THE APPLICATION OF THE PERKIN REACTION TO PHENOLIC ALDEHYDES.

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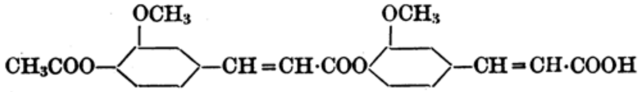
It has been shown by Tiemann and his collaborators(1) that acetyl derivatives of hydroxycinnamic acids are formed when phenolic aldehydes, such as vanillin and p-hydroxybenzaldehyde, are heated with acetic anhydride and fused sodium acetate. However, the melting points of the acetyl derivatives obtained by this method were always not sharp. This fact was accounted for by Vorländer(2) as due to the characteristic nature of liquid crystals in the case of p-acetyloxycinnamic acid, and by Kobayashi in the case of acetylferulic acid(3), as a special peculiarity of the acid. According to my observation, I am inclined to the opinion that these substances are impure.

The author applied Perkin's reaction to vanillin and p-hydroxybenzaldehyde respectively, and subjected the products to fractional crystallisation. In the former case, the condensation product was separated into two substances and in the latter, into three.

The product obtained from vanillin consisted of a mixture of acetylferulic acid, $C_{12}H_{12}O_5$, m. p. 195–195. 5,° and substance (A) of unknown structure, $C_{22}H_{20}O_8$, m. p. 250° (decomp.), which are separated by fractional crystallisation from alcohol and glacial acetic acid, the latter being the less soluble.

The presence of one acetyl, one carboxyl and two methoxyl groups in the latter substance was proved and, on hydrolysis, it was converted into ferulic acid in an almost quantitative yield. From these facts and from its method of formation it seemed possible that the constitutional formula of this substance might be (I), although the number of double bonds was not determined.



$$CH_3COO-C_6H_3(OCH_3)-CH=CH\cdot COO-C_6H_3(OCH_3)-CH=CH\cdot COOH \qquad (I)$$

Owing to the decomposition of this acid at the melting point, it seemed desirable to prepare at first its stable derivative for indentification. The methyl ester was first synthesised by the action of diazomethane on the acid and found to be suitable for this purpose, the melting point being 204–205.5°.

The methyl ester of the substance corresponding with formula (I) was synthesised by the condensation of acetylferuloyl chloride with ferulic acid

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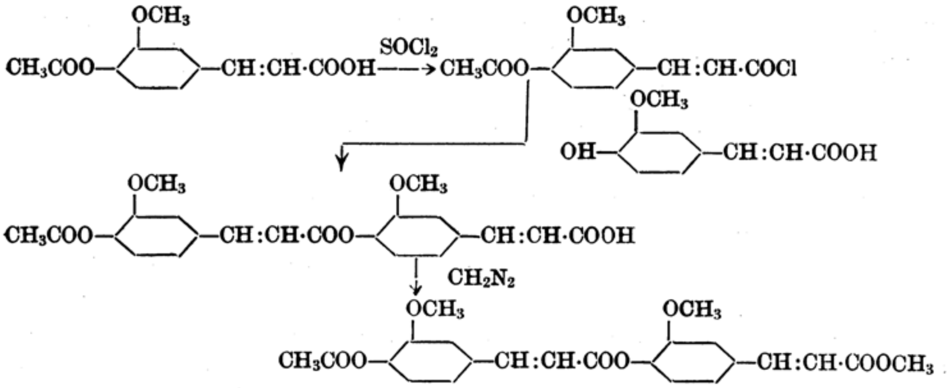
(1) *Ber.*, 10 (1877), 65; 11 (1878), 647.

(2) *Ber.*, 39 (1906), 808.

(3) *Bulletin of the Institute of Physical and Chemical Research* (in Japanese), 4 (1925), 575.

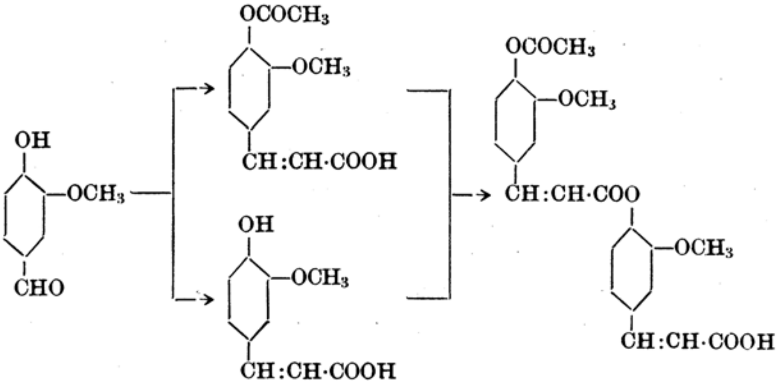
in the presence of pyridine and subsequent methylation with diazomethane, as shown in the following scheme:



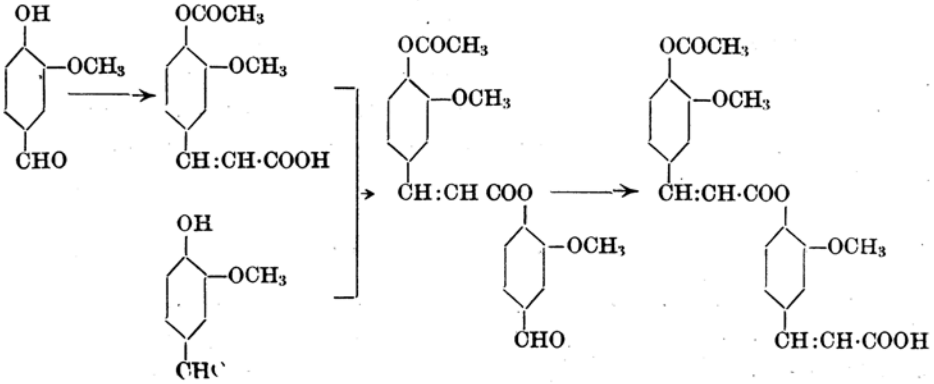
This synthetic methyl ester was identical in every respect with the methyl ester of substance (A).

The mechanism of the formation of substance (A) is accounted for by one of the following schemes, viz. (B) or (C):

(B)



(C)

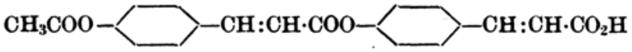


This view receives some support from the fact that the derivatives of cinnamic acid were the sole products of the action of acetic anhydride and fused sodium acetate on derivatives of vanillin which contain no phenolic hydroxyl, such as acetylvanillin and veratraldehyde.

In the case of p-hydroxybenzaldehyde, the condensation product was separated into three substance, (a) m.p. 205–205.5°; (b) m.p. 222–223° (decomp.); and (c) m.p. 231° (decomp.).

Substance (a) had the composition, $C_{11}H_{10}O_4$, and was identified as p-acetyloxycinnamic acid by analysis, molecular weight determination and by the fact that it was converted into p-hydroxycinnamic acid by hydrolysis in a good yield.

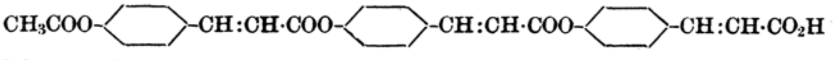
Substance (b), $C_{20}H_{16}O_6$, gave, on hydrolysis, p-hydroxycinnamic acid in an almost quantitative yield and was converted into its methyl ester, $C_{21}H_{18}O_6$, m.p. 166–167°. It is very probable judging by analogy with the case of vanillin that the constitutional formula of this substance would be 4-p-acetyloxycinnamoyl oxycinnamic acid (II),



(II)

The author synthesised the methyl ester corresponding with formula (II) in an exactly similar manner to the preparation of methyl acetylferuloylferulic acid. The synthetic methyl 4-p-acetyloxycinnamoyloxycinnamate was identical in all respects with the methyl ester of substance (b).

Substance (c) was insoluble in almost all organic solvents or camphor, and slightly soluble in hot nitrobenzene. As its molecular formula has not yet been determined, an empirical formula, $C_{29}H_{22}O_8$, only is at present assigned to it. It was converted into p-hydroxycinnamic acid by treatment with caustic soda and yielded a methyl ester having an empirical formula, $C_{30}H_{24}O_8$, when methylated with diazomethane. The author considers it to be best represented by formula (III).



(III)

The mechanism of the formation of substance (b) is explained as in the case of that of acetylferuloylferulic acid, and in the support of this view, the condensation product with anisaldehyde was only 4-methoxycinnamic acid.

The application of Perkin's reaction to the other phenolic aldehydes are now in progress.

Experimental Part.

The Application of the Perkin Reaction to Vanillin. *Isolation of Acetylferuloylferulic Acid,* $[(CH_3CO_2)(CH_3O)C_6H_3\,CH{:}CH{\cdot}CO_2](CH_3O)C_6H_3{\cdot}CH{:}CH{\cdot}CO_2H$. Vanillin (225 gr.) was heated with a mixture of acetic anhydride (675 gr.) and fused sodium acetate (225 gr.) in an oil-bath for 6 hours, when yellow crystals melting at 186–193°, were obtained, which on fractionally recrystallising from alcohol (95%) separated into three fractions: (a) m.p. 190–194°, 70 gr.; (b) m.p. 194–195.5°, 49 gr; and (c) m.p. 223–229°, 10 gr. The last fraction was further recystallised from alcohol and then from glacial acetic acid, from which it separated in faint, yellow crystals melting at 250° (decomp.). (Found: C=64.21; H=5.10. Mol. wt., by Rast's method⁽¹⁾, 413.6. $C_{22}H_{20}O_8$ requires C=64.07; H=4.86%; Mol. wt.=412.2).

Hydrolysis. The substance was hydrolysed by means of a 10% aqueous sodium hydroxide on a wire-gauze and on acidification with hydrochloric acid and recrystallisation of the product from dilute alcohol, faint, yellow crystals, m.p. 167.5–168°, were obtained and found to be identical with ferulic acid.

Determination of Groups. The acetyl group was determined by F. Kögl & P. P. Postowsky's method⁽²⁾ and the methoxyl groups, by the micro-Zeisel method (Pregl, "Die Quantitative Organische Mikroanalyse". p. 178). (Found: CH_3CO = 10.52; 10.23; CH_3O = 14.97; 15.13. $C_{18}H_{11}O_5(OCH_3)_2(CH_3CO)$ requires CH_3CO=10.44; CH_3O=15.06%). The numbers of the carboxyl group were determined by conversion into its Ba-salt and subsequent analysis. (Found: CO_2H=10.98. $C_{21}H_{19}O_6(CO_2H)$ requires CO_2H=10.91%).

The Methyl Ester. The substance was esterified with diazomethane in ethereal suspension. After evaporating the ether and recrystallising the product from a mixture of ether and benzene, faint, yellow crystals, m.p. 204–205.5°, were obtained. No alternation of melting point was observed on mixing it with a specimen which was obtained synthetically by the method described on p. 21.

Synthesis of Methyl Acetylferuloylferulate. *Acetylferuloyl chloride,* $(CH_3CO_2)(CH_3O)C_6H_3CH:CH\,COCl$. Acetylferulic acid (2 gr.) was treated with thionyl chloride (6 gr.) in a water-bath. After evaporating the excess of thionyl chloride in a vacuum, the raw product was recrystallised from benzene, care being taken to avoid any access of moisture. Faint, brown crystals thus purified melted at 133°–134°:

5.568 mg. gave 3.035 mg. AgCl. (Found: Cl=13.49. $C_{12}H_{11}O_4Cl$ requires Cl=13.97%).

Methyl Acetylferuloylferulate, $[(CH_3CO_2)(CH_3O)C_6H_3\cdot CH:CH\cdot CO_2](CH_3O)C_6H_3\,CH:CH\,CO_2CH_3$. To a solution of 3 gr. of ferulic acid in 15 gr. of pyridine, kept at −15°, the acetylferuloyl chloride obtained from 5 gr. of acetylferulic acid was added and allowed to stand overnight. The product was acidified with dilute sulphuric acid and the precipitate was purified from acetone, glacial acetic acid and then from dilute alcohol. The product

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(1) *Ber.*, **55** (1922), 1051.

(2) *Ann.*, **440** (1924), 34.

thus purified was treated with an ethereal solution of diazomethane. After recrystallising from a mixture of ether and benzene, faint, yellow crystals, m.p. 204–205.5°, were obtained.

5,275 mg. gave 12.490 mg. CO_2 and 2.660 mg. H_2O. (Found : C=64.70 ; H=5.64. $C_{23}H_{22}O_8$ requires C=64.57 ; H=5.20%).

Application of the Perkin Reaction to the Derivatives of Vanillin not Containing the Free Phenolic Group. (*a*) *Application to Acetylvanillin.* After heating acetyl vanillin (2 gr.) with fused sodium acetate (1.56 gr.) and acetic anhydride (4.7 gr.) in an oil-bath and recrystallising the product from alcohol, faint, yellow crystals, m.p. 192–193.5°, (m.p. of acetylferulic acid is 195–195.5°), were obtained. However, no acetylferuloylferulic acid could be isolated.

(*b*) *Application to Veratraldehyde.* A mixture of veratraldehyde (10 gr.), fused sodium acetate (12 gr.) and acetic anhydride (27.6 gr.) was heated to boiling for 6 hours. After removing the excess of acetic anhydride, the reaction product was extracted with ether, washed well with water, dried and evaporated. On standing it in a vacuum desiccator, a small quantity of solid was separated from the residual oil and recrystallised from alcohol, from which it separated in colourless crystals, m.p. 181° (yield, 0.5 gr.). 3 : 4-Dimethoxycinnamic acid is stated by Milobedzka to melt at 180–181°.

Application of the Perkin Reaction to p-Hydroxybenzaldehyde. A mixture of p-hydroxybenzaldehyde (15 gr.), acetic anhydride (56 gr.) and fused sodium acetate (18.7 gr.) was heated at 195–200° for 6 hours. After removing the excess of acetic anhydride and boiling twice with water, the residue, m.p. 168–188°, (12 gr.) was separated at first into two parts by using boiling alcohol.

The Part Soluble in Boiling Alcohol. This part was again separated into two portions by using hot water, namely the fraction soluble and insoluble in hot water. On recrystallising each portion from alcohol, colourless crystals (a), m.p. 205.5–206°, were obtained from the former, and faint, yellow crystals (b), m.p. 222–223° (decomp.), from the latter :

4.029 mg. of subst. (a) gave 9.882 mg. CO_2 and 2.026 mg. H_2O ; 0.350 mg. in 3.945 mg. of camphor gave $\Delta t=15.6°$ (Found : C=64.02 ; H=5.38 ; Mol. wt.=227.5. $C_{11}H_{10}O_4$ requires C=64.07 ; H=4.86% ; Mol. wt.=206.8).

4.022 mg. of subst. (b) gave 10.085 mg. CO_2 and 1.805 mg. H_2O ; 0.105 mg. in 2.070 mg. of camphor gave $\Delta t=5.6°$ (Found: C=68.19; H=5.00 ; Mol. wt.= 362.3. $C_{22}H_{16}O_6$ requires C=68.16 ; H=4.58% ; Mol. wt.=352.1).

The Part Insoluble in Boiling Alcohol. As this part was insoluble in water or in most organic solvents, it was first freed from impurities by boiling it successively with water, with alcohol and with glacial acetic acid,

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(1) *Ber.*, **43** (1910), 2166.

and then recrystallised six times from nitrobenzene, when it separated as a grey, amorphous substance (c), m.p. 231° (decomp.):

4.733 mg. gave 12.139 mg. CO_2 and 2.026 mg. H_2O. (Found: C=69.94; H=4.57. $C_{28}H_{22}O_8$ reguires C=69.89; H=4.45%).

Hydrolysis. Each of these three substances was hydrolysed with a 15% aqueous sodium hydroxide, when in all these cases only one colourless substance, m.p. 206–207°, was obtained in the almost theoretical yield. G. Eigel(2) gave 206° as the melting point of p-hydroxycinnamic acid.

The Methl Ester of (*b*). Substance (b) was treated with diazomethane in ethereal suspension and the product then purified as in the preparation of methyl acetylferuloylferulate, when faint, yellow crystals, m.p. 166–167°, were obtained and produced no depression of the melting point by admixture with methyl 4-p-acetyloxycinnamoyloxycinnamate which was synthetically obtained by the method described later.

The Methyl Ester of (*c*). The methyl ester, prepared similarly as described above, melted at ca. 200° on being rapidly heated:

4.620 mg. gave 11.860 mg. CO_2 and 2.094 mg. H_2O. (Found: C=70.01; H=5.07. $C_{30}H_{24}O_8$ requires C=70.28; H=4.73%).

Synthesis of Methyl 4-p-Acetyloxycinnamoyloxycinnamate, $[(CH_3CO_2)C_6H_4{\cdot}CH{:}CH{\cdot}CO_2]\ C_6H_4{\cdot}CH{=}CH{\cdot}CO_2CH_3$.

Acetyloxycinnamoyl Chloride, $(CH_3CO_2)\ C_6H_4{\cdot}CH{:}CH{\cdot}COCl$. 4-Acetoxycinnamic acid (0.5 gr.) was converted into its acid chloride, by treating with 2.5 gr. of thionyl chloride similarly as in the preparation of acetylferuloyl chloride, when it separated in colourless crystals, m.p. 118–119°:

7.153 mg. gave 4.446 mg. AgCl. (Found: Cl=15.37. $C_{11}H_9O_3Cl$ requires Cl=15.78%).

Methyl 4-p-Acetyloxycinnamoyloxycinnamate. p-Hydroxycinnamic acid (0.062 gr.) was dissolved in a mixture of 0.6 gr. of pyridine and 3 c.c. of absolute ether and kept at −15°. On acidifying with dilute sulphuric acid, faint, yellow precipitate separated, which was recrystallised once from alcohol, and was employed in the preparation of the methyl ester with diazomethane without further purification. The raw product was twice recrystallised from alcohol, when it melted at 166–167°.

4.865 mg. gave 12.273 mg. CO_2 and 2.389 mg. H_2O. (Found: C=68.79; H=5.49. $C_{21}H_{18}O_6$ requires C=68.82; H=4.95%).

The Application of the Perkin Reaction to 4-Methoxybenzaldehyde. *Synthesis of 4-Methoxycinnamic acid,* $(CH_3O)C_6H_4\ CH{:}CH\ CO_2H$. A mixture of 9 gr. of anisaldehyde, 30 gr. of acetic anhydride and 10 gr. of fused sodium acetate was heated to boiling for six hours. The reaction product thus

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(2) *Ber.*, **20** (1887), 2529.

obtained was treated in a similar manner to the purification of veratraldehyde. After removing the excess of acetic anhydride and boiling it with water, 0.6 gr. of faint, yellow crystals, melting at 165° to a milky liquid and becoming clear at 185°, were isolated from the crude product.

In conclusion, the author desires to express his sincere thanks to Professor Hiroshi Nomura for his kind guidance and encouragement.

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