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GUAIACOL- AND CREOSOL-ACETIC ACIDS AND SOME OF THEIR DERIVATIVES.

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The attention of chemists and physicians has for years been directed upon creosote from beechwood tar, and in particular upon the principal ingredients of the same, guaiacol and creosol, and their value in the treatment of tuberculosis has been generally admitted. It has been shown by several investigators that creosote is a general and effective germicide, and its therapeutic value is dependent largely upon this fact, as it will kill bacilli wherever it comes in contact with them in the system. Creosote possesses other virtues as a medicinal agent, such as stimulating the secretions and increasing the appetite, but these belong more properly to a therapeutic treatment of the subject. Buchholtz has shown that creosote is at least four times as effective a germicide as phenol; so that, other things being equal, it would naturally be preferred to the latter. Besides its direct germicidal effect, creosote possesses the undesirable property of irritating the mucous membrane of the stomach, and so pronounced is this effect that it is sufficient to practically prevent its use as such internally. It was, therefore, the aim of the chemists to produce compounds of creosote or its chief constituents, guaiacol and creosol, which are non-irritating, and which were easily split up in the system into their components, and which consequently retain their full germicidal power.

Numerous preparations have been manufactured, such as duotal, creosotal, guaiacol phosphate, benzoate, salicylate, cinnamate (styracol), camphorate (guacamphol), thiocol, æthakol, guajaceticin, etc.

More than fifteen years ago experiments were carried out by us in order to produce compounds of guaiacol and creosol, which possessed the above mentioned properties, and as a result of these investigations the products described below were obtained. Although in the meantime some of these compounds have been manufactured and described by other investigators, we thought it to be of interest to give a short account of these products, the more so as some of them were obtained by a process differing from that given in this paper, and as the description of these products is rarely found in the literature.

The guaiacol or creosol radicals were introduced into the acetic acid radical, and from the resulting substituted acids, the various salts, esters, and amides were prepared. Unfortunately, these substances, as we found out later, have therapeutically little value, since the guaiacol or creosol, unlike in those esters of

organic or inorganic acids, in which these compounds figure as alcohols, is split off only partially.

*Guaiacol-Acetic Acid.*¹ $\text{C}_6\text{H}_4 \begin{smallmatrix} \diagup \text{OCH}_3 \\ \diagdown \text{OCH}_2\text{COOH} \end{smallmatrix}$

By adding 125 parts of guaiacol to a mixture of 95 parts of monochloroacetic acid, and 80 parts of sodium hydroxide in about half a liter of water, and boiling the mixture for some time, the originally alkaline solution will turn acid, indicating that partial saponification or hydrolysis of the product takes place. The yield of this method, therefore, is not very satisfactory, and we found the following process preferable: Neutralize a mixture of water and 125 parts of guaiacol by adding just enough sodium hydroxide to form sodium guaiacolate, and do the same with a mixture of water and monochloroacetic acid to form sodium monochloroacetate. Mix both solutions and add enough water to make the liquid measure one liter. Then add caustic soda solution to make the mixture slightly alkaline. The mixture is heated to boiling for about four hours in a balloon flask supplied with a reflux condenser. The solution, which will not turn acid under these conditions is cooled and treated with an excess of hydrochloric acid, when the guaiacol-acetic acid separates out as a light brown colored oil, which soon solidifies. To remove uncombined guaiacol, the acid is treated with a solution of sodium carbonate, and then shaken out with ether. After separating the ethereal solution, the aqueous solution is acidified, and the precipitated guaiacol-acetic acid collected. It is then dissolved in much warm water, when on cooling it crystallizes out in the form of long, fine white needles, which melt at 121°, and decompose by continued heating with water into guaiacol and acetic acid. It is readily soluble in alcohol, ether, benzene, and chloroform.

The sodium salt of guaiacol-acetic acid crystallizes from water in white needles and is readily soluble in water, while the corresponding potassium salt which also crystallizes in white needles is rather difficultly soluble in water.

Copper guaiacol-acetate, $(\text{C}_7\text{H}_7\text{O}_2 \cdot \text{CH}_2 \cdot \text{COO})_2 \text{Cu}$, crystallizes from water in fine blue needles.

Lead guaiacol-acetate, $(\text{C}_7\text{H}_7\text{O}_2 \cdot \text{CH}_2 \cdot \text{COO})_2 \text{Pb}$, is difficultly soluble in water, and crystallizes in wart-like masses of colorless needles.

Silver guaiacol-acetate, $(\text{C}_7\text{H}_7\text{O}_2 \cdot \text{CH}_2 \cdot \text{COO}) \text{Ag}$, crystallizes from water like the lead salt and is quite sensitive to light.

*Creosol-Acetic Acid.*² $\text{C}_6\text{H}_3 \begin{smallmatrix} \diagup \text{CH}_3 \\ \diagdown \text{OCH}_3 \\ \diagdown \text{OCH}_2\text{COOH} \end{smallmatrix}$

This acid is formed by a similar method as was used in making guaiacol-acetic acid, viz., heating a mixture of the sodium salts of monochloroacetic acid and creosol in solution, with a slight excess of caustic soda. About 10 percent of the creosol is not acted upon and may be recovered as such. After boiling the mixture for several hours, then cooling and acidifying it, the creosol-acetic acid is precipitated and recrystallized from hot water. It forms long white needles which melt at 108°, and are sparingly soluble in water though readily soluble in the usual solvents.

¹Manufactured by Elberfeld Farbenfabriken in Germany, and covered by D. R. P. 85,490. Also obtained by Auwers and Haymann by saponification of the ethylester (B. B. XXVII, 2804).

²Manufactured by Lederer and covered by D. R. P. 83,538.

Potassium creosol-acetate forms long fine white needles when crystallized from water. It is readily soluble in hot water, though difficultly soluble in alcohol.

The copper salt is difficultly soluble in water from which it crystallizes in blue wart-shaped crystals. The lead salt which crystallizes similarly, is readily soluble in water. The silver salt crystallizes in groups of needles and lamellæ, is soluble in water, colorless, and quite sensitive to light. It may be of interest to mention that the lead and copper salts of both guaiacol- and creosol-acetic acids have low melting points.

*Guaiacol-acetic acid ethyl ester.*³ $C_6H_4 \begin{smallmatrix} \diagup OCH_3(1) \\ \diagdown O.CH_2.COOC_2H_5 \end{smallmatrix}$

By adding to guaiacol-acetic acid about five times its weight of absolute ethyl alcohol, and passing dry hydrochloric acid gas through the solution or by heating the above mixture of the acid and alcohol with concentrated sulphuric acid (about one-third of the weight of the guaiacol-acetic acid taken) for five hours, this substance is formed. On pouring the mixture into a large volume of cold water, the ester will separate as a light yellow colored heavy oil, which, when redistilled boils at 270-271°. It possesses a pleasant cinnamon-like odor, is insoluble in water, and easily soluble in alcohol and ether.

Creosol-acetic acid ethyl ester. $C_6H_3 \begin{smallmatrix} \diagup CH_3 \\ \diagdown OCH_3 \\ \diagdown O.CH_2.COOC_2H_5 \end{smallmatrix}$

This compound was prepared similarly to the guaiacol compound and was found to possess a similar but more distinct, pleasant, aromatic odor, and the same solubilities and color. It boils at 276-277°.

*Guaiacol-acetic acid amide.*⁴ $C_6H_4 \begin{smallmatrix} \diagup O.CH_3 \\ \diagdown O.CH_2.CONH_2 \end{smallmatrix}$

If the above-described guaiacol-acetic acid ethyl ester is shaken continuously in a well-cooled bottle with an excess of concentrated ammonia water (35 percent NH_3) for about fifteen to twenty minutes, and then allowed to stand, the oil will be changed to a mass of white needles of guaiacol-acetic acid amide and the contents of the bottle will become a solid crystal cake. As the rapid formation of the amide is apt to cause some of the uncombined oil to be included in masses of the former, it is desirable to frequently break these masses of needles up by means of a stirrer or glass rod until no more lumps or masses are observed. It was often found necessary to rub these masses up in a mortar to insure complete conversion into the amide, and the best yields were obtained if the reaction was allowed to continue for about twenty-four hours. The crystals of the amide were filtered off, washed with cold water to remove the excess of ammonia, and recrystallized from hot water, using an excess of water to prevent the amide from separating out as oil, which it will do if too little water has been taken for dissolving it. If all the ammonia is not removed by washing with cold water, some of the amide will be saponified when it is heated with the water for recrystallization. It crystallizes in fine white needles arranged in fan-shaped clusters and melts at 138°. It is soluble in hot water, alcohol, and ether, and is colorless and tasteless.

³Obtained by Auwers and Haymann by the action of sodium guaiacolate on monochloroacetic ester (B. B. XXVII, 2804).

⁴Manufactured and covered by D. R. P. 108,342 by the Actien Ges. fuer Anilinfabrikation, Berlin. Obtained by the action of chloracetamide on sodium guaiacolate.

The amide is saponified by moderate heating with solutions of caustic alkalis.

Creosol-acetic acid amide. $\text{C}_6\text{H}_3 \begin{array}{c} \diagup \text{CH}_3 \\ \text{---} \text{OCH}_3 \\ \diagdown \text{O} \cdot \text{CH}_2\text{CONH}_2 \end{array}$

This substance is prepared from creosol, just as the guaiacol-acetic acid amide is prepared from guaiacol, and crystallizes from warm water in fine white needles, which are odorless and tasteless. Its melting point is 127° and like the guaiacol-acetic acid amide it is saponified by caustic alkalis. Its solubilities are the same as those of guaiacol-acetic acid amide.

Below we append a tabular statement of some of the compounds of the various phenols with monochloroacetic acid and their melting or boiling points:

	M. P.	B. P.
Phenol acetic acid.....	96°	285°
Phenol acetic acid ethyl ester.....		251°
Phenol acetic acid amide.....	101.5°	
α -Naphthol-acetic acid.....	190°	
α -Naphthol-acetic acid ethyl ester.....	173°	
α -Naphthol-acetic acid amide.....	155°	
β -Naphthol-acetic acid.....	$151/152^\circ$	
β -Naphthol-acetic acid ethyl ester.....	$48/49^\circ$	
β -Naphthol-acetic acid amide.....	147°	
Thymol-acetic acid.....	148°	
Thymol-acetic acid ethyl ester.....		290°
Thymol-acetic acid amide.....	$96/97^\circ$	
Guaiacol-acetic acid.....	121°	
Guaiacol-acetic acid ethyl ester.....		$270/271^\circ$
Guaiacol-acetic acid amide.....	138°	
Creosol-acetic acid.....	108°	
Creosol-acetic acid ethyl ester.....		$276/277^\circ$
Creosol-acetic acid amide.....	127°	

We have also prepared the corresponding compounds of purified creosote from beechwood tar. We have made thus, creosote-acetic acid, its ethyl ester and its amide, all of which are mixtures and possess the same properties as those of the compounds which constitute them.

RESEARCH LABORATORIES OF SHARP & DOHME, Baltimore, June, 1912.

ESTIMATION OF IRON IN REDUCED IRON.

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Many methods for the determining of iron in reduced iron have been devised in recent years. In reviewing the various processes offered, opinion seems to be about equally divided as to whether the percentage of the total iron or of the metallic iron shall be taken as standard by which the value of reduced iron is to be gauged.

For estimating the total iron, the method which is described in the text of the Dutch, German and Italian Pharmacopœias stands out most prominently. In this process the iron is dissolved in acid, the resulting ferrous salt oxidized with potassium permanganate and the ferric salt estimated iodometrically in the usual way.

For the estimation of metallic iron only, the mercuric chloride method as given