenzoyl chloride and *p*-hydroxybenzoyl-*p*-hydroxybenzoic acid in alkaline solution. For the preparation of the second, carbomethoxyvanilloyl-*p*-hydroxybenzoyl chloride and *p*-hydroxybenzoyl-*p*-hydroxybenzoic acid served.

Here, all operations were rendered difficult by the slight solubility and reactivity of the materials. Both tetradepsides could be obtained crystalline. They are very difficultly soluble in most organic solvents and melt with decomposition.

Under the name of tetra-*p*-oxybenzoide, H. Schiff[1] has described a product that resulted by heating *p*-hydroxybenzoic acid with phosphorus oxychloride, and which has the same composition as the above tetradepside. A repetition of Schiff's experiment has shown that this preparation differs from ours and, thus, we do not believe it can be considered an ordinary polydepside.

Further application of the process to the synthesis of higher depsides has been abandoned on account of the increasing experimental difficulties and because the knowledge of such forms would seem to present no further great interest.

In conclusion I append the following list of depsides prepared by us. The earlier known substances, either artificially prepared or found in nature are designated by an asterisk(*). Those marked by † will be described shortly.

Didepsides.

*Di-*p*-hydroxybenzoic acid (*Ber.*, **42**, 217 (1909)).
Di-*m*-hydroxybenzoic acid†.
*Di-salicylic acid (Salicylo-salicylic acid of Böhringer and Son).
Di-protocatechuic acid (*Ann.*, **384**, 238).
Di-gentisic acid (*Ann.*, **384**, 230).
Di-β-resorcylic acid (*Ann.*, **384**, 233).
p*-Di-orsellinic acid (lecanoric acid) (*Ber.*, **46, 1143 (1913)).
o-Di-orsellinic acid (*Berl.*, *Akad.*, **1913**, 507).
m-Digallic acid (*Ber.*, **46**, 1124 (1913)).
Di-syringic acid†.
Di-*o*-cumaric acid (*Ann.*, **391**, 363).
Di-ferulic acid (*Ann.*, **391**, 362).
Di-β-hydroxy naphthoic acid (*Ann.*, **391**, 356).
p-Hydroxybenzoyl-*m*-hydroxybenzoic acid†.
m-Hydroxybenzoyl-*p*-hydroxybenzoic acid†.
Salicylo-*p*-hydroxybenzoic acid†.
Vanilloyl-*p*-hydroxybenzoic acid (*Ann.*, **372**, 51).

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[1] *Ber.*, **15**, 2588 (1882).

Feruloyl-*p*-hydroxybenzoic acid (*Ann.*, **391**, 360).
α-Hydroxy naphthoyl-*p*-hydroxybenzoic acid (*Ann.*, **391**, 354).
Orsellinoyl-*p*-hydroxybenzoic acid (*Ber.*, **46**, 1141 (1913)).
Protocatechuyl-*p*-hydroxybenzoic acid (*Ber.*, **42**, 1484 (1909)).
Galloyl-*p*-hydroxybenzoic acid (*Ber.*, **41**, 2888 (1908)).
Pyrogallol carboyl-*p*-hydroxybenzoic acid (*Ber.*, **46**, 2396 (1913)).
Syringoyl-*p*-hydroxybenzoic acid†.
p-Hydroxybenzoyl syringic acid†.
Pentamethyl-*m*-digallic acid (*Ber.*, **45**, 2718 (1912)).
Pentamethyl-*p*-digallic acid (*Ber.*, **46**, 1130 (1913)).
Vanilloyl-vanillin (*Ann.*, **372**, 63).

Tridepsides.

*Di-*p*-hydroxybenzoyl-*p*-hydroxybenzoic acid (*Ann.*, **372**, 38),
Vanilloyl-*p*-hydroxybenzoyl-*p*-hydroxybenzoic acid (*Ann.*, **372**, 55).

Tetradepsides.

Tri-*p*-hydroxybenzoyl-*p*-hydroxybenzoic acid (*Ann.*, **372**, 43),
Vanilloyl-*p*-hydroxybenzoyl-*p*-hydroxybenzoic acid (*Ann.*, **372**, 59).

Lichen Substances.

The only natural sources of the depsides have, until now, been the lichens, those peculiar plant forms, which, according to the discovery of Simon Schwendener, arise through symbiosis of algae and molds. To these singular morphological properties correspond also their peculiar position in chemical respects, and particularly, their content of depsides. Among the latter, the best known is lecanoric acid, which has long been regarded as an ester-like anhydride of orsellinic acid, without anything certain having been found out about the position of the depside group.

Very closely related is evernic acid, which can be regarded, on account of its splitting by bases, as an ester-like anhydride of orsellinic acid and everninic acid. The synthetic investigations which I, in conjunction with my son, Hermann O. L. Fischer,[1] have so far carried out, have been limited to these two acids.

The synthesis of lecanoric acid is carried out in the following manner: After the preparation of the crystalline dicarbomethoxyorsellinoyl chloride had succeeded, this was coupled with orsellinic acid in aqueous alkaline acetone solution at —15° and the resulting dicarbomethoxy compound saponified by a two-hour treatment with excess *N* sodium hydroxide at 20°. Thereby a diorsellinic acid results in good yield and this has proven identical in every respect with a sample of the natural lecanoric acid, which we owe to the kindness of Mr. O. Hesse in Feuerbach.

The final proof of identity rests on a comparison of the change of the natural and the artificial preparations into the methyl ester of trimethyllecanoric acid by diazomethane. This ester possesses a sharp melting point, which was the same for both preparations and also for their mixture.

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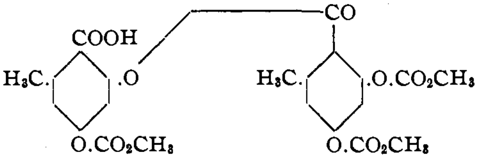
[1] *Ber.*, **46**, 1138 (1913); further, *Sitzungsber. d. Berliner Akademie*, **1913**, p. 507.

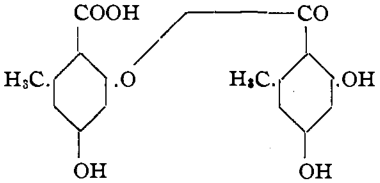
Simultaneously with these investigations, my former co-worker, K. Hoesch[1] has derived orsellinic acid itself from orcyl aldehyde, prepared by the Gattermann synthesis, in which he oxidized the carbomethoxy compound of the latter with permanganate, and then split off the carbomethoxy groups, just as Freudenberg and I[2] recommended for the change from vanillin into vanillic acid.

Besides the synthesis, we could also supply the proof that the depside union was in the *p*-position. This was already probable by the very strong red-violet coloration of the dicarbomethoxylecanoric acid with ferric chloride. Still more conclusive is the preparation of *o*-diorsellinic acid and its difference from lecanoric acid.

For this second synthesis, we first attempted to couple dicarbomethoxyorsellinoyl chloride with the monocarbomethoxyorsellinic acid, which contained the free phenol group in the *o*-position, in alkaline acetone solution. The failure of the experiment caused us to choose the previously mentioned indirect way from monocarbomethoxyorcyl aldehyde. This can be coupled without difficulty in alkaline acetone solution, with dicarbomethoxyorsellinoyl chloride. The tricarbomethoxyorsellinoylorcyl aldehyde resulting, in good yield, can have only the following structure:



By oxidation with permanganate, it is transformed into the tricarbomethoxy *o*-di-orsellinic acid, from which there results, on saponification with dilute ammonia, with very good yield the *o*-di-orsellinic acid.



This differs from lecanoric acid in many properties; in particular by the coloration with ferric chloride, with which it shows in aqueous alcohol solution not the intense purple color but rather a brown-red coloration.

We had hoped that the *o*-di-orsellinic acid would be identical with the gyrophoric acid, which likewise is found in lichens, and which, according to its splitting by alkali, has been held to be isomeric with lecanoric acid. But the comparison of the synthetic preparation with a sample of natural gyrophoric acid, which likewise Mr. O. Hesse most kindly placed at our

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[1] *Ber.*, 46, 886 (1913).

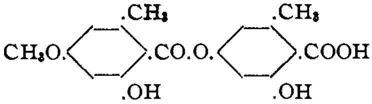
[2] *Ann.*, 372, 68 (1910).

disposal, has proven their complete dissimilarity, and from this we draw the conclusion that the gyrophoric acid cannot be a didepside of orsellinic acid, but must possess some other constitution. This observation shows how very useful syntheses are in deciding important structural questions in the chapter of the lichen substances.

As an other example of this I can cite the structure of evernic acid, which my son and I have cleared up in the following way: The acid, a sample of which we obtained again from Mr. Hesse was, similarly to lecanoric acid, dissolved by an ethereal solution of diazomethane on long standing and shaking and transformed into a beautifully crystalline neutral ester, which we have identified by melting point, mixed melting point, solubility and analysis, with the methyl ester of trimethyllecanoric acid.[1]

Thus evernic acid must be a monomethyllecanoric acid, and since the everninic acid resulting from its hydrolysis is a *p*-methyllecanoric acid,[2] in evernic acid the methyl group must be in the *p*-position to the depside group.

Therefore, this gives, as the only possibility for evernic acid, the following structural formula:



I hope that now the synthesis of evernic acid can also be carried out from everninic acid and orsellinic acid according to the method of synthesis of lecanoric acid.

Tanning Substances.

Under this name are now collected together a large number of plant substances which possess the common property of combining with animal hides. They fall in wholly different groups as soon as one employs a chemical view-point for their classification. Our investigations are limited to the tanning substance of the nutgalls, the so-called tannin, and a few substances belonging to the same type. I can describe them in short as acyl-like compounds of sugar with phenolcarbonic acids.

The history of the tannins, which dates back into the 18th century is so extensive, that I, therefore, must desist from giving it completely here. Thus, I will be content by giving again, with slight amplification what is quoted in the first paper by Freudenberg and myself "On Tannin and the Synthesis of Similar Substances."

Adolf Strecker,[3] on the basis of extended investigations, came to the conclusion that tannin was a compound of glucose and gallic acid, for

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[1] The investigation will be published shortly.

[2] E. Fischer and K. Hoesch, *Ann.*, **391**, 35 (1912).

[3] *Ann.*, **81**, 248 (1852); **90**, 328 (1854).

which he derived the formula $C_{27}H_{22}O_{17}$. That would correspond to a combination of 3 mols of gallic acid and one mol of glucose. When he later succeeded,[1] first by silver nitrate or arsenic acid and then also by phosphorus oxychloride,[2] in obtaining a glue-precipitating substance from gallic acid, H. Schiff[2] declared this to be the essential constituent of tannin, gave for it the formula $C_{14}H_{10}O_9$ and named it digallic acid. This formula had been recommended long before by Mulder but was contested by Strecker. The result of Strecker in regard to the formation of glucose from tannin was later substantiated by several investigators; for example Ph. van Tieghem[3] and H. Pottevin,[4] who effected the hydrolysis with the enzyme of *Aspergillus niger*. The results fluctuated noticeably in regard to the quantity of sugar. Further, since, on the other hand, the formation of sugar has been wholly disputed, the view of Schiff has so well maintained itself, that tannin has been represented in the text-books until recently rather generally as digallic acid. In opposition to this, stands its optical activity, which was observed by Ph. van Tieghem, C. Scheibler, Flavitzky and Gunther,[5] and was used by the last as an argument against the formula of Schiff. Experiments are not lacking to remove this theoretical difficulty,[6] but the determination of the molecular weights and the careful observations of P. Walden[7] on the electrical conductivity, the light absorption and the behavior towards arsenic acid, has undoubtedly shown that tannin and Schiff's digallic acid are different. The difference became still greater when I succeeded in obtaining digallic acid in a crystalline condition and establishing its composition with certainty.[8] Meanwhile, M. Nierenstein, from numerous investigations had reached the conclusion that tannin is essentially a mixture of digallic acid and optically-active leucotannin. This view cannot stand criticism. It is in opposition to the older observations on molecular weight and acidity of tannin, and our further investigations[9] have not given the

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[1] J. Löwe, *J.*, **1867**, 446; **1868**, 559.

[2] H. Schiff, *Ber.*, **4**, 232, 967 (1871); *Ann.*, **170**, 43 (1873); *Ber.*, **12**, 33 (1879); *Chem. Ztg.*, **19**, 1680; cf. also the citation on p. 1172; further, the contradictory statements of Freda (*Gazz. chim. ital.*, **8**, 9 and 363 (1878) and **9**, 327 (1879)) and Biginelli, *Chem. Zentr.*, **1909**, II, 1861, 1863; **1910**, II, 23; *Gazz. chim. ital.*, **39**, II (1909); *Rend. Soc. Chim. Ital.*, 11 (1911)

[3] *Annal. d. Sciences naturelles V. Serie Botanique*, **1867**, 210.

[4] *Compt. rend.*, **132**, 704 (1901).

[5] Cf. historical by E. v. Lippmann, *Ber.*, **42**, 4678 (1909).

[6] Cf. Dekker, *Ber.*, **39**, 2497 (1906) and Nierenstein, *Ibid.*, **41**, 77 (1908); **42**, 1122 (1909); **43**, 628 (1910).

[7] *Ber.*, **30**, 3151 (1897); **31**, 3167 (1898). His observations were substantiated and supplemented by Manea (*Diss., Geneva*, **1904**).

[8] *Ber.*, 41, 2890 (1908); further, E. Fischer and K. Freudenberg, *Ibid.*, **46**, 1124 (1913).

[9] E. Fischer, *Ber.*, **41**, 2890 (1908): further, E. Fischer and K.F reudenberg. *Ann.*, **384**, 225 (1911).

slightest support for the correctness of Nierenstein's conclusions. The same judgment holds for the assertions of R. J. Manning, who claimed to have isolated from tannin a pentaethyl ester of pentagalloyl glucoside, for the preparation described by him is none other than ethyl gallate.[1] In opposition to Nierenstein, K. Feist[2] arrived at the view that tannin was really a compound of glucose and he has expressed the feeling that tannin from Turkish nutgalls is a combination of glucogallic acid with two ester-like bound molecules of gallic acid. As foundation for this view, he used his observation that a crystalline compound of gallic acid and glucose could be isolated from Turkish nutgalls, which he regarded as an α-glucoside of gallic acid or its anhydride.[3]

In the first place, we have accorded to the results of Feist a greater weight,[4] than he really deserves. His complete publication[3] shows that noticeable inconsistencies exist in the analyses, and, above all, shows that the synthetic β-glucoside of gallic acid[5] prepared by H. Strauss and myself differs so greatly from the preparation of Feist that I can no longer regard the latter as a simple glucoside of gallic acid. What Feist in reality had in hand is not yet clear to me.

Of much more importance have proven the statements of Herzig and his students on the origin and splitting of methylotannin and I will later come back to this more fully.

Our first investigation was concerned with the fundamental question whether the glucose found by Strecker and his followers was really a constituent or only a chance impurity of tannin. For this, above all, the purest possible preparation was necessary. Since the earlier known process for the purification of tannin seemed faulty to us, we have worked out a special method. It consists in extracting the aqueous solution of the best technical tannin, saturated with a slight excess of alkali, with ethyl acetate.[6] In the description of the process we were anticipated by Paniker and Stiasny,[7] who discovered it independently. As a particular advantage of the same, we regard the condition that, by it, all real acids or, as we believe, all substances with a free carboxyl are removed. This conclusion is also important for judgment of the structure of tannin, for it appears to me that it contains no free carboxyl and, therefore, cannot be a derivative of a glucosidogallic acid. We have applied the purification process to different kinds of commercial tannin and thereby obtained preparations which we could regard as essentially identical. In addition,

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[1] Cf. H. C. Biddle and W. B. Kelley, THIS JOURNAL, **34**, 918 (1912).

[2] *Ber.*, **45**, 1493 (1912); further, *Chem. Zentr.*, **1908**, II, 1352.

[3] *Arch. Pharm.*, **250**, 668 (1912).

[4] Fischer and Freudenberg, *Ber.*, **45**, 2713 (1912).

[5] Fischer and Strauss, *Ibid.*, **45**, 3773 (1912).

[6] Fischer and Freudenberg. *Ibid.*, **45**, 919 (1912).

[7] *J. Chem. Soc.*, **99**, 1819 (1911).

I will here emphasize the fact that we have used only the tannin thus purified for all the determining experiments and, indeed, a preparation that proved identical with a product prepared from Chinese nutgalls (Zacken-gallen), and for which the specific rotation in 1% aqueous solution was +70° to 75°. That this preparation was entirely homogeneous one cannot state with more certainty, since an essential property of homogeneous bodies, the crystalline habit, has so far not been observed for it. On the other hand, the absence of this property cannot be regarded as a proof for a high degree of impurity, since with such high molecular substances as tannin the crystalline condition is to be regarded as a more than lucky chance.

With the purified preparation we first repeated the investigation of Strecker on the hydrolysis with sulfuric acid; whereby it has become evident that, for the completion of the action with 5% acid, about 70 hours' heating at 100° is necessary, while by use of 11% acid, as Strecker employed 24 hours suffices. We believe that this slow course of the hydrolysis often has hindered the finding of sugar in the control of Strecker's investigation. To this is due the relatively small quantity of sugar noted, which we found as a rule to be between 7 and 8%, while Strecker observed 15 to 22%. That the higher figures of Strecker were due to his different raw material —at that time tannin was prepared preferably from Turkish nutgalls— is highly probable, but can only be decided by new investigations. Besides, we have purified tannin according to other methods, for example through the potassium salt, and on subsequent determination of the sugar reached the same results. Since, finally, control experiments with mixtures of gallic acid and glucose made clear the error of the method employed, there remains no longer any reason to doubt the results of hydrolysis also in the quantitative respect. They led to the conclusion that in the purest tannin investigated by us one mol of glucose is combined with about 10 mols of gallic acid. Naturally the thought occurred to us to isolate intermediate products, in order, from their composition, to secure further data for judging the structure. But these investigations have been completely fruitless, due to the unpleasant properties of these substances which exclude every guarantee of their homogeneity.

Besides gallic acid, no other phenolcarbonic acid has so far been found in tannin, and our own investigations in this respect have given nothing new. The same holds for the hydrolysis with excess alkali, which begins at ordinary temperatures and on exclusion of air yields large quantities of alkali salt of gallic acid in relatively pure condition. Also here it appears to be very difficult to isolate homogeneous intermediate products. Under these conditions, it appeared desirable to proceed in the synthetic way in order to obtain an insight into the structure of the tannins. We have proceeded from the conception, that tannin contains no carboxyl and that thus all the gallic acid must be bound as an ester. This condition will be fulfilled if we can regard tannin as an ester-like combination of one mol glucose with five mols digallic acid according to the manner of pentacetyl glucose. Bold as the hypothesis may appear at first glance, it has become the center point of all further investigation and through it has gained in probability. However, we must first choose a more modest goal for the synthesis, the pentagalloyl glucose, as the digallic acid is too difficultly accessible and also because its complicated composition introduces particular difficulty on the experimental side.

Pentagalloyl Glucose.

For the complete acylation of glucose, there have been found until now three methods: (1) Boiling with acid anhydride in presence of sodium acetate or zinc chloride. The best known example is the preparation of pentacetyl glucose, from which results, according to the catalizer used, the α- and β-form. (2) Treatment with acid anhydride in presence of pyridine (Behrend). According to whether one starts with α- or β-glucose, there results the α- or β-form. (3) Treatment with acid chloride in aqueous alkali solution (E. Baumann). The process has only been completely studied for benzoyl chloride, and gives only one pentabenzoyl glucose of m. p. 186–8°. For gallic acid, none of these processes was applicable, and even for the chloride of tricarbomethoxygallic acid the application was excluded in aqueous alkaline solution, because there would inevitably follow the destruction of the carbomethoxy groups. We were thus forced to search for a new process and have found it in the combined action of the chloride with tertiary bases, for which quinoline has proven to serve particularly well. As a solvent we used dry chloroform, the chloride being very easily taken up in this. However, the glucose is especially difficultly soluble in it. But if it was shaken in finely pulverized condition with chloroform, quinoline and a moderate excess of tricarbomethoxygalloyl chloride for 24 hours, complete solution ensued. By precipitation with methyl alcohol, the product of this coupling may be easily isolated. After appropriate purification, there is formed a feathery, colorless, amorphous powder. We have designated it as pentatricarbomethoyxgalloyl glucose. By careful saponification with excess of alkali in aqueous acetone solution at the ordinary temperature, there was obtained from this a tannin which we regarded as pentagalloyl glucose and which now shows surprisingly close similarity to tannin. An essential difference was evident only in optical rotation and the quantity of gallic acid which resulted on hydrolysis with sulfuric acid.

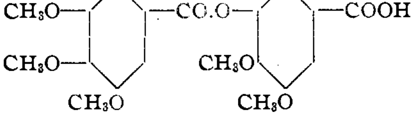
However, I will not be reticent on the difficulty which the establishment of the empirical composition of such amorphous products involves, especially since the percentages for carbon and hydrogen differ only very slightly between pentagalloyl and tetragalloyl glucose. But we have convinced ourselves in simpler cases, for example, in derivatives of benzoic, hydroxybenzoic and salicylic acids, where the analytical differences for penta- and tetraacyl bodies are very much greater, that the process in fact gives the pentaacyl compound, and thus there exists no important ground for assuming that with galloyl bodies the reaction follows another course.

In spite of all this, the homogeneity of pentagalloyl glucose is very doubtful; we hold it rather to be a mixture of two stereoisomers, for the investigation to be cited later, on the benzoylation of glucose in the same way, has shown that different products result, which owe their origin to the α- or β-glucose. Here the pure α- or β-benzoyl glucose can be isolated by crystallization, but the yield and other considerations show that in the crude product there exists a mixture of the two forms. The same could well hold in the case of the galloyl bodies, only here the separation of the pure substances is not possible on account of their amorphous nature.

The pentagalloyl glucose is closely related to tannin in all its properties, so that with its artificial preparation the principal aim of the synthesis seems to be attained. But before one can speak of a complete solution of the tannin question its synthesis also must be realized. How far we have approached to this goal, the investigation on the synthesis of tannin and methylotannin will show.

Methylotannin results, according to the researches of Herzig[1] and his students, from the action of diazomethane on tannin. Since it is wholly indifferent towards alkali, one must assume that it contains neither carboxyl nor free hydroxyl groups. On hydrolysis, it yields according to Herzig, trimethylgallic acid and the unsymmetrical *m,p*-dimethylgallic acid. Combining these observations with the previously advanced conception of the constitution of tannin, the conclusion follows that tannin is essentially an ester-like compound of glucose with five mols *m*-digallic acid, and the corresponding methylotannin the combination of glucose with five mols pentamethyl *m*-digallic acid.

The following investigation on the synthesis of methylotannin rests on these considerations, and demanded large quantities of the hitherto unknown pentamethyl *m*-digallic acid:



This was prepared from trimethylgalloyl chloride and *m,p*-dimethyl ether gallic acid, and for the latter we discovered a new, rather good method

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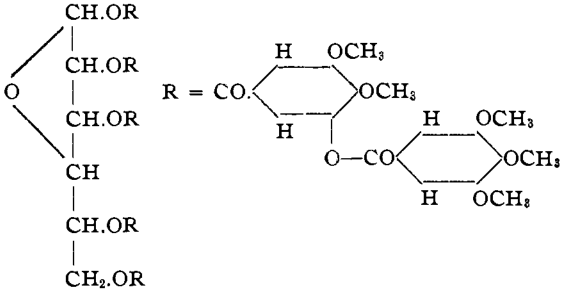
[1] *Ber.*, 38, 989 (1905); *Monatsh.*, 30, 543 (1909).

of preparation,[1] by coupling in an aqueous alkaline solution.[2] In the same manner the isomeric pentamethyl-*p*-digallic acid[3] resulted from trimethylgalloyl chloride and syringic acid. For differentiating the two isomers, the methyl esters, which have been recently described by Mauthner,[4] serve very well, since they possess sharp melting points.

The pentamethyl-*m*-digallic acid yields, further, a beautifully crystalline chloride, and we have coupled this with α- as well as β-glucose, according to the method mentioned before. In both cases products resulted which are to be regarded as penta-acyl derivatives of glucose or, more exactly, as penta-(pentamethyl-*m*-digalloyl)-glucose.



They differ between themselves in optical rotation. Both are dextrorotatory in acetylene tetrachloride and benzene, but the preparation from α-glucose shows a noticeably higher rotation. By repeated resolution the optical rotation changes, and we, therefore of necessity come to the conclusion that both preparations are mixtures, most probably of two stereoisomers, *i. e.*, are derivatives of α- or β-glucose. We have now compared the preparations with a methylotannin, that we prepared from carefully purified tannin from Chinese nutgalls (Zacken-gallen) according to Herzig's directions, and have shown their great similarity, particularly with the preparation from β-glucose, the optical rotation in acetylene tetrachloride is very nearly the same.

We can scarcely doubt from these observations that the two synthetic penta-(pentamethyl-*m*-digalloyl)-glucoses are very closely related to methylotannin and probably possess the same or very similar structures. But no answer can yet be given as to a final identification; for with these high molecular amorphous bodies the general comparison methods of organic chemistry fail, and we must here, as yet, content ourselves with probabilities. Furthermore, I will not be reticent as to the fact that we have tried also to build up tannin itself artificially from *m*-digallic acid.

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[1] Fischer and Freudenberg, *Ber.*, **45**, 2717 (1912).

[2] *Ibid.*, **45**, 2718 (1912).

[3] *Ibid.*, **46**, 1130 (1913).

[4] *J. prakt. Chem.*, [2] **85**, 310 (1912).

To this end, we have first worked out the previously mentioned reliable and satisfactory method for obtaining the acid itself.

We have further proven its structure by complete methylation with diazo methane, *i. e.*, by changing it into the methyl ester of pentamethyl-*m*-digallic acid.[1] We must make here the surprising statement that the first crystallized digallic acid, which according to the synthesis from tricarbomethoxygalloyl chloride and 3,5-dicarbomethoxygallic acid appeared to be the *p*-compound,[2] has not this structure, but probably consists chiefly of *m*-digallic acid.[3] For, complete methylation yields every time the methyl ester of pentamethyl-*m*-digallic acid, m. p. 128°. The results show again how important complete methylation is for comparison of complicated depsides.

We have tried, further, to change *m*-digallic acid into its pentacarbomethoxy compound. The reaction appeared to succeed with chlorocarbonic methyl ester and dimethyl aniline, and later the acid was isolated from the crude product by careful treatment with alkali bicarbonate. But now the difficulties began. We have in no way succeeded in obtaining the carbomethoxy compound crystalline, and the chloride derived from it also remained amorphous. Therefore, the finally attempted coupling with sugar was so unsuccessful that we cannot speak of any exact results. The synthesis of tannin in the meaning intended by us, which I hoped to be able to announce to you today, is thus as yet an unsolved problem.

Also the question of structure is not thoroughly answered. One can only say that our hypothesis is as yet the best expression for the observations. But it must not be forgotten that the results of elementary analysis, or of hydrolysis, give no certain differentiation between a compound of glucose with 9, 10 or 11 mols gallic acid, respectively.

To this is also added the uncertainty whether tannin, after the best purification, is homogeneous. It could just as well be a mixture of very similar substances, for example a penta-(digalloyl)-glucose with a tetra-(digalloyl)-glucose or tri-(digalloyl)-di-(galloyl)-glucose, etc.

Further, it is possible, if not also probable, that the tanning substance contains in place of glucose one of its polysaccharides.

Finally I must, in order to obviate misunderstanding, again emphasize the fact, that our observations have been limited to the tannin from Chinese nutgalls (Zacken gallen), which today seems to be the chief constituent of commercial tannin. It is thus not excluded that other relationships of sugar and gallic acid will be encountered, with tannins of other origin, for example, that from Turkish nutgalls.

In fact, according to the latest experiments of Dr. Freudenberg, a tannin

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[1] E. Fischer and K. Freudenberg, *Ber.*, 46, 1127 (1913).

[2] *Ibid.*, 41, 2890 (1908); *Ann.*, 384, 225 (1911).

[3] *Ber.*, 46, 1118 (1913).

from the so-called Aleppo-gallen (Merck), purified by the above process, shows noticeable differences. It is slightly levorotatory in aqueous solution and gave, on hydrolysis, more than 10% glucose.

But all these questions are of inferior signification, in comparison with the proof that the synthetic pentagalloyl glucose is a tanning substance of the tannin class.

Other Natural Tanning Substances of the Tannin Class.

There are numerous examples of sugar-containing tanning substances. But in the majority of cases treated, they are amorphous, slightly investigated products; many of them appear to be true glucosides,[1] particularly those which yield on hydrolysis aromatic phenol ketones. On the other hand, those which contain phenolcarbonic acids as constituents, appear not to be glucosides but, like tannin, to be ester-like derivatives of sugar. To this class belong, first of all, two crystalline tanning substances, the chebulinic acid of myrabolans and the Hamamelis-tannin crystallized by Gruttner in Böhm's laboratory, with which we have carried out some experiments. The first, which according to H. Thoms is identical with the "eutannin" recently introduced in the trade, yields, under exactly the same conditions as tannin, by hydrolysis with sulfuric acid, glucose which we have proven with all certainty.[2] However, the quantity of gallic acid is noticeably small. Apparently the tanning material is an incompletely acylated compound of glucose, or one of its polysaccharides, and gallic acid. Recently, the investigations of H. Thoms and his student, W. Richter, on eutannin,[3] have appeared, and contain many valuable observations, but leave the sugar content of the tanning substance doubtful. On the other hand, I must say that I cannot assent to the speculations thus founded. The chebulinic acid demands a new, complete, investigation before one can pronounce a final judgment on its structure.

The Hamamelis-tannin also gives, on hydrolysis with sulfuric acid, a sugar which is entirely different from glucose, and appears to be a hitherto unknown body.[4]

These observations show that the tanning substances can also be a source for new members of the sugar series. Dr. Freudenberg will exhaustively investigate the sugar of Hamamelis-tannin.

Whether the crystalline tanning substance of tea described by A. W Naninga[5] also belongs here, is still to be proven.

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[1] The earlier custom of calling all natural derivatives of glucose, which are not simple carbohydrates, glucosides, cannot be retained. I regard as glucosides only those substances which are similarly constituted to the methyl or phenyl glucosides.

[2] E. Fischer and K. Freudenberg, *Ber.*, **45**, 918 (1912).

[3] Work of the *Pharmazeut. Institut d. Univ. Berlin*, **9**, 78, 85 (1912).

[4] E. Fischer and K. Freudenberg, *Ber.*, **45**, 2712 (1912).

[5] *Mededeelingen uit's Lands Plantentuin Nr.*, **46**; *Onderzoekingen betreffende de Bestanddeelen van het Theeblad.*

Generalization of the Tanning Material Synthesis.

The process which served for the building up of pentagalloyl glucose is easily applicable to other phenolcarbonic acids. As has been mentioned before, the penta-*p*-hydroxybenzoyl-glucose[1] was so obtained. It is very difficultly soluble in water and its elementary analysis undoubtedly shows it to be a penta-acyl compound. The pentasalicyloglucose which will be fully described in a later publication, possesses entirely similar properties. Just as difficultly soluble in water is the corresponding derivative of caffeic acid, which I had Mr. R. Oetker[2] prepare. The compound of pyrogallolcarbonic acid, which we have designated as pentapyrogallol carboylglucose,[3] has proven particularly interesting. It is isomeric with pentagalloyl glucose and shows in general the same behavior, although it shows a noticeable difference in its solubility in water. While the galloyl compound is easily taken up in cold water, the isomeric substance is very difficultly soluble in hot water and is practically insoluble in cold water. The same also holds for its dark colored iron compound.

On first glance, this difference in substances of so similar a structure as the two tanning materials, appears very surprising. But it loses in significance when one remembers that tannin and also the similar pentagalloyl glucose are inclined to form colloidal aqueous solutions. This property is present only to a slight degree or not at all in the isomeric compound. Such observations merit attention for the study of colloidal solutions, for they show how dependent their formation is on small differences in the structure of the materials. On the other hand, the formation of hydrosols is of highest importance for the role which such substances play in the living world, and this applies also to their chemical characteristics, as proven by the case of the pentagalloyl glucose; for here it was not easy, on account of the difficulty in preparing aqueous solutions, to verify the astringent taste and the precipitation by glue solution.

For all the above-mentioned glucose derivatives, the same thing holds, as I have before drawn attention to in connection with the homogeneity of pentagalloyl glucose, *i. e.*, they are probably mixtures of the two stereoisomeric derivatives of α- and β-glucose.

Like the sugars, the phenolcarbonic acids can be coupled with the true glucosides, as the preparation of the tetragalloyl α-methylglucoside has proved.[4] That this also shows the characteristic properties, for example, the taste and the precipitation phenomena of tanning substances, is not surprising, since it is well known that ethyl gallate shows noticeable precipitability by glue solution. With the methyl glucoside derivatives

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[1] E. Fischer and K. Freudenberg, *Ber.*, 45, 933 (1912).

[2] Will be published shortly.

[3] E. Fischer and M. Rapaport, *Ber.*, 46, 2397 (1913).

[4] Fischer and Freudenberg, *Ibid.*, 45, 934 (1912).

there is obviously missing the complication which arises, as in the glucose derivatives, from the simultaneous formation of α- and β-forms.

According to the behavior of methylglucoside, it cannot be doubted that the simple polyhydric alcohols will serve for the same synthesis. We have so far combined only glycerol[1] with gallic acid, submitting the product merely to a hasty investigation, since such bodies exhibit no particular interest.

Benzoylation and Cinnamoylation of Sugars and Polyhydroxylated Alcohols.

By the application of the new acylation method to the simple aromatic chlorides, some new and noteworthy results were obtained. The benzoylation of glucose has been carried out formerly only in aqueous alkaline solution, giving as a final product a pentabenzoyl glucose which melted at 186–8°, and for which I, in conjunction with B. Helferich, found in chloroform solution $[\alpha]_D^{20} = 25.4°$.[2] But the yield of this high melting preparation was very unsatisfactory (about 15% of the theory). A preparation of about the same rotation and similar melting point can be obtained with a much better yield, according to the new process, by shaking β-glucose with a mixture of benzoyl chloride, quinoline and chloroform. On the other hand, α-glucose gave, under the same conditions, an isomeric pentabenzoate with a much higher rotation, $[\alpha]_D^{20} = 107.6°$, whose melting point, however, was rather inconstant.[3]

That steric rearrangement takes place from the α- to the β-form or conversely, was quite probable according to the resulting yield, and was proven by the following experiment: A mixture of α-glucose, benzoyl chloride, quinoline and chloroform, in the proportions used earlier, remained standing 20 days after complete solution had taken place. There had then separated a rather large quantity of crystalline β-pentabenzoyl glucose.

Still easier than the benzoylation, is the cinnamoylation of sugar with cinnamic acid chloride and quinoline. I have prepared with Mr. R. Oetker, in this way, the pentacinnamoyl derivatives of α- and β-glucose, galactose, mannose, and the hexacinnamoyl mannite. They are all beautifully crystalline substances. By this process, the pentabenzoyl and pentacetyl mannose (m. p. 114–6°; $[\alpha]_D^{20} = -24.8°$) were obtained crystalline. The detailed description of this investigation will soon follow.

Experiments on the Partial Acylation of Sugar and Polyhydroxylated Alcohols.

All the previously mentioned acylation experiments were directed towards the preparation of the end product and thus were carried out with

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[1] Fischer and Freudenberg, *Ber.*, **45**, 935 (1912).

[2] *Ann.*, **383**, 88 (1911).

[3] *Ber.*, **45**, 2725 (1912).

an excess of acid chloride. To conduct the reaction only to an intermediate stage, the experimental conditions are also unfavorable; for the sugar on shaking goes gradually into solution in the acylating liquid and is thus at the beginning in contact with an excess of the chloride.

In other methods of acylation, for example, by acetylation with acetic anhydride or benzoylation according to Baumann, it is just as difficult to isolate partially acylated sugars in pure condition. One must, therefore, seek for a new method for the preparation of such products, and here reflection suggests the partial protection of the hydroxyls of the sugar by other groups which afterwards can be easily split off again. The acetone derivatives of the sugars and polyhydric alcohols, which were discovered by me, appear to be particularly useful for this purpose. Some years ago, I carried out such experiments with acetone-glycerol,[1] in order to prepare a monobenzoyl derivative with benzoyl chloride in alkaline solution. Unfortunately, the results were negative; for, under the conditions chosen, the acetone residue was split off and tribenzoyl glycerol formed. Perhaps this splitting can be avoided by excluding water according to the new acylation method, and I am already occupied in this direction. If, in such a way, the partial coupling of sugars with phenolcarbonic acids can be realized, just as Irwin has recently succeeded in the partial methylation of glucose, it will mark an important advance in the synthesis of tanning substances. For, as I have mentioned before, chebulinic acid probably belongs in this class of partially acylated sugars, and it is to be hoped that the same is the case with many other natural products which are easily soluble in water, and thus differ from the completely acylated glucose derivatives, which are as a rule difficultly soluble.

Physiological and Practical Significance of the Synthesis of Tannins.

The knowledge that ester-like compounds of sugar and phenolcarbonic acids form a great class of tannin-like tanning substances, is doubtless of importance to the plant physiologists. Especially interesting appears to me the fact that the sugar of plants can be used for esterification just as well as glycerol or the monohydric alcohols. The organism tolerates free acid, in general, only at definite places, as in the maw of animals or in unripe fruits, or in bark and shells, where they probably act as defensive agents. Generally it endeavors to neutralize the acid group. This happens often by salt formation, but much oftener by amide formation, as in the proteins, or by ester formation, as in the fats. Under this now comes the esterification of sugars. Since sugars are much more widely distributed than glycerol, I do not doubt that such ester derivatives will be met still oftener in the plant kingdom and perhaps in the animal kingdom also.

I have in mind not alone the phenolcarbonic acids, but more especially

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[1] *Ber.*, 28, 1170 (1895).

the numerous hydroxy acids of plants. That one has so far overlooked their sugar derivatives, does not surprise me, since they are probably easily soluble and easily saponified bodies. It has long been my wish to prepare such combinations synthetically, but the method for this must first be found. Probably the carbomethoxy derivatives recently discovered by me and my son will play a part in it.[1] Previously I had to be contented with directing the interest of plant physiologists to these things. Perhaps we will find such esters in sweet fruits, which, in the unripe condition, contain noticeable quantities of glycollic acid and its homologs. I have myself carried out some experiments on this point, but so far without decisive results. I hope, later, to be able to communicate more definitely on this as well as on the unequal distribution of acids in the shell and meat of certain fruits, for example, the early plums.

Both the naturalist and the synthetic chemist are often confronted by the question as what practical purpose the results of his work can serve, and to myself in a circle of scholars, as I exhibited the artificial tannin and an ink prepared from it, which aside from the water was entirely synthetically derived, the question was put: Is it cheaper than the ordinary ink? The answer was naturally negative, and so it must be also for the synthetic tanning substance, so far as concerns its use in the tannery; for here only very cheap substitutes, such as the recently introduced neradol of Stiasny, come into consideration.

But the matter appears otherwise when we consider that tannins in small quantities are constituents of important comestibles, such as wine, tea, coffee and numerous sweet fruits, on whose taste it has an influence not to be underestimated. If once synthetic chemistry breaks into this important field, of which I have no doubt, then, probably the synthesis of tanning substances will be honored also in its technical applications.

High Molecular Substances.[2]

Among the before-mentioned products of the tannin synthesis many substances of rather high molecular weight are found; for with the penta-(tricarbomethoxy galloyl) glucose this total amounts to 1810, and for the penta-(pentamethyl-*m*-digalloyl) glucose it rises to 2051; which has given the inducement to apply this smoothly running ester formation with the members of the sugar group to still more complicated acids. For this purpose the higher fatty acids at first appear particularly useful, such as, stearic, behenic and melissic, but finally we have found, in the derivatives of gallic acid, especially its tribenzoyl compound, a still better material; it yields a beautifully crystalline chloride, which can be completely purified and can be prepared comparatively easily in large quantity. By combination with mannite a neutral ester was prepared which has a molecular

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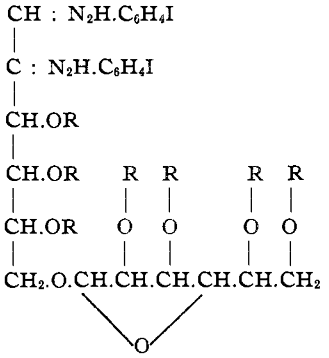
[1] *Ber.*, 46, 2659 (1913).

[2] E. Fischer and K. Freudenberg, *Ber.*, **46**, 1116 (1913).

weight of 2967. The verification of the composition of such substances is rendered very difficult by the condition that the analytical differences for carbon and hydrogen are not sufficiently great to determine the number of acyl groups with certainty. On this account we have incorporated in the molecule halogenated groups, in order to have the percentage of halogen as a measure for the molecular weight of the final product. For this purpose, we have used the *p*-iodophenyl maltosazone, which on the one hand is distinguished by its fine crystalline state, and on the other hand by a high content of halogen (33%). Its coupling with tribenzoylgalloyl chloride yielded hepta-(tribenzoylgalloyl)-*p*-iodophenyl maltosazone, which, though amorphous, still possesses very fine properties, and on analysis gave such sharp figures that we have no hesitation in proclaiming it as a chemical individual. Its structure follows from the snythesis and corresponds to the following formula, in which R denotes the tribenzoyl gallic acid:



$R = CO.C_6H_2(O.CO.C_6H_5)_3$

Hepta-(tribenzoyl galloyl)-*p*-iodophenyl-maltosazone, $C_{220}H_{142}O_{58}N_4I_2$. (Molecular weight 4021.)

The only uncertainty in the formula is the structure of the maltose residue, *i. e.*, the coupling of the two glucose residues, a question, which in the foregoing case has no significance. The molecular weight amounts to 4021. The substance with this molecular weight stands at the head of all organic substances of known structure derived wholly by synthesis.

We have finally proven, by freezing point determination in bromoform solution, that it, as well as a moderately closely related substance, for example, hexa-(tribenzoyl galloyl)-mannite, still satisfactorily obeys Raoult's law. The hepta-(tribenzoyl galloyl)-*p*-iodophenyl-maltosazone exceeds in molecular weight the highest product of the polypeptide synthesis, the *l*-leucyl-triglycyl-*l*-leucyl-triglycyl-*l*-leucyl-octaglycyl-glycine, by more than three times, and I believe, that it is also superior to the majority of natural proteins. However, for the beautifully crystalline oxyhemoglobin, as is well known, a molecular weight of 16,000, has been derived from its iron content, but against such calculations the objection can always be made, that the existence of crystals in no way guarantees chemical individuality, particularly since it can be regarded as an isomorphous mixture, such as the mineral kingdom so often presents to us in the silicates. Such objections vanish with synthetic products, whose formation can be controlled by analogous reactions.

The molecular physicists would do well in the study of high molecular substances to confine themselves to the synthetic products of known structure. I will continue the experiments on the building up of giant molecules with the aid of the processes described.

Certainly it offers in other respects a great incentive to test the productiveness of our methods. As is well known, the modern physicist is endeavoring to split up matter into smaller and smaller pieces. One is long since past the atom, and how long the electrons will be for us the smallest particles of matter, cannot be predicted. It seems to me that organic synthesis is called upon to accomplish the converse, *i. e.*, to accumulate larger and larger masses in the molecule, in order to see how far the compression of matter can go, in the meaning of our present conceptions.[1]

I hope that the results to date will give an effective stimulus in this direction.

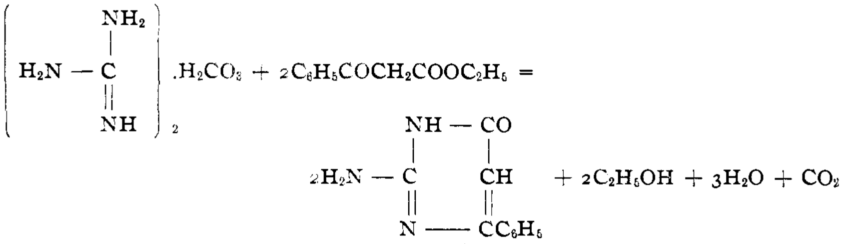
[CONTRIBUTIONS FROM THE SHEFFIELD CHEMICAL LABORATORY OF YALE UNIVERSITY.]

RESEARCHES ON PYRIMIDINES. LXX. THE ISOMERISM OF 4-PHENYLISOCYTOSINE.

BY TREAT B. JOHNSON AND ARTHUR J. HILL.

Received March 23, 1914.

Jaeger[2] observed, in 1891, that guanidine carbonate and ethyl benzoylacetate interact smoothly, when heated in alcoholic solution, with formation of 2-amino-4-phenyl-6-oxypyrimidine (4-phenylisocytosine, (I) melting at 294°. The reaction may be expressed as follows:



(I)

Warmington[3] later reinvestigated this reaction and made the inter-

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[1] Cf. H. Crompton, *Proc. Chem. Soc.*, **28**, 193 (1912).

[2] *Ann.*, **262**, 372.

[3] *J. prakt. Chem.*, [2] **47**, 214 (1893).