8. Further clinical study is needed to estimate the uses and limitations of this new oxytocic.

REFERENCES.

(1) A. M. Mendenhall, "Solution of Pituitary and Ruptured Uterus," *J. A. M. A.*, April 1929.

(2) O. Kamm and associates, *J. A. C. S.*, 50, No. 2573 (1928), 601.

(3) Quoted by Fernández de Castro, M.D. *Thesis*, 1925.

(4) G. G. Colin, *Consideraciones acerca de la Farmacologiá y Normalización de los ocitócicos, con especial referencia al estudio del Zoapalle.*—Unpublished report. Read at the May meeting (1929) of the Mexican Chemical Society.

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PARA-METHOXY CINNAMIC ACID. A REVISION.

BY P. A. FOOTE.

Synonymy:

1. Methyl par(a)oxy phenyl acrylic acid[1] (1878).
2. Methyl ether of paracoumaric acid[2] (1887).
3. Methylnaringeninsaeure[3] (1887).
4. Methyl paracoumaric acid[4] (1881).
5. Para methoxy phenyl acrylic acid[5] (1918).

History.—Para-methoxy cinnamic acid was first prepared by Perkin[6] in 1877. Its ethyl ester was observed by Thresh,[7] in 1884, in *Hedychium spicatum*. Van Romburg,[8] who, in 1900, found that the larger part of the oil of *Kaempferia Galanga* consisted of this crystalline ester, supposed that he had noted its first occurrence in nature.

Occurrence.—Free or as ethyl ester it has been found in the following plants:

Hedychium spicatum, Ham. (Fam. *Zingiberaceæ*). Thresh[9] discovered the ethyl ester in 1884 in the oil of the rhizome.

Kaempferia Galanga Linné (Fam. *Zingiberaceæ*) Van Romburgh,[10] in 1900, found that the larger part of the oil distilled from the rhizome consisted of this crystalline ester. This was substantiated by Panicker, Puthan, Rao & Simonsen[11] in 1926.

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[1] Perkin, *J. Chem. Soc.*, 33, p. 211.

[2] Eigel, *Ber.*, 20, p. 2527. Coumaric acids are hydroxy cinnamic acids.

[3] Will, *Ibid.*, 20, p. 294. Naringeninic acid is *p*-hydroxy cinnamic acid, originally so-called because, with phloroglucinol, it results upon hydrolysis of naringenin, which, in turn, is obtained upon hydrolysis of the glucoside hesperidin.

[4] Koerner and Menozzi, *Gaz. Chim. Ital.*, 11, p. 549.

[5] Matzuo, *J. Biol. Chem.*, 35, p. 291.

[6] *J. Chem. Soc.* (3), 1, p. 388.

[7] *Pharm. J.*, 44, p. 361.

[8] *Königl. Akad. Wet. te Amsterd.*, 3, p. 38.

[9] *Pharm. J.*, 44, p. 361.

[10] *Königl. Akad. Wet. te Amsterd.*, 3, p. 38.

[11] *J. Indian Inst. Sci.*, 9A, p. 133.

Leptandra, *Veronica virginica* Linné (Fam. *Scrophulariaceæ*). In 1910 Power and Rogerson[1] isolated the acid from the rhizome and roots. They assumed that it occurred as ester.

As a complex in larger molecules, *p*-methoxy-cinnamic acid has been shown to be present in the following compounds:

1. Carthamin.—In 1910 Kametaka and Perkin[2] obtained it by oxidizing the crude methylation product of carthamine, the red pigment of safflower, *Carthamus tinctorius*, fam. *Compositæ*.

2. Yangonin.—In 1914 Borsche and Gerhardt[3] obtained it, together with anisic acid, upon saponification of yangonin, a constituent of kawa kawa, the root of *Piper methysticum*, fam. *Piperaceæ*.

Genetic Relations.—The occurrence of *p*-methoxy cinnamic acid as ethyl ester has already been referred to. Of greater interest is the occurrence of the corresponding aldehyde in the oil of Levant wormseed observed by Daufresni[4] in 1907. This suggests the occurrence of the corresponding alcohol as well.

$$2\ CH_3O.C_6H_4.CH{:}CH\ CHO \begin{cases} \rightarrow CH_3OC_6H_4CH{:}CHCH_2OH \\ \rightarrow CH_3OC_6H_4CH{:}CHCOOH \end{cases}$$

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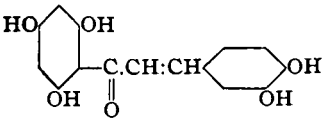
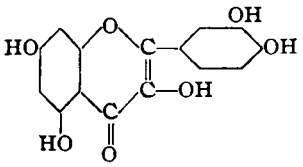
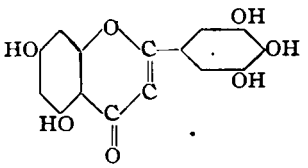
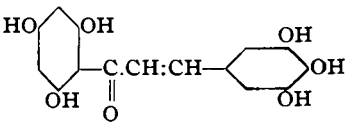
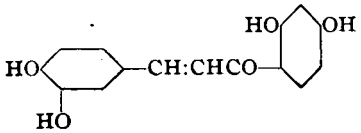
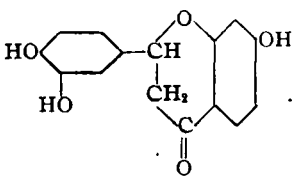
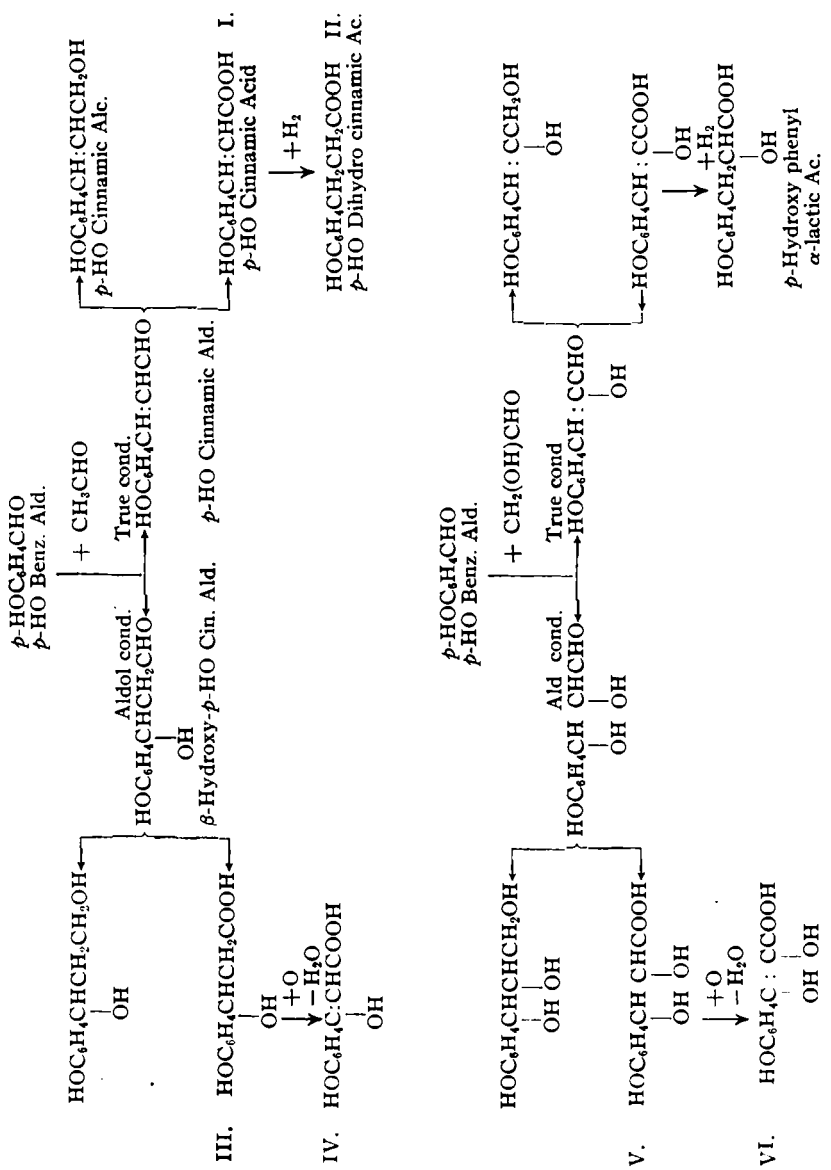
[1] *J. Chem. Soc.*, 97, p. 1944.
[2] *Ibid.*, 97, p. 1415.
[3] *Ber.*, 47, p. 2902.
[4] Dekker, 1928, *Ph. Zentrh.*, 69, p. 69. Comparable to this is the di-hydroxy acid forming eriodictyol  which cycles to quercetin  . Likewise myricetin  may be considered as the cycling of a compound  which was formed from phloroglucinol and the trihydroxy acid. The dihydroxy acid would yield butein  which on reduction may cycle to give butin  .

(Perkin and Hummel, 1904, *Chem. Soc.*, 85, 1459.)

The synthesis of the aldehyde from *p*-methoxy benzaldehyde (anisic aldehyde) and acetaldehyde and the occurrence of the former in Levant wormseed, as stated above, suggest another relationship

$$CH_3OC_6H_4CHO + H_2CHCHO \longrightarrow CH_3OC_6H_4CH{:}CHCHO + H_2O$$

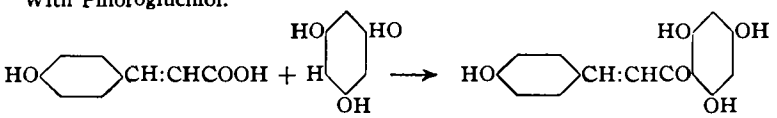
These and other relationships of well-known plant products are indicated in the following table:



I.—CONDENSATION OF $HOC_6H_4CH{:}CHCOOH$ WITH PHENOLS.

p-HO Cinnamic Ac.

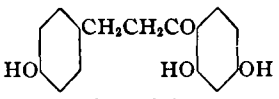
A. With Phloroglucinol.



Naringenin (*Ph. Zentrh.*, 69, p. 69).

II.—CONDENSATION PRODUCTS OF *p*-HYDROXY DIHYDRO CINNAMIC ACID WITH PHENOLS.

A. With Resorcinol.



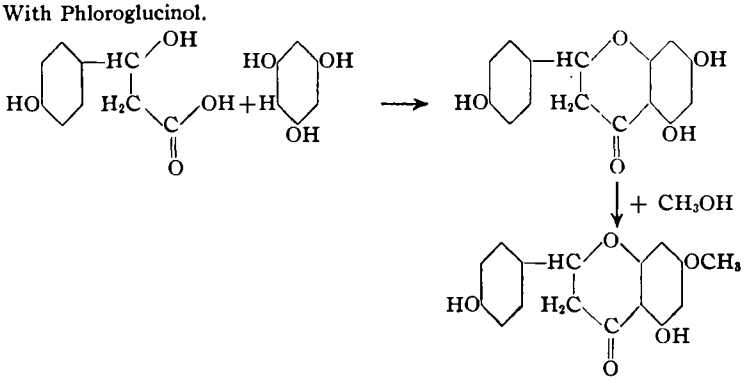
Phloretin[1]

As glucoside it occurs in several species of the rose family, *e. g.*, in *Pirus malus*, the apple tree.

III.—CONDENSATION PRODUCTS OF $HOC_6H_4CHCH_2COOH$ WITH PHENOLS.

OH

A. With Phloroglucinol.

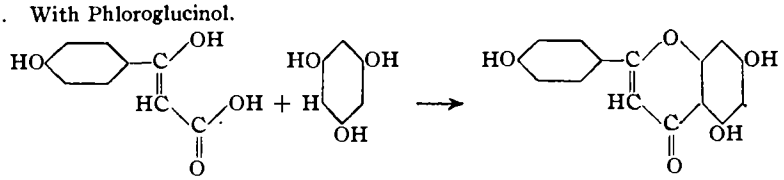


Sakuraretin[2]

IV.—CONDENSATION PRODUCTS OF $HOC_6H_4C{:}CHCOOH$ WITH PHENOLS.

OH

A. With Phloroglucinol.



Apigenin[3]
Apigenin methyl ether-
Acacetin

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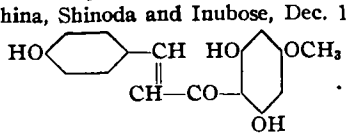
[1] Richter, Vol. II, p. 226, regards it as a derivative of *p*-hydroxyhydratropic acid $HOC_6H_4CH(CH_3)COOH$. (Michael, *Ber.*, 27, 1894, p. 2686.) The above formula is based on the work of Bougalt, *Compt. rend.*, 131, 1900, p. 43.

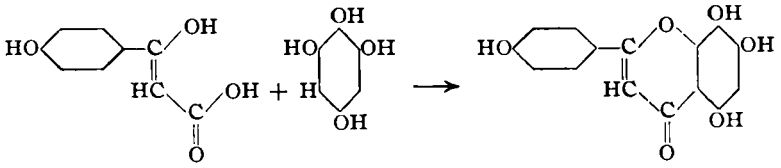
[2] Asahina, Shinoda and Inubose, Dec. 1927, *J. Pharm. Soc. Japan*, p. 133. Either this



structure or

[3] Perkin, 1900, *Chem. Soc.*, 71, p. 430.

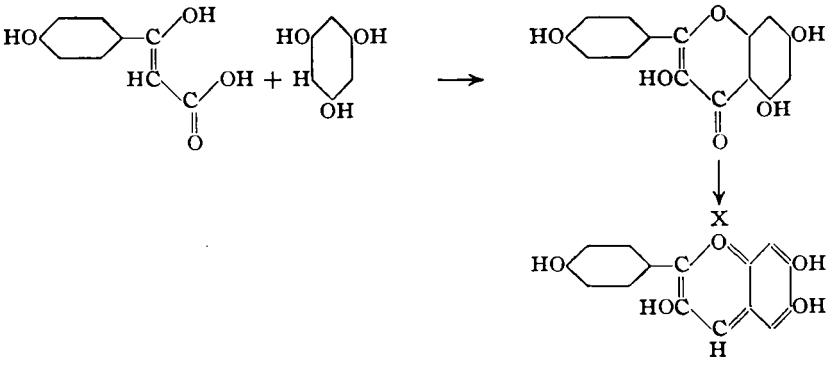
B. With 1:3:4:5 Tetrahydroxy Benzene.



Scuttelarin[1]

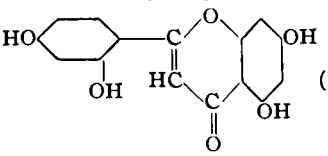
V.—Condensation Products of $HOC_6H_4C(OH)=C(OH)COOH$ with Phenols.

A. With Phloroglucinol.

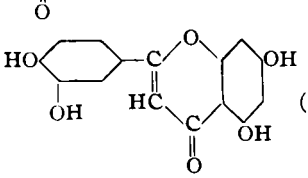


Pelargonidin (chloride)[2]

The dihydroxy acid would yield the supposed formula of lotoflavin



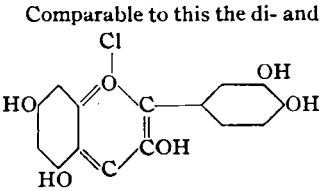
(Dunstan and Henry, *Phil. Trans.*, 1901, 194, p. 515), also its isomer luteolin



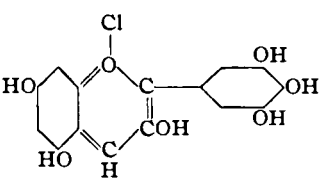
(Kostanecki *et al.*, *Ber.*, 33, 3410).

[1] Goldschmiedt and Zerner, 1910, *Monats.*, 31, p. 439.

[2] Willstätter, 1925, *Ber.*, 57, p. 1938 (*Ph. Zentrh.*, 69, p. 68). Comparable to this the di- and trihydroxy acids would produce, respectively, cyanidinchloride

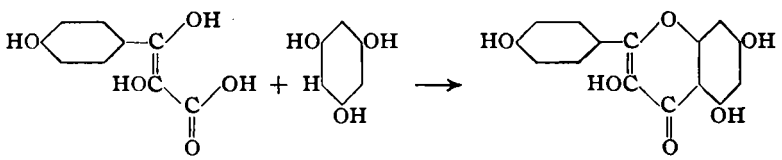


and delphinidin chloride

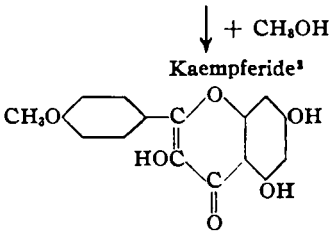


VI.—CONDENSATION PRODUCTS OF $HOC_6H_4C(OH):CCOOH$ WITH PHENOLS

A. With Phloroglucinol.



Kaempferol[1]

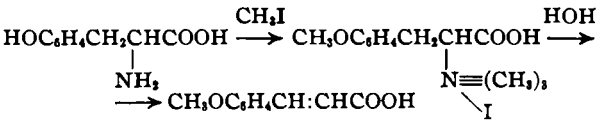


Kaempferide[2]

Methods of Formation.—1877. Perkin[3] prepared the acid by condensation of anisic aldehyde with sodium acetate using acetic acid anhydride as condensation agent.

$$CH_3OC_6H_4CHO + H_2CHCOONa \longrightarrow CH_3OC_6H_4CH{:}CHCOONa$$

1881. Koerner and Menozzi[4] obtained it by methylation of tyrosine (an acid occurring in many seedlings) and subsequent treatment.



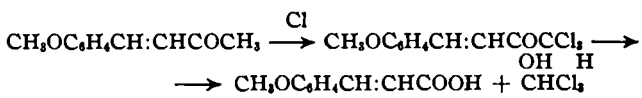
1887. Eigel[5] methylated *p*-hydroxy cinnamic = *p*-coumaric acid.

$$CH_3I + HOC_6H_4CH{:}CHCOOH \longrightarrow CH_3OC_6H_4CH{:}CHCOOH$$

1887. Finding that the Perkin method gave a poor yield, Einhorn and Grabfield[6] applied Claisen's method:

$$CH_3OC_6H_4CHO + H_2CHCOCH_3 \longrightarrow CH_3OC_6H_4CH{:}CHCOCH_3$$

This ketone was acted upon with hypochlorous acid.



1898. Knoevenagel[7] condensed anisic aldehyde with aniline and acted upon

[1] Kostanecki, 1901, *Ber.*, 34, p. 3723.
[2] Kostanecki and Rozycki, 1891, *Ibid.*, 24, p. 3723.
[3] *J. Chem. Soc.* (3), 1, p. 88.
[4] *Gaz. Chim. Ital.*, 11, p. 549.
[5] *Ber.*, 20, p. 2527.
[6] *Ann.*, 243, p. 362.
[7] *Ber.*, 31, p. 2585.

the resulting anilide with malonic acid and finally decarboxylated the resulting dicarboxylic acid.

$$CH_3OC_6H_4CHO + H_2NC_6H_5 \longrightarrow CH_3OC_6H_4CH{:}NC_6H_5 + H_2C\begin{matrix}COOH\\COOH\end{matrix}$$

$$CH_3OC_6H_4CH{:}C\begin{matrix}COOH\\COOH\end{matrix} \xrightarrow{-CO_2} CH_3OC_6H_4CH{:}CHCOOH$$

1909. Bunge[1] condensed anisic aldehyde with brom ethyl acetate and reduced the resulting bromide of the ester with zinc.

$$CH_3OC_6H_4CHO + H_2CBrCOOC_2H_5 \longrightarrow CH_3OC_6H_4CH{:}CBrCOOC_2H_5 \xrightarrow{H_2} \longrightarrow CH_3OC_6H_4CH{:}CHCOOC_2H_5$$

1914. Borsche,[2] upon saponification of yangonin, obtained the free acid together with anisic aldehyde.

Isomerism.—On account of the double linkage, *p*-methoxy cinnamic acid ought to be capable of existing in two forms, the cis and trans

$$HOC_6H_4CH \\ \| \\ HOOCCH$$

and

$$HOC_6H_4CH \\ \| \\ HCCOOH$$

Rotarski[3] in 1908 expressed the opinion that the acid existed in one form only. However, in 1911 Stoermer[4] prepared the labile form by exposing the ordinary acid to the rays of the uviol lamp. He recorded the following constants for the two forms:

	Stabile.	Labile or allo.
Heat of combustion	1164.2[1]	1173.6
Dissociation constant	2.1×10^6	9.29×10^6
No. of l. of H_2O to diss. one mol.	2500	90.6

[1] Kg. cal. per mol.

Chemical Properties.—These will be discussed under the respective derivatives of the acid.

Salts.—Salts of the following metals have been prepared by Perkin:

Sodium	Calcium	Iron
Copper	Strontium	
Silver	Barium	

The sodium salt was prepared by boiling the acid with an aqueous sodium carbonate solution. The other salts were prepared from the sodium salt by double decomposition.

Eigel[5] prepared the ammonium salt as well as the silver and barium salts.

Thresh[6] prepared the salts of potassium, copper, silver and iron.

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[1] *J. Russ. Phys.-Chem. Soc.*, 41, p. 460.

[2] *Ber.*, 47, p. 2902.

[3] ————?

[4] *Ber.*, 44, p. 637.

[5] *Ibid.*, 20, p. 2527.

[6] *Pharm. J.*, 44, p. 361.

The potassium and silver salts were likewise prepared by van Romburgh[1] as one means of identifying the acid.

The aniline salt of the labile form was obtained by Stoermer[2] in 1911, but the aniline salt of the stable form he was unable to isolate.

Esters.—The only esters reported are the methyl ester and the ethyl ester, the former prepared by Perkin[3] (1877) and the latter by Vorlaender[4] (1896).

Methyl Ester.—This was prepared by Perkin[3] (1877) by condensation of the acid with methyl alcohol. Again in 1881 he[5] prepared it from the acid chloride and methyl alcohol.

Ethyl Ester.—Its occurrence in nature has already been mentioned. Vorlaender[4] (1896) prepared the ester by condensation of anisic aldehyde and ethyl acetate.

$$CH_3OC_6H_4CHO + H_2CHCOOC_2H_5 = CH_3OC_6H_4CH{:}CHCOOC_2H_5$$

Bunge,[6] in 1909, prepared it by treating anisic aldehyde with bromo ethyl acetate and reducing the condensation product with zinc.

$$CH_3OC_6H_4CHO + BrCH_2COOC_2H_5 + H_2 \longrightarrow CH_3OC_6H_4CH{:}CHCOOC_2H_5 + H_2O + HBr$$

Addition Products.—The dibrom addition product of the free acid was prepared by Eigel[7] in 1877 after the dibrom addition product of the methyl ester had been prepared the previous year by Valentini[8] (1886). In addition Eigel obtained a tribromide, *viz.*,

$$CH_3OC_6H_3Br[3]\ CHBrCHBrCOOH$$

The dibromide was also prepared by Manchot[9] in 1912.

By treating the dibromide with alcoholic potash Reychler[10] in 1897 obtained *p*-methoxyphenylpropiolic acid ($CH_3OC_6H_4C : CCOOH$), which he decarboxylated upon heating in an aniline solution giving *p*-methoxyphenyl acetylene ($CH_3OC_6H_4C : CH$). When heated with water it gave instead methyl anisyl ketone ($CH_3OC_6H_4COCH_3$) and carbonic acid.

A more detailed study of the bromo derivatives was made by Hariharan & Sudborough[11] in 1925 who in the course of their work prepared the following compounds:

p-Methoxyphenylacetylene tetrabromide $CH_3OC_6H_4CBr_2CHBr_2$
Tri-*p*-anisylbenzene $C_6H_3(C_6H_4OCH_3)_3$
Tri-*p*-hydroxytriphenyl benzene $C_6H_3(C_6H_4OH)_3$
p-Bromophenylhydrazone of methyl anisyl ketone $p\text{-}CH_3OC_6H_4C(Me){:}N.NHC_6H_4Br$
p-Methoxy α,β-dibromostyrene $CH_3OC_6H_4CBr{:}CHBr$

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[1] *Kon. Akad. Weten. Amster.*, 3, p. 38.
[2] *Ber.*, 44, p. 637.
[3] *J. Chem. Soc.* (3), 1, p. 388.
[4] *Ann.*, 294, p. 253.
[5] *J. Chem. Soc.*, 39, 409.
[6] *J. Russ. Phys.-Chem. Soc.*, 41, p. 460.
[7] *Ber.*, 20, p. 2527.
[8] *Gaz. chim. ital.*, 16, p. 424.
[9] *Ann.*, 387, p. 278.
[10] *Bull. soc. chim.* (3), 17, p. 510.
[11] *J. Indian Inst. Sci.*, 8A (XI), p. 189.

p-Methoxy phenylpropiolic acid $CH_3OC_6H_4C : C.COOH$
p-Methoxy α-bromocinnamic acid
p-Methoxy α-bromo allocinnamic acid
p-Methoxy β-bromo cinnamic acid
p-Methoxy β-bromo allocinnamic acid
p-Methoxy α,α,β-tribromo-β-phenyl propionic acid
p-Methoxy α,α,β-2-tetrabromo-β-phenylpropionic acid
Ethyl *p*-methoxy-α bromo-cinnamate
Methyl *p*-methoxy-α,α,β-tribromo-β-phenyl propionate

Other Derivatives.—Perkin[1] in 1877 by means of PCl_5 obtained the acid chloride which he converted to the acid amide by treatment with ammonia. Stoermer[2] in 1911 also prepared the amide of both the stable and unstable forms. Weerman[3] in 1918 also prepared the amide.

An α methyl substitution product of the ethyl ester was obtained by Wallach[4] in 1908 by treating anisic aldehyde with ethyl α Br propionate and reduction by zinc in a benzene solution as follows:

$$CH_3OC_6H_4CHO + CH_3CHBrCOOC_2H_5 \longrightarrow CH_3OC_6H_4CH=C(CH_3)COOC_2H_5 + HBr + H_2O$$

Para acetyl oxycinnamic acid was obtained by Tiemann and Herzfeld[5] in 1877 by condensing sodium para oxybenzoic aldehyde with sodium acetate in the presence of acetic anhydride.

$$NaOC_6H_4CHO + NaOAc + Ac_2O \longrightarrow ACOC_6H_4CH:CHCOOH$$

The ethyl ester of the α-cyan acid was prepared by Bechert[6] in 1894 by condensing anisic aldehyde with cyan acetic acid in the presence of ethyl alcohol. He then prepared the dibromide of the ester as well as the α cyan acid:

$$CH_3OC_6H_4CHO + H_2C(CN)COOH + C_2H_5OH \longrightarrow CH_3OC_6H_4CH = C(CN)COOC_2H_5 + 2H_2O$$
$$CH_3OC_6H_4CH:C(CN)COOC_2H_5 + Br_2 \longrightarrow CH_3OC_6H_4CHBrC(CN)BrCOOC_2H_5$$
$$CH_3OC_6H_4CH:C(CN)COOC_2H_5 + H_2O \longrightarrow CH_3OC_6H_4CH:C(CN)COOH + C_2H_5OH$$

He also prepared the following salts K, Ag, Pb, Ba, Fe, Cu, Zn, Hg and Ca.

The *m*-nitro derivative of both the acid and its methyl ketone and their bromides were prepared by Einhorn and Grabfield[7] in 1887. The *m*-nitro acid was obtained by treating the acid with HNO_3 and H_2SO_4 at 0° C. while the *m*-nitro methyl ketone was obtained by condensing *m*-nitro anisic aldehyde with acetone.

α-Phenoxy-*p*-methoxycinnamic acid was obtained by Stoermer and Voht[8] in 1915 by condensing anisic aldehyde with phenoxy sodium acetate, acetic anhydride being used as a dehydrating agent.

$$CH_3OC_6H_4CHO + H_2C(OC_6H_5)COONa + Ac_2O = CH_3OC_6H_4CH:C(OC_6H_5)COOH + CH_3COOH + CH_3COONa$$

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[1] *Loc. cit.*
[2] *Loc. cit.*
[3] *Receuil de Trav. chim. des Pay Bas*, 37, p. 1.
[4] *Ann.*, 357, p. 72.
[5] *Ber.*, 10, p. 63.
[6] *J. pr. Chem.* [2], 50, p. 1.
[7] *Loc. cit.*
[8] *Ann.*, 409, p. 36.

The allo acid was then obtained by exposure to uviol lamp rays.

Pharmacology.—The only work along this line was by Matsuo[1] in 1918 who showed that the reduced acid, *p*-methoxypropionic, when injected into a rabbit was excreted in the urine as anisic acid and the glycocoll derivative of anisic acid ($CH_3OC_6H_4CONHCH_2COOH$).

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SOME NOTES ON THE U. S. P. SODIUM BORATE TEST FOR TRAGACANTH.

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At a meeting of the sixth annual Plant Science Seminar held in Boston, Mass., last August, it was brought out in one of the papers presented that samples of Gum Tragacanth now coming into the market do not respond satisfactorily to the U. S. P. sodium borate test.[1] Although this material, in every way, appears to be of very fine quality and responds to other prescribed tests for identity, it is being rejected by one of our large eastern manufacturing concerns as not being strictly U. S. P.

With my curiosity aroused as to the reason why samples now obtained should practically all fail to respond to this test while samples of ten years ago tested satisfactorily, I returned from the conference with the intention of investigating the old samples of Tragacanth carried in the Pharmacognosy drug stock at the College of Pharmacy, which represents a part of the valuable collection of vegetable and animal drugs started by Dr. Newcomb and which collection is still being enlarged by the department.

A paper entitled "A Comparative Precipitation Method for the Qualitative Identification of Each of the Common Gums" appeared in the January issue of the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION (page 34), by Weinberger and Jacobs, and deals with the common commercial gums and mucilages such as Acacia, Tragacanth, Indian Gum, Irish Moss, Agar, etc., and qualitative identification is based upon the quantity of 95% alcohol necessary to precipitate completely each gum from a 1 per cent solution. Gabel has also recently reported on "The Effect of Heat on Tragacanth and Its Mucilage"[2] and it is hoped that the information contained in this paper and that to be obtained in further experiments, will add some useful information to our knowledge of the properties of Gum Tragacanth. The work is not complete as it stands at the time of this report and for this reason the results herein should be accepted as preliminary ones only.

The directions of the U. S. P. X sodium borate test for Tragacanth are essentially the same as those of the previous revision. This is mentioned to show that

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[1] *J. Biol. Chem.*, 35, p. 29.

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[1] JOUR. A. PH. A., 18 (1929), 698.

[2] *Ibid.*, 17 (1928), 1206.