Table C.—Values Obtained with Different Types of Experimental Neoarsphenamines.

Class.	p_H in 20% sol.
A	8.01–8.74
B	6.31–6.99
C	7.62–7.87
D	6.62
E	8.04
F	6.74
G	7.01
H	6.99
I	7.97

Table D.—p_H of Market Brands of Neoarsphenamine.

Sample no.	p_H in 20% sol.
A	5.78
B-1	8.30
B-2	8.07
C	8.48
D	8.20

The results show a range of 6.31 to 8.74 for the experimental preparations and 5.80 to 8.48 for the market samples.

SUMMARY.

1. The method of Elvove and Clark for the determination of the p_H of solutions has been successfully applied to neoarsphenamine.

2. The range of p_H for different types of experimental and commercial neoarsphenamine is shown.

3. The effect of dilution on the p_H of neoarsphenamine solutions is indicated and two possible explanations are suggested.

Research Department,
E. R. Squibb & Sons,
Brooklyn, N. Y.

MEDICINAL WOOD TAR CREOSOTE: I. METHOXYL CONTENT AS A CRITERION OF THE COMPOSITION OF CREOSOTE.*

BY DARRELL V. SICKMAN[1] AND ROBERT P. FISCHELIS.

Wood tar has been used for one purpose or another since the dawn of recorded history. The Egyptians used it to preserve their mummies and the preservative action of "wood smoke" has been made use of in various industries, from the earliest times to the present day. Reichenbach (1), in 1832, determined that the antiseptic properties of wood tar resided in the alkali-soluble portion of this crude material and he named this particular fraction "Kreosot."

For a long time creosote was confused with phenol (2) which was discovered as a constituent of coal tar by Runge, in 1834. Early investigators considered creosote to be a chemically homogeneous substance and tried the effect of oxidizing agents, chlorine, metallic potassium, sulphur, etc., upon it. However, these experiments shed very little light upon the constitution of creosote.

That creosote is not identical with phenol was first shown by von Gorup-Besanez (3) in 1841. In 1858, Hlasiwetz (4) established the fact that creosote contains guaiacol and creosol, which was later confirmed by Müller (5). An account of all work done on creosote up to 1867 is given in an interesting article by

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* Scientific Section, A. Ph. A., Rapid City meeting, 1929.

[1] Maltbie Chemical Company Research Fellow, Princeton University, 1928–29.

von Gorup-Besanez (6). In 1869 Max Biechele (7) again analyzed creosote, and in the same year Marasse (8) showed that other phenols besides guaiacol and creosol were present in creosote. The higher boiling phenols were extensively investigated by A. W. Hoffmann (9) and Liebermann (10), who showed that these were derivatives of pyrogallol. Tiemann (11), the discoverer of vanillin and the ionones, with his students carefully examined creosote, and established the structure of creosol.

Pastrovich (12) isolated an interesting phenol from creosote which he called cœrulignol. It is considered exceedingly caustic and toxic, a drop placed on the tongue causing bleeding. A characteristic blue color is produced when cœrulignol is treated with barium hydroxide, and nearly all the pharmacopœias list the application of this test to creosote to insure the absence of cœrulignol. Pastrovich considered cœrulignol to be 4-*n* propyl guaiacol; but pure *n*-propyl guaiacol formed by the reduction of eugenol shows none of these properties, so that the nature of this substance must be regarded as unknown.

Kebler (13) reported on the examination of six commercial samples of creosote in 1889, and describes a method for estimating guaiacol in creosote. A thorough study of creosote was not made until 1894 when Béhal and Choay (14) made a more or less quantitative investigation of official creosotes and isolated a number of new phenols from creosote. Very little chemical work has been done on creosote in the lasty thirty years, with the exception of an examination of the pyrogallol derivatives of maple creosote and the isolation of a new phenol, 4-vinyl guaiacol.

COMPOSITION OF CREOSOTE.

The known constituents of crude wood tar creosote are as follows:

Phenol (3*c*), (6), (8), (11*c*), (14)
Ortho, meta and para cresols (3*c*), (6), (8), (11*c*), (14)
Ortho ethyl phenol (14)
1,3,5-xylenol (14)
1,3,4-xylenol (8), (14), (11*a*, *b*)
Pyracatechol (5)
Guaiacol (3*c*), (6), (13), (14)
Creosol (4), (13), (14)
4-ethyl guaiacol (14)
4-vinyl guaiacol (16)
4-*n*-propyl guaiacol (12)
Pyrogallol dimethyl ether (9), (15)
Methyl pyrogallol dimethyl ether (9), (15)
Propyl pyrogallol dimethyl ether (9), (15)

The derivatives of pyrogallol are highly toxic, and are carefully removed from medicinal creosote.

A detailed analysis of official French beechwood creosote boiling between 200° and 210° is given by Béhal and Choay (14*b*) as follows:

Phenol	5.2
1–2 cresol	10.4
1–3 and 1–4 cresols	11.6
1–2 ethyl phenol	3.6
1–3–4 xylenol	2.0
1–3–5 xylenol	1.0
Phenols, various	6.2
Guaiacol	25.0
Cresol and its homologs	35.0
	100.0

The same authors give the following as the comparative composition of beech and oak creosotes:

	Beech.	Beech.	Oak.
Distillation range, °	200–220	200–210	200–210
Specific gravity	1.085	1.085	1.068
Monophenols	39.0	39.0	55
Guaiacol	19.7	26.5	14
Creosol and its homologs	40.0	32.1	31
Loss	1.3	2.4	....

The most important conclusions which can be drawn from these results are that the proportion of guaiacol in creosote is far smaller than is ordinarily assumed, some authors stating that creosote is 90% guaiacol. It would also seem that all the guaiacol, as well as a considerable proportion of the creosol present, distil below 210°. The oak creosote apparently contains less guaiacol and more monophenols than the beechwood, but this is fortuitous, as the specific gravity of the oak creosote is far below U. S. P. standards, while that of the beechwood creosote is unusually high. As the specific gravity of phenol is 1.065, the cresols about 1.04 and that of guaiacol is 1.14, it may be said in general, that the higher the specific gravity of a sample of creosote the greater is the proportion of guaiacol and creosol it contains.

The desirability of securing accurate information on the actual guaiacol and creosol content of creosote is obvious and becomes of particular importance to manufacturers of medicinal preparations which depend largely upon their creosote content for therapeutic effect. Up to the present time, very little experimental work has been done on the pharmacology of the individual constituents of creosote. It is therefore impossible to ascribe the therapeutic effect of creosote to any single constituent or group of constituents of creosote. It is likewise difficult to accept or reject any sample of creosote meeting U. S. P. requirements, on the ground that it is high or low in content of a single constituent or several constituents. It is generally assumed, however, that an appreciable percentage of guaiacol and creosol is essential to assure medicinal value. Proceeding on that assumption it would appear to be essential to provide a quantitative estimation for guaiacol and creosol in creosote.

EXPERIMENTAL.

Although a few methods have been proposed for determining guaiacol in creosote, it was found impossible to obtain reliable or consistent results with them. As guaiacol and its homologs contain a methoxyl group, which is easy to determine quantitatively, it was thought that the methoxyl content of creosote would give a valuable criterion of the proportion of these substances present in the sample. It should be pointed out that, owing to the difference in the molecular weights of guaiacol and creosol which make up the bulk of the dihydroxy phenols present, and the fact they are present in relatively variable proportions, it is not possible to calculate exactly either the amount of each present or of both taken together.

The method used was that of Hewitt and Jones (17), using pyridine to absorb the methyl iodide. The apparatus used was that of H. Meyer (18) but nitrogen instead of CO_2 was used to carry the methyl iodide over into the pyridine. The absorption apparatus was that of Pieper, Acree and Humphrey (15), and gave com-

plete satisfaction. A less elaborate apparatus would doubtless give just as good results. In this method, the sample is heated with concentrated hydriodic acid in a stream of nitrogen. The hydriodic acid breaks the $\equiv C-O-CH_3$ grouping, forming methyl iodide. The nitrogen is bubbled through pyridine, which absorbs the methyl iodide quantitatively and converts it into an easily ionizable combination. When the reaction is complete, the pyridine is poured into a measured volume of $N/10$ silver nitrate, acidified and the excess silver determined by Volhard's method. A determination may be made in $1^1/_2$ to 2 hours.

The results of work on sixteen samples of creosote are given in the table.

DISTILLATION OF CREOSOTE AT DIFFERENT TEMPERATURES AND PERCENTAGES OF GUAIACOL AND CREOSOL.

		Volume of Distillate from 100-cc. Sample. between Degrees C: Mentioned										
Sample no.	Sp. gr.	Below 200°C.	200° to 205°	205° to 210°	210° to 215°	215° to 220°	200° to 210°	210° to 220°	200° to 220°	W.	X.	Y.	Z.
1	1.0751	0	30	24	14	16	54	30	84	11.22	44.9	49.9	C
2	1.0790	0	16	39	21	15	55	36	91	12.22	48.9	54.4	C
3	1.0772	0	20	37	21	13	57	34	91	11.98	47.9	53.3	C
4	1.0771	0	15	40	23	13	55	36	91	11.94	47.8	53.1	C
5	1.0746	0	10	43	24	15	53	39	92	10.98	43.9	48.9	C
6	1.0804	0	0	23	43	21	23	64	87	13.07	52.3	58.2	N
7	1.0780	0	0	36	35	20	36	55	91	12.60	50.4	56.1	N
8	1.0830	0	10	47	24	13	57	37	94	13.20	52.8	58.2	N
9	1.0834	0	3	43	28	16	46	44	90	13.24	53.0	58.92	N
10	1.0781	0	20	36	23	14	56	37	93	12.37	49.5	55.2	N
11	1.0816	0	0	10	51	23	10	74	84	16.30	65.2	72.6	N
12	1.0800	0	5	45	28	14	50	42	92	13.96	55.8	62.8	N
13	1.0802	0	9	41	27	15	50	42	92	14.50	58.0	64.5	N
14	1.0827	0	3	29	31	18	32	49	81	14.20	56.8	63.2	N
15	1.0782	0	5	41	27	14	46	41	87	12.70	50.8	56.5	N
16	1.0731	0	3	34	26	19	37	45	82	12.25	49.0	55.6	N
U. S. P. X Standard	1.076								90				
B. P. Standard	1.080								75				

Explanation of abbreviations: W—Methoxyl per cent; X—Methoxyl calculated as guaiacol; Y—Methoxyl calculated as creosol; Z—U. S. P. Glycerol test; C—Clear solution; N—Normal.

All samples of creosote were obtained on the open market, and all samples except 14, which was a semi-refined creosote, and 16, which was marked B. P. 1882, were offered as U. S. P. Only 15 and 16 are beechwood, the others apparently coming from a mixture of hardwoods. The specific gravity, distillation data, and glycerol tests were made according to the U. S. P. X. All the samples behaved normally in the other U. S. P. tests. The U. S. P. X requires a specific gravity of not less than 1.076 and that not less than 90% by volume shall distil between 200° and 220°.

Most of the samples examined were of good quality as judged by the U. S. P. standards. Sample 11 is apparently the residue left after the guaiacol had been removed, and is mostly creosol. The methoxyl content is roughly in the same order as the specific gravity. Apparently the U. S. P. requirements of specific gravity and distillation range are sufficient to insure a methoxyl content of 11% or more, corresponding to a guaiacol and creosol content of 44–49 per cent.

It is quite apparent from these results that creosote is only about one-half

guaiacol and creosol, and as there is at least twice as much creosol as guaiacol present, according to Béhal and Choay's work quoted above, guaiacol can scarcely be the principal ingredient of medicinal creosote.

As the table shows, creosote varies widely in composition, and unfortunately most of the tests devised for ascertaining its quality are valueless. If the dihydroxy phenols are assumed to be the medicinally active ingredients, a methoxyl determination will indicate the proportion of them present far more accurately than any method of which the writers have knowledge. The methoxyl determination is rapid and inexpensive, and if used in conjunction with the distillation test of the U. S. P. and the specific gravity, leaves no doubt of the composition of the creosote. Creosote is an extremely complicated mixture and this simple method of evaluating it should not be ignored.

We desire to express our thanks to Professor Gregg Dougherty of Princeton University for his kindly interest and very helpful suggestions with regard to the general problem of creosote chemistry, and particularly the experimental phases reported in this paper. The experimental work has been done under the 1928-29 Maltbie Chemical Company Fellowship for Creosote Research at Princeton.

SUMMARY.

1. A brief history of the chemical examination of creosote is given.

2. The composition of medicinal creosote is discussed, and its difference from guaiacol is pointed out.

3. A simple method (not new) of determining the methoxyl content of creosote is given and its importance in evaluating creosote is discussed.

4. A number of creosote samples from the open market have been examined in the light of the U. S. P. tests and methoxyl content.

5. It is shown that approximately 50% of medicinal creosote consists of derivatives of pyrocatechol, and that there is no distinction between beechwood and other hardwood creosotes.

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