

4. The conclusion is reached from a study of the distribution coefficients that these solvents possess definite possibilities as immiscible solvents to be used in extracting certain alkaloids from aqueous solution.

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STUDIES ON CALCIUM CREOSOTATE. I. CHEMICAL OBSERVATIONS ON THE WATER-SOLUBLE CONSTITUENTS.*¹

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According to Gordonoff (1) creosote is more extensively used than any other therapeutic agent in the treatment of pulmonary disorders. The oral administration of creosote is attended with numerous objections the most pronounced of which, even after small doses, is its tendency to produce nausea and vomiting. Various attempts have been made to overcome these objectionable features of creosote therapy by diverse modifications of creosote and its constituents.

Calcium creosotate, prepared by the interaction of equal parts of calcium oxide and creosote, is a dark brown powder of empyreumatic odor and phenolic taste, which has enjoyed extensive clinical use as a creosote substitute for a period of more than twenty years. In view of the fact that a search of the literature discloses an almost complete lack of information on this drug and particularly since it has been admitted to U. S. P. XI, it would seem advisable to subject it to a thorough investigation.

The U. S. P. states that calcium creosotate is a mixture of the calcium compounds of creosote. When equal parts of calcium oxide and creosote are allowed to interact, the mixture attains a rather high temperature. This would lead one to suspect that the original creosote might be somewhat altered in the course of preparation of calcium creosotate. It would therefore seem important to determine whether or not calcium creosotate approximates creosote chemically.

All attempts to extract calcium creosotate with organic solvents were unsuccessful. When extracted with water a small percentage of the calcium creosotate goes into solution; the major portion of the drug, however, is water insoluble. Since aqueous solutions of calcium creosotate are to be used in certain future experiments the present investigation has been limited to a study of the chemical nature of the water-soluble constituents of the drug. An aqueous solution of calcium creosotate which would contain a definite amount of the powdered drug would be desirable. Since this is impossible solubility experiments were carried out in an attempt to establish a relationship between the amount of water-soluble constituents and

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calcium creosote powder. Various sized samples of calcium creosote were extracted with distilled water and the calcium and phenolic content of the aqueous extracts determined.

Solutions of the water-soluble bodies of calcium creosote have been hydrolyzed and the phenols removed and distilled in an effort to determine whether they approximate chemically, the phenolic bodies of creosote. In addition to reviewing the literature on the chemistry of creosote, Sickman and Fischelis (2) have advanced data to show that most official creosote samples have methoxyl numbers which are more or less within a definite range. In the present paper the hydrolyzed water-soluble phenols of calcium creosote have been compared with the phenols of their precursor creosote using methoxyl numbers and the U. S. P. X specifications for creosote as comparative criteria.

If calcium oxide and creosote are allowed to interact *in the presence of water* "calcium creosote solution" is obtained and this is of much greater phenolic concentration than an aqueous solution prepared from calcium creosote powder. The phenols obtained from a solution prepared from calcium creosote powder and the phenolic bodies of "calcium creosote solution" have been compared with the phenols of creosote.

Experimental.—Samples of calcium creosote powder ranging from 1.0 Gm. to 36.0 Gm. were placed in 240-cc. bottles, 200 cc. of carbon dioxide-free water added and shaken at a moderate rate on a shaking machine. As shown in Table I the 1- and 2-Gm. samples were not completely extracted after 6 hours shaking; however, at the end of 12 hours shaking these samples were completely extracted. When the residues from these samples were reextracted for 12 hours only traces of phenols were obtained. When the other samples were reextracted for twelve hours appreciable amounts of phenols could be obtained.

Using the method of J. Moir (3) all solutions were assayed for phenolic content by colorimetric comparison with a standard creosote solution. This method is based on the fact that phenols, except those in which the *p*-position is blocked, in the presence of a diazotized solution of *p*-nitraniline, will give a red color when made alkaline. The deep red color of the original calcium creosote solutions did not introduce an error in the determinations because in the dilutions used the calcium creosote solutions, before adding the diazo reagent, were practically colorless. Attempts were made to dilute the calcium creosote solutions so that the phenolic content of the samples assayed would approximate the concentration of the standard which was 4.0 mg. of creosote per 100 cc.

Just before using, the *p*-nitraniline reagent (1.5 Gm. *p*-nitraniline, 40 cc. conc. HCl and 500 cc. distilled water) was cooled to 0° C. and sodium nitrite solution (20%) added until decolorization took place. Of each of the diluted calcium creosote samples twenty-five cc. were placed in a 100-cc. volumetric flask containing 10.0 cc. of the diazotized *p*-nitraniline reagent, shaken and allowed to stand for several minutes. Seven cc. of NaOH solution (15.0%) were then added and the volume adjusted to 100 cc. with distilled water. A standard solution of creosote (2 mg. creosote in 1 cc.) was treated in the same manner as the calcium creosote solutions and comparisons made in a colorimeter.

Total ash obtained by evaporation and incineration of 25.0-cc. portions of the solutions has been obtained from each sample of calcium creosote powder and expressed as calcium oxide in Table I. This is permissible since preliminary tests had shown that oxalate precipitation values agreed in all respects with the total ash results. Discrepancies in the amounts of water-soluble phenols obtained from given amounts of the powdered drug prompted the determination of total organic matter present in the powdered drug. Calcium creosote powder which had been dried to constant weight over sulfuric acid was completely incinerated, the residual calcium oxide weighed, and the loss in weight calculated as organic matter.

One hundred cc. of creosote of the same lot used in the preparation of calcium creosote

powder and "calcium creosote solution" were distilled and subjected to the analytical procedures shown in Table II.

Two and four-tenths Kg. of calcium creosote powder were extracted with 16 liters of distilled water, the aqueous extract removed from the residual drug by filtration and the water-insoluble residue washed with four liters of distilled water. The filtrate and washings were acidified with concentrated HCl and subsequently extracted with ethyl ether. This extract was washed with distilled water until the washings showed no cloudiness upon the addition of silver nitrate. After allowing the extract to stand over anhydrous sodium sulfate for several days the ether was removed by distillation under reduced pressure, 100 cc. of the residue remaining in the flask distilled at atmospheric pressure according to Method II of the U. S. P. X and the boiling point range recorded. The per cent methoxyl and specific gravity of the distillate were also determined.

In order to approximate the calcium creosote hydrolysis and extraction as nearly as possible a sample of the creosote from which the calcium creosote was prepared was placed in aqueous solution, acidified with HCl and the phenols extracted and treated in the same manner as the hydrolyzed calcium creosote phenols. The analytical procedure on the phenolic distillate was the same as that used on the hydrolyzed calcium creosote phenols. Twelve liters of six months old "calcium creosote solution" (creosote content 1.8%) were hydrolyzed and distilled and the distillate examined in the same manner as the original creosote and hydrolyzed water-soluble phenols from calcium creosote powder.

RESULTS AND DISCUSSION.

In Fig. 1 the creosote and calcium oxide content per cc. of each solution in Table I have been plotted against grams of calcium creosote powder extracted by 200 cc. of distilled water. It is to be observed that the calcium oxide content in-

TABLE I.—PHENOLIC AND CALCIUM CONTENT OF CALCIUM CREOSOTE POWDER IN CARBON DIOXIDE FREE WATER. ROOM TEMPERATURE 25° C.

Calcium Creosote per 200 Cc. Water. Grams.	Hours Shaken.	Creosote Extracted by 200 Cc. Dist. Water. Grams.	Creosote per Cc. of Solution. Mg.	Ca as CaO per Cc. of Solution. Mg.
1.0	6	0.202	1.01	..
"	12	0.274	1.37	1.83
2.0	6	0.446	2.23	..
"	12	0.536	2.68	2.68
4.0	6	0.704	3.52	..
"	12	0.704	3.52	2.80
6.0	6	0.850	4.25	..
"	12	0.850	4.25	3.48
8.0	12	0.960	4.80	3.71
12.0	12	1.152	5.76	4.00
16.0	12	1.400	7.00	4.21
20.0	12	1.538	7.69	4.45
24.0	12	1.798	8.99	4.86
30.0	12	1.828	9.14	5.01
36.0	12	1.826	9.13	4.94

creases with increased phenolic concentration. It is also obvious that with increased phenolic concentration there is a relative decrease in calcium oxide content. In the smallest sample the calcium oxide content is greater than the phenolic content and in the next higher sample the two concentrations are equal. Thereafter the phenolic values are always higher than the calcium. It is obvious that the calcium oxide content *per se* of the solutions in Fig. 1 is always in excess of 1.4 mg. per cc., the approximate solubility of calcium hydroxide at 25° C.

If an arbitrary assignment of a number representing the average molecular weight of the phenols of creosote is made it is possible to roughly estimate the theoretical amount of calcium oxide necessary to combine with a given amount of creosote phenols. In a complex mixture such as creosote quantitative estimations of the constituent phenols become a difficult task. The nearest approach to a determination of the percentage composition of creosote is the work of Behal and Choay (4). Inspection of their results indicates that 124, the molecular weight of guaiacol, is a representative figure for the average molecular weight of the creosote phenols. The inaccuracies involved in this assignment are manifold, particularly so in view of the fact that evidence which will be presented later indicates that the phenols of calcium creosotate are not entirely comparable chemically with the

TABLE II.

Material Distilled.	Volume Distilled. Cc.	B. P. Range. ° C.	Distillate Distilling above 200° C. Per Cent.	Residue. Cc.	Sp. Gr. 25° C.	MeO Per Cent.
Creosote	100	200-215	100	2	1.085	12.5
Phenols extracted from acid aqueous solution of creosote	100	195-215	70	2	1.085	12.1
Water-soluble phenols from calcium creosotate powder	100	192-215	45	3	1.060	8.5
Phenols from "calcium creosotate solution"	100	192-215	50	2	1.050	4.5
U. S. P. X requirements for creosote	..	200-220	90	..	Not less than 1.075
Sickman and Fischelis for typical creosote samples	10.88 to 16.3

creosote phenols. However, it is of assistance in visualizing the possible nature of the mixtures in Fig. 1. If calculations are made in this manner the *observed* calcium values shown in Table I and Fig. 1 are always in excess of the theoretical amount necessary to combine with the *observed* phenol concentration. Calculated on the basis of formation of diphenolic salts it can be shown that the *excess* calcium increases with increased phenolic concentration so that in the more concentrated solutions the *excess* calcium greatly exceeds the solubility of calcium hydroxide. If calculations are made to determine the amount of calcium necessary to form monophenolic salts the excess calcium is practically the same in all the solutions of low phenol concentration but as the saturation point of the solutions is approached the amount of excess calcium gradually becomes smaller. While the data are insufficient from which to draw conclusions concerning the nature of the phenolic compounds it does appear that the calcium creosotate phenols are in solution as their calcium salts in equilibrium with an inorganic calcium compound.

Reference to Table I discloses the fact that the phenolic saturation point of the solutions, approximately 0.9 per cent creosote, is reached at the 24.0-Gm. sample. An interesting fact is disclosed in this table concerning the amount of water-soluble phenols obtained from the 1- and 2-Gm. samples. Inasmuch as equal parts of

calcium oxide and creosote are used in the preparation of calcium creosotate one might expect fifty per cent of the drug to be made up of water-soluble phenols. From Table I it is evident that the amounts of water-soluble phenols are considerably below this figure. Determination of the total organic matter in calcium creosotate powder, disclosed the fact that 56 per cent of the powdered drug was made up of organic matter. This coupled with the low phenolic concentrations of the solutions in Table I leads one to suspect that part of the creosote phenols used in the preparation of calcium creosotate have been altered in some manner so that they are no longer water soluble.

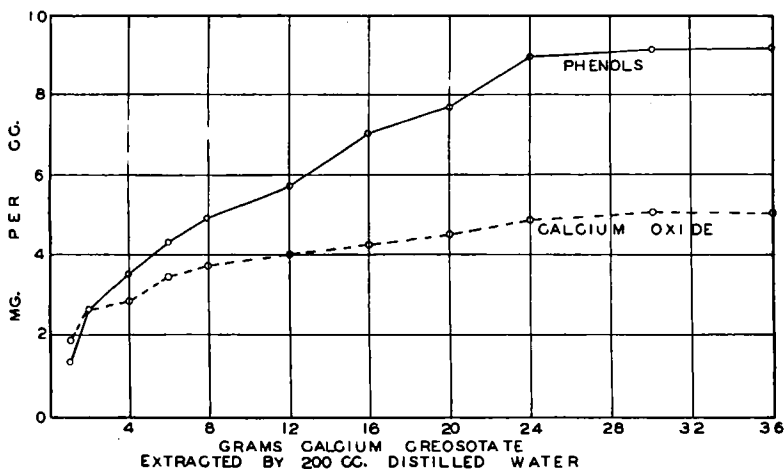


Fig. 1.—Samples of calcium creosotate powder which have been extracted by 200 cc. of distilled water are expressed in grams, and plotted against mg. creosote \circ — \circ and mg. calcium oxide \circ — \circ extracted during a 12-hour shaking period.

In Table II one finds that the creosote used in the preparation of the calcium creosotate examined in these experiments meets the U. S. P. X requirements. It is to be noted that the entire sample distils above 200° C. and the specific gravity of 1.085 is above the minimum of 1.075 required by the U. S. P. In addition to this the 12.5 per cent methoxyl is within the range found by Sickman and Fischelis for typical official creosote samples. However, it is to be noted that the phenols obtained from a sample of the same creosote after it had been placed in aqueous solution and acidified with HCl show some variations. The boiling point has been lowered and accordingly the amount which distils above 200° C. has been reduced. In contrast with the original creosote the boiling point range for these bodies is found to be 195 – 215° C. The U. S. P. X states that not less than 90 per cent of the creosote sample should distil above 200° C. With the volumes used, the entire sample of the original creosote distilled above 200° C., whereas only 70 per cent of the mixture obtained from the aqueous solution of creosote distilled above this temperature. On the other hand the specific gravity and the per cent methoxyl remain practically unchanged. The hydrolyzed water-soluble phenols of calcium creosotate powder show still greater variations. In addition to a lowered boiling point range and consequent diminution in the amount of material distilling above

200° C. the specific gravity requirement of not less than 1.075 is not attained by these bodies which have a specific gravity of only 1.060. The methoxyl per cent of 8.5 which is considerably below the value of 12.5 found for the original creosote indicates a lower guaiacol and creosol content. It may be suspected that if calcium salts of the phenols of creosote are formed in the preparation of calcium creosotate the methyl group of the methoxyl of part of the guaiacol and creosol might be replaced by calcium. Hydrolysis, then, would be productive of dihydroxy benzene and dihydroxy toluene compounds. However, if this does take place one would expect the boiling point of the mixture to be raised. Since guaiacol is very unstable in alkaline medium the true explanation of the decreased methoxy compound content probably lies in the alkalinity of the calcium creosotate. In any event, judging from the specific gravity and methoxyl data, the guaiacol or creosol, or guaiacol and creosol content of the hydrolyzed water-soluble phenols of calcium creosotate does not approximate that of the phenols of the original creosote. The hydrolyzed phenols obtained from "calcium creosotate solution" show essentially the same characteristics as those obtained by extraction of the powder with distilled water. The specific gravity and per cent methoxyl are even lower than the values found for the hydrolyzed phenols from the solution prepared from calcium creosotate powder. These lower specific gravity and methoxyl values appear logical if the alkalinity of the solution is a factor involved in the diminution of the methoxy compound content, because the phenolic bodies of "calcium creosotate solution" were exposed to the alkalinity for a period of 6 months as compared with a few days for the phenols obtained from the solution of calcium creosotate powder.

SUMMARY.

(1) The calcium and phenolic content of solutions obtained by water extraction of calcium creosotate powder indicates that the phenolic bodies may be in solution as calcium salts in equilibrium with an inorganic calcium salt.

(2) Evidence is presented to show that portions of the original creosote phenols have been altered in some manner in the preparation of calcium creosotate so that they are no longer water soluble.

(3) The boiling point range of a phenolic mixture obtained by ethyl ether extraction of an aqueous solution of creosote acidified with HCl, was somewhat lower than that of the original creosote.

(4) Data are presented to show that the hydrolyzed water-soluble phenols of calcium creosotate are not entirely representative of the original creosote phenols. This variation is due to a diminution in the methoxy compound content of the water-soluble calcium creosotate phenols as compared with that of the original creosote phenols.

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