SCIENTIFIC SECTION

COLOR REACTIONS IN THE SYSTEM, PHENOL-ALDEHYDE-ACID.

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In the course of time many color reactions have been described for various compounds of interest to the organic and to the biologic chemist. Among such compounds may be mentioned alcohols, aldehydes, ketones, carboxylic acids, carbohydrates, phenols and alkaloids. The purpose of this paper is to bring out the fact that a great many of these color tests in biological chemistry revolve about the system, phenol-aldehyde-acid. Phenols and aldehydes interact in the presence of a dehydrating agent to form chromogenic compounds.

By means of this system we can prepare reagents to test for any one of its three components. Thus, to test for phenol it is necessary to make up a reagent containing aldehyde and acid; to test for aldehyde, a reagent containing phenol and acid; and to test for acid, a reagent containing aldehyde and phenol. By the use of this system we can therefore secure tests for

1. Phenols of all types, such as mono, di- and triphenols, phenolic ethers and esters, phenolic glucosides and phenolic alkaloids.
2. (*a*) Aldehydes.
   (*b*) Aldehydogenic substances.
   - I. Alcohols which yield aldehydes on oxidation.
   - II. Trihalogen alkyl derivatives, like chloroform, bromoform or iodoform, which on treatment with alkali yield a salt of formic acid, a carboxylic acid regarded as possessing aldehydic properties.
   - III. Carboxylic acids, like citric, oxalic or lactic acid, which react in the presence of sulphuric or hydrochloric acid to form aldehydes.
   - IV. Carbohydrates which yield the aldehyde, furfural, on treatment with sulphuric or hydrochloric acid.
   - V. Alkaloids, like narcotine, narceine and hydrastine, which yield the aldehyde, opianic acid, on treatment with acid.
3. Inorganic acids, such as hydrochloric or sulphuric acid.

TESTS FOR PHENOLS.

In order to identify phenols it is necessary to make up a reagent which would complete the system, phenol-aldehyde-acid. Such a reagent would consist of an aldehyde and an acid. Melzer's reaction for phenols in general and Mörner's reaction for the phenolic amino acid, tyrosine, are illustrations of the practical application of the system, phenol-aldehyde-acid.

TABLE I.

Author of reaction.	Test for phenols.	Reagent. Aldehyde.	Acid.	End result.
Melzer	Benzophenol	Benzaldehyde	H_2SO_4	Violet-blue
Mörner	Tyrosine	Formaldehyde	H_2SO_4	Green
Udransky	Morphine	Furfural	H_2SO_4	Purple, changing to blood-red

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TABLE I.—*Concluded.*

Author of reaction.	Test for phenols.	Reagent. Aldehyde.	Acid.	End result.
Pettenkofer	Morphine	Furfural, indirectly through the action of acid upon sucrose	H_2SO_4	Purple, changing to blood-red
	Oxydimorphine	Furfural, indirectly through the action of acid upon sucrose	H_2SO_4	Purple, changing to blood-red
Levine and Magiera	All types of phenols	Formaldehyde	H_2SO_4	Usual color purplish red, although there are many individual variations

In 1896 Marquis first reported his test for the opium alkaloids depending upon the color produced with formaldehyde in the presence of concentrated sulphuric acid. These alkaloids are either phenols or phenolic ethers. They fit in, therefore, with the scheme of the system, phenol–aldehyde–acid. Levine and Magiera have shown that the Marquis reagent is a valuable and practical general reagent for phenols.

TABLE II.—MARQUIS' TEST FOR PHENOLIC ALKALOIDS.

Test for phenolic alkaloids.	Reagent. Aldehyde.	Acid.	End result.
Morphine	Formaldehyde	H_2SO_4	Purplish red changing to violet, and finally becoming blue
Oxydimorphine	Formaldehyde	H_2SO_4	Green*
Codeine	Formaldehyde	H_2SO_4	Violet
Apomorphine	Formaldehyde	H_2SO_4	Violet
Narcotine	Formaldehyde	H_2SO_4	Olive-green, changing to yellow

* According to Fulton, oxydimorphine gives a red color, the green being due to the presence of oxidizing impurities.

TABLE III.—OTHER TESTS FOR PHENOLIC ALDEHYDES.

Test for phenolic alkaloids.	Reagent. Aldehyde.	Acid.	End result.
Codeine	Chloral hydrate	H_2SO_4	Carmine-red
Codeine	Furfural	H_2SO_4	Purplish red
Narcotine	Furfural	H_2SO_4	Greenish yellow color passing through yellow, brownish yellow, brown and brown-violet, and intense blue-violet

TESTS FOR ALDEHYDES.

We find that some of the well-known reagents for aldehydes consist of a mixture of phenol and concentrated hydrochloric or sulphuric acid. The reagent, phenol and acid, and the aldehyde complete the reaction system, phenol–aldehyde–acid.

TABLE IV.—TESTS FOR FORMALDEHYDE.

Test for aldehydes.	Reagent. Phenol.	Acid.	End result.
Formaldehyde	Benzophenol	H_2SO_4	Red ring
Formaldehyde	Resorcin	H_2SO_4	Red color

Formaldehyde	Naphthoresorcin	HCl	Flocculent precipitate, darkening on standing
Formaldehyde	Guaiacol	H_2SO_4	Violet ring
Formaldehyde	Pyrogallol	H_2SO_4	Chocolate-brown color
Formaldehyde	Phloroglucin	HCl	Finely divided precipitate, solution becoming orange in color
Formaldehyde	Gallic acid	H_2SO_4	Green ring, changing to deep blue ring
Formaldehyde	Thymol	H_2SO_4	Brown ring
Formaldehyde	α-Naphthol	H_2SO_4	Blue ring

TABLE V.—TESTS FOR OTHER ALDEHYDES.

Test for aldehydes.	Reagent. Phenol.	Acid.	End result.
Paraformaldehyde	α-Naphthol	H_2SO_4	Dark brown ring
Paraformaldehyde	Thymol	H_2SO_4	Upper layer of ring, blue; lower layer of ring, deep pink
Acetaldehyde	α-Naphthol	H_2SO_4	Greenish brown ring
Acetaldehyde	Thymol	H_2SO_4	Deep red ring
Paraldehyde	α-Naphthol	H_2SO_4	Dark brown ring
Paraldehyde	Thymol	H_2SO_4	Deep brown ring
Chloral hydrate	α-Naphthol	H_2SO_4	Greenish blue ring
Chloral hydrate	Thymol	H_2SO_4	Reddish brown ring
Glyoxylic acid	α-Naphthol	H_2SO_4	Green and bluish ring
Glyoxylic acid	Thymol	H_2SO_4	Deep pink ring

FURFURAL.

Furfural is an aldehyde which is a derivative of the five-membered heterocyclic ring, furfurane. It is obtained in the decomposition of carbohydrates by means of concentrated hydrochloric or sulphuric acid. Its importance as a degradation product of carbohydrate is shown by the fact that some of the best known tests for carbohydrates in general or for specific types of carbohydrates depend upon its formation.

TABLE VI.—TESTS FOR FURFURAL.

Author of reaction.	Test for aldehyde.	Reagent. Phenol.	Acid.	End result.
Molisch	Furfural	α-Naphthol	H_2SO_4	Reddish violet zone
Levine	Furfural	Thymol	H_2SO_4	Dark green zone
Bial	Furfural	Orcinol	HCl	Green solution or a green flocculent precipitate

Ketones may replace aldehydes in the reaction system, phenol–aldehyde–acid.

TABLE VII.—TESTS FOR KETONES.

Tests for.	Reagent. Phenol.	Acid.	End result.
Acetone	α-Naphthol	H_2SO_4	Greenish brown ring
Acetone	Thymol	H_2SO_4	Brown ring
Pyruvic acid	α-Naphthol	H_2SO_4	Yellowish green ring
Pyruvic acid	Thymol	H_2SO_4	Yellowish brown ring
Ethyl acetoacetate	α-Naphthol	H_2SO_4	Upper layer of ring, green; lower layer of ring, reddish
Ethyl acetoacetate	Thymol	H_2SO_4	Reddish brown ring

TESTS FOR ALDEHYDOGENIC COMPOUNDS.

The system, phenol–aldehyde–acid, can be conveniently employed for the alcohols which yield aldehydes on oxidation. Methyl and ethyl alcohol may be detected through their respective oxidation products, formaldehyde and acetaldehyde. Glycerol may also be detected through its oxidation products. When this trihydroxy alcohol is oxidized by chlorine or bromine, dihydroxyacetone is formed and eventually aldehyde, methyl glyoxal. After oxidizing the glycerol, the excess of bromine or chlorine is driven off. An alcoholic solution of orcinol, resorcinol or the phenolic alkaloid, codeine, is used together with concentrated sulphuric acid as the reagent to detect glycerol through its oxidation product, an aldehyde. In the Mandel-Neuberg test for glycerol, oxidation is brought about by means of sodium hypochlorite. The aldehyde, glycerose, which is formed, is made to react with orcinol and hydrochloric acid to give a beautiful green color.

TABLE VIII.—TESTS FOR GLYCEROL.

Tests for aldehydogenic compounds.	Reagent. Phenol.	Acid.	End result.
Glycerol	Orcinol	H_2SO_4	Beautiful violet or greenish blue
Glycerol	Resorcinol	H_2SO_4	Wine-red color
Glycerol	Codeine	H_2SO_4	Beautiful greenish blue on heating

TESTS FOR TRIHALOGEN DERIVATIVES OF METHANE.

Chloroform, bromoform and iodoform react with potassium hydroxide to form potassium formate. Since formic acid may be structurally regarded as being an aldehyde as well as a carboxylic acid, we may state that the reaction system, phenol–aldehyde–acid, can be used as a means of detecting the halogen derivatives. That this is the case is evident from the Schwarz resorcinol test and the Lustgarten naphthol test for chloroform, bromoform or iodoform.

TESTS FOR CHLOROFORM.

Author of reaction.	Test for aldehydogenic halogen derivatives.	Reagent. Phenol.	Alkali.	End results.
Schwarz	Chloroform	Resorcinol	NaOH	Yellowish red color attended by a beautiful yellow fluorescence
Lustgarten	Chloroform	α or β-Naphthol	KOH	Evanescent blue color, changing in contact with air to green, then to brown

In the above tests alkali is used instead of acid. The alkali is used to decompose the trihalogen derivatives. That acid can take part in the reactions is shown by the fact that the evanescent blue solution obtained with Lustgarten's reagents can on acidification be converted into a red dyestuff.

TESTS FOR ALIPHATIC CARBOXYLIC ACIDS.

Certain acids, among them oxalic, citric, succinic, malic, tartaric, glycolic and lactic acids, react on treatment with strong sulphuric to yield formaldehyde, formic acid or acetaldehyde. Owing to the formation of aldehyde, these acids readily respond to tests with reagents containing a phenol and concentrated sulphuric or hydrochloric acid.

TABLE IX.—TEST FOR ALIPHATIC CARBOXYLIC ACIDS.

Test for aldehydogenic acids.	Reagent. Phenol.	Acid.	End result.
Succinic acid	Resorcin	H_2SO_4	Yellowish red solution with green fluorescence
Malic	α-Naphthol	H_2SO_4	Blue color, changing to green on heating

Tartaric	α-Naphthol	H_2SO_4	Intense blue color
Tartaric	Resorcin	H_2SO_4	Bright red color
Tartaric	Pyrogallic	H_2SO_4	Fine violet-blue color
Cysteine	Thymol	H_2SO_4	Pink ring
Cysteine	α-Naphthol	H_2SO_4	Violet ring
Lactic	Thymol	H_2SO_4	Yellowish brown ring
Lactic	α-Naphthol	H_2SO_4	Yellowish green ring
Oxalic	Thymol	H_2SO_4	Pink ring
Oxalic	α-Naphthol	H_2SO_4	Purple ring
Citric	Thymol	H_2SO_4	Pink ring
Citric	α-Naphthol	H_2SO_4	Purple ring
Citric	β-Naphthol	H_2SO_4	Greenish yellow, changing to bright yellow on heating

According to Deniges, *p*-cresol, guiacol and codeine can be used as reagent for the detection of glycolic or lactic acid. Glycolic on treatment with sulphuric acid yields formaldehyde, while lactic acid under similar treatment yields acetaldehyde and formic acid.

Carbohydrates themselves are either aldehydes or ketones. On this account they should respond to the system, phenol–aldehyde–acid. In addition, the carbohydrates on treatment with concentrated sulphuric or hydrochloric acid yield the aldehyde, furfural. Formic acid and the ketonic acid, levulinic acid, are also formed in the reaction with concentrated acid.

TABLE X.—TESTS FOR CARBOHYDRATES.

Author of reaction.	Test for carbohydrates.	Reagent. Phenol.	Acid.	End result.
Molisch	All carbohydrates, glycolipins and glycoproteins	α-Naphthol	H_2SO_4	Reddish violet zone
Seliwanoff	Ketoses	Resorcin	HCl	Red color and separation of brown-red precipitate on heating
Tollen	Glycuronates	Naphthoresorcinol	HCl	After heating, mixture extracted with ether, which assumes violet-red color
Bial	Pentose	Orcinol	HCl and $FeCl_3$	Green color and green flocculent precipitate

Cotarnine and hydrastinine contain an aldehyde group. Both of these alkaloids react with phenols in the presence of concentrated sulphuric acid. Some other alkaloids decompose with concentrated sulphuric acid to give aldehydes. Narcotine, narceine and hydrastine yield on hydrolysis the aldehyde, opianic acid.

TABLE XI.—TESTS FOR ALDEHYDE-ALKALOIDS OR ALDEHYDOGENIC ALKALOIDS.

Test for alkaloids.	Reagent. Phenol.	Acid.	End results.
Cotarnine	Thymol	H_2SO_4	Brownish ring, changing to purplish brown
Cotarnine	α-Naphthol	H_2SO_4	Brownish orange ring
Cotarnine	Pseudomorphine	H_2SO_4	Strong bright green color in the presence of nitric acid
Hydrastinine	Thymol	H_2SO_4	Brownish pink ring, changing to cherry-red
Hydrastinine	α-Naphthol	H_2SO_4	Brown ring
Hydrastinine	Pseudomorphine	H_2SO_4	Strong blue-green color in the presence of nitric acid
Narcotine	Thymol	H_2SO_4	Purplish pink ring, changing to reddish brown
Narcotine	α-Naphthol	H_2SO_4	Orange ring
Narcotine	Pseudomorphine	H_2SO_4	Strong bright blue-green color in the presence of nitric acid

Narceine	Thymol	H_2SO_4	Reddish brown ring
Narceine	α-Naphthol	H_2SO_4	Brownish yellow ring
Narceine	Resorcinol	H_2SO_4	Carmine to cherry-red ring
Narceine	Tannin	H_2SO_4	Yellowish brown at first, soon turning to green
Narceine	Pseudomorphine	H_2SO_4	Strong bright green color in the presence of nitric acid
Hydrastine	Thymol	H_2SO_4	Purplish pink changing to violet
Hydrastine	α-Naphthol	H_2SO_4	Brownish ring
Hydrastine	Pseudomorphine	H_2SO_4	Strong blue-green color in the presence of nitric acid

The reactions of the aldehyde alkaloids and the aldehydogenic alkaloids with thymol and with α-naphthol have been described by Levine. The color reactions obtained with pseudomorphine in the presence of nitric acid have been reported by Fulton. This investigator has recently pointed out that the addition of an oxidizing agent like bromine or nitric acid in the system, phenol–aldehyde–acid, changes the color obtained in the same system free from oxidizing agent.

It is interesting to note the fact that John Uri Lloyd in his popular novel, *Stringtown on the Pike*, published in 1900, introduces into the murder trial, of Red Head, a fallacy with regard to the fading purple test used for strychnine. This test is obtained on treatment of strychnine in sulphuric acid with an oxidizing agent like potassium dichromate. Lloyd points out that a mixture of hydrastine and morphine produces the same result. From our viewpoint, morphine and hydrastine fit in with the reaction system, phenol–aldehyde–acid. Morphine is a phenol, and hydrastine yields the aldehyde, opianic acid, on treatment with sulphuric acid. The addition of an oxidizing agent to the system is in harmony with Fulton's idea of an oxidizing agent in our reaction system converting the initial color of the reaction into some other color. It now becomes simple to understand that when Lloyd treats a mixture of morphine and hydrastine with concentrated sulphuric acid, a pale yellow color forms, gradually deepening as it stands. On the addition of a fragment of potassium dichromate a play of color develops ranging from purple to maroon-red.

TESTS FOR FREE INORGANIC ACID.

The reaction system, phenol–aldehyde–acid, is a useful one in detecting inorganic acid, such as hydrochloric or sulphuric acid. Boas' test and Günzberg's test serve to detect free hydrochloric acid in gastric contents. The reagents used, phenol and aldehyde, complete the triple system, phenol–aldehyde–acid.

TABLE XII.—TESTS FOR FREE INORGANIC ACID.

Author of reaction.	Test for free acid.	Reagent. Phenol.	Aldehyde.	End result.
Boas	Free acid in stomach contents	Resorcinol	Cane sugar (yielding furfural with acid)	Rose-red color after heating
Günzberg	Free acid in stomach contents	Phloroglucin	Vanillin	Purplish red color after heating

To obtain a positive reaction with the Boas and the Günzberg test heating is required in order to concentrate the small amount of free acid present in gastric contents.

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V. E. Levine and E. A. Magiera, "The Formaldehyde-Sulphuric Acid Reaction of the Opium Alkaloids," *Journal of Laboratory and Clinical Medicine*, 12 (1927), 773.

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V. E. Levine, "A General Test for Carbohydrates," *Proceedings of the Society for Experimental Biology and Medicine*, 22 (1930), 831.

New Group Conception.—A century of progress—International Exposition, Chicago, 1933. Rising from colored concrete terraces the fourth Fair building—Hall of Science—in which the Pharmacy Exhibit will be placed. Space is now being assigned for the exhibits. See April JOURNAL, page 313.

EUROPEAN PHARMACEUTICAL CONVENTIONS.

The Society for Chemical Industry will meet in London during the week of July 13th. A Liebig celebration will be held at Giesen, Germany, July 19th. Holland Pharmaceutical Association will meet at Utrecht, July 6th–8th. The British Pharmaceutical Conference will meet at Manchester, July 20th.

IMPORTS OF CRUDE DRUGS.

Crude drugs in recent years have attained an increasing prominence in import trade of the United States coincident with the rapid growth of the American pharmaceutical, proprietary medicine, insecticide and other consuming industries, according to the Commerce Department's Chemical Division.

The increasing domestic requirements are reflected in the gradually expanding volume of United States imports of crude drugs, which increased over 140 per cent during the past 10 years, from 68,215,000 pounds in 1921 to 165,176,000 pounds in 1930. While production of many of these products is widely diffused throughout the world, most of the drugs upon which industry is principally dependent possess well-defined areas of cultivation.

This is true of cinchona bark, originating principally in the Netherland East Indies; nux vomica, which is produced largely in British India and French Indo-China; senna in Egypt and British India; licorice root in Soviet Russia, Turkey and Iraq; pyrethrum flowers in Japan and Yugoslavia; derris root in the Malay Peninsula and Borneo; aloes in the Dutch West Indies; papain in Ceylon; ergot in Russia and Spain; psyllium seed in France; orris root in central and southern Europe and buchu leaves in South Africa.