Louisville	15	19	17	12	12	12	14	15
New Orleans	21	20	19	23	20	29	32	56
Chicago	119	117	119	119	130	174	176	272
St. Louis	74	92	82	69	69	63	88	95
Kansas City	11	13	11	10	9	10	11	12
Baltimore	53	56	56	60	58	52	53	57
Boston	39	45	45	42	40	37	34	31
Detroit	35	87	77	79	72	72	74	78
Minneapolis	20	19	20	20	20	29	31	39
St. Paul	13	15	15	16	15	16	17	24
Omaha	12	11	15	14	13	11	12	12
Newark	13	14	15	19	15	17	22	21
Buffalo	15	16	16	15	19	17	15	14
Brooklyn	41	43	46	48	51	61	70	65
New York	106	130	153	205	220	221	249	244
Cincinnati	38	36	38	43	42	37	43	41
Cleveland	23	31	35	37	36	34	50	60
Columbus	22	32	29	21	20	17	17	15
Portland (Ore.)	11	9	8	8	7	9	8	8
Philadelphia	112	120	121	129	128	141	159	171
Pittsburgh	34	30	30	30	32	31	34	32
Wilkes-Barre	....	....	....	....	....	33	35	18
Manila	32	15	3	3	3	2	3	3
Providence	14	14	12	11	11	9	10	9
Nashville	38	28	22	14	13	11	15	10
Dallas	10	11	6	12	15	18	15	8
Richmond	9	10	9	11	11	15	28	42
Seattle	16	17	18	17	14	11	24	23
Milwaukee	14	16	14	16	20	16	13	15
Havana	....	....	21	27	24	20	25	24
35 Cities	1105	1204	1214	1302	1313	1379	1528	1660

PHYTOCHEMICAL NOTES.*

No. 87. Methoxyl Determinations of Monarda Oils.

BY D. C. L. SHERK.‡

The investigation of the methoxyl constituents of Monarda oils was undertaken in the hope that this additional constant for the oil would be useful and characteristic, and that, moreover, it might prove an aid in the identification and isolation of new constituents.

Ethers of the hydroxy derivatives of cymene are known to exist in a few oils. The dimethyl ether of hydrothymoquinone constitutes the bulk of arnica root oil,[1,2] and ayapana oil[3] and the oil of *Eupatorium capillifolium*.[4] The methyl ether of thymol occurs in "Samphire oil"[5] and Pickles[6] claims to have isolated a monomethyl ether of hydrothymoquinone from *Cyprus origanum* oil which consists principally of carvacrol.

Accordingly Zeisel's method for the determination of the methoxyl value was applied to the oils. The apparatus was essentially that designed by Zeisel[7] and the procedure was practically the same; except that the gas carrying the vapors of alkyl halide was washed by passing through an alkaline solution of

* From the laboratory of Edward Kremers.

‡ Fritzsche Brothers Fellow, 1919–1920.

arsenous oxide, as recommended by Gregor,[8] and the halide was absorbed in an absolute alcoholic solution of silver nitrate slightly acidified with nitric acid, also suggested by Gregor. For each run a quantity of silver nitrate was weighed out and for standardizing the apparatus similar quantities were weighed out and factors determined. At the end of each run the alcoholic silver nitrate solution was diluted with about four volumes of water and the silver remaining in solution titrated by Volhard's method. Determinations were run uniformly for three to four hours and in certain cases where tars were analyzed the procedure was modified to the extent that acetic anhydride was added to keep the tar in solution and prevent the formation of an impenetrable resin.

The samples of oils that were tested represent the accumulation of several years in the laboratory and are presented in the order of the most recent ones first, beginning with the 1919 crop. Of *Monarda punctata* there are three samples along with their cohobated portions. Of earlier oils mostly the non-phenol residue was available. Of *Monarda fistulosa* besides the crop of 1919 with the cohobated oils there were also some other original oils and fractions available for a number of years back.

Monarda Punctata.

	Description of oil	$-OCH_3$ p. c.
1919	Florida variety. Original oil	0.36
	2nd and 3rd cohobation	0.32
	Highlands sample. Original oil	0.05
	1st cohobation	0.12
1919	Lone Rock. Original oil	0.17
		0.16
	2nd and 3rd cohobation	0.26
1918	8-25—Chiefly leaves and stems	0.11
		0.18
	From ripe and long dried flower heads	0.23
		0.21
1917	Mature flower heads, non-phenol	0.42
		0.47
	Princeton, non-phenol	0.12
	Non-phenol	0.40
1916	8-2—Randall	0.08
	E. R. M. cohobation	0.11
1913	Alabama E. R. M.	0.33

By way of check, methoxy determinations were made on vanillin, yielding 20.17 p. c., 20.70 p. c. and 20.46 p. c., respectively. Hence the average is 20.44 p. c., whereas the theory calls for 20.4 p. c.

Monarda Fistulosa.

	Description of oil.	$-OCH_3$ p. c.
1919	Cleaned material. Original oil	0.26
		0.28
	Non-phenol	0.29
	2nd cohobation	0.11
	3rd and 4th cohobation	0.60
		0.70
	Loose material. 2nd cohobation	0.10
	3rd and 4th cohobation	0.58
1918	8-18—Plants mature	0.30
		0.29
	Long dried and ripe flower heads	0.44
		0.40
1918	8-23 and 24—Plants over-mature	0.43
1915-1916	By cohobation, E. R. M. "non-phenol"	0.45
	Same truly non-phenol	0.54
1916	Sample of 1915 oil	0.08
1913	8- 7—Original oil	0.15
	8- 7—Non-phenol	0.14
	8- 7—Cohobated oil F. and T.	0.12
	7-25—Crop 1913	0.26
	7-30—N. W. (1)	0.14
	8- 7—N. W. (2)	0.16
	7-30—Camp Randall, F.	0.13
1912	.....	0.32
		0.37
	"Mo."	0.39
		0.47
1911	7-6—Madison (Light stems)	0.28
1910	Variety b Light stems	0.38
	Variety b Purple stems	0.18
		0.16
	Variety b "Mo."	0.60
		0.51

These results indicate that substances containing methoxyl groups are regular constituents of Monarda oils. The examination of *M. fistulosa* oils shows a uniformity of distribution of these constituents between the original and non-phenol portions of the oil. The 1919 sample and the 1915–16 sample seem to point to the fact that a close parallel exists because both of these oils contained about 62 percent phenols and had been treated in the same manner.

The methoxyl derivatives of cymene known to be constituents of volatile oils are thymol methyl ether and hydrothymoquinone dimethyl ether. Both of these have no phenolic properties and would, according to theoretical behavior, not be separated in the process of extraction but would be concentrated. Hence the removal of 60 percent of the oil as phenols should result in an increase of the methoxyl value in the first case of from 0.27 to about 0.68 and in the second case from 0.45 to 1.13 in the non-phenol residual portion; whereas in the first case the increase was within the error of experiment and in the second to only 0.54. Such a concentration of methoxyl represents the following concentration of original constituent calculated on the basis of the monophenolic and diphenolic ethers:

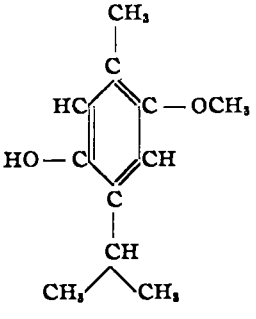
0.27 p. c. OCH_3 = 1.43 p. c. thymol methyl ether
0.45 p. c. OCH_3 = 2.38 p. c. thymol methyl ether
0.27 p. c. OCH_3 = 0.84 p. c. hydrothymoquinone dimethyl ether
0.45 p. c. OCH_3 = 1.41 p. c. hydrothymoquinone dimethyl ether

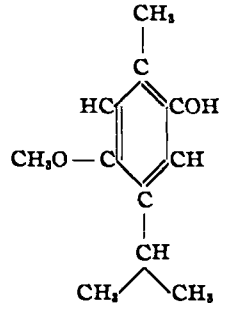
The presence of a methoxyl constituent which separates with the phenol and has phenolic properties has been suggested by Pickles as a monomethyl ether of hydrothymoquinone and the behavior of these fractions also indicates the presence of such a constituent. On the basis of this compound these results are obtained:

0.27 p. c. OCH_3 = 1.58 p. c. hydrothymoquinone monomethyl ether
0.45 p. c. OCH_3 = 2.61 p. c. hydrothymoquinone monomethyl ether

Having thus indicated the presence of such a substance an attempt was made to isolate it by following the scheme outlined by Pickles, and also by working up some phenol residues of *M. punctata* oil from which as much crystalline thymol as possible had been removed.

Pickles[6] obtained two phenols from Cyprus Origanum oil, the chief of which is carvacrol. This was extracted completely from aqueous alkaline solution by shaking with ether. Acidification then yielded a small quantity of another phenol of which only 0.4 Gm. was obtained. Analysis corresponded to the formula $C_{11}H_{16}O_2$ and he thought it to be a hydroxymethoxy cymene. This would probably identify it with one of the two isomeric monomethyl ethers of hydrothymoquinone:





Semmler[8] obtained what was probably a mixture of these two isomers by heating the dimethyl ether with hydriodic acid and red phosphorus in a closed tube to 90°. Its composition corresponded to that formula.

Two kilos of oil of *Monarda fistulosa* were extracted in portions with five percent sodium hydroxide. After separation of the alkali solution it was shaken with about an equal volume of ether three times and the extraction of the oil was repeated, using this same alkali solution. In this manner a minimum of alkali was required and it was hoped that a separation and concentration of the phenol constituents of the oil might be effected. The carvacrol, recovered from the extract by distilling off the ether, was distilled in a current of superheated steam at 180° and the distillate was found at the last to yield crystals of hydrothymoquinone, indicating that the dihydroxy phenols may be extracted by ether from their solution in sodium hydroxide of this concentration.

Acidification of the alkaline liquors gave an oil which was recovered by extracting the solution with ether and the ether recovered on the water-bath. The recovered oil was treated with excess of barium carbonate and water and boiled under a reflux to remove acid. The tar separated with the salt. The aqueous solution was drawn off and the tarry residue extracted with alcohol, the alcoholic solution filtered, the alcohol evaporated, and the residue fractionated at 3 mm. This yielded a pale reddish oil which deposited red and yellowish crystals. The amount was slight. The distillate was analyzed as follows:

	Methoxy (OCH_3).
I	1.09 p. c.
II	1.21 p. c.
III	1.12 p. c.
Average,	1.14 p. c.

The tar remaining was analyzed also:

	Methoxy.
I	1.17 p. c. (in acetic anhydride)
II	0.95 p. c. (in acetic anhydride)

The oil itself gave a methoxyl value of 0.27 for the original and 0.29 for the non-phenol portion.

This proves first that the other phenolic constituents of the oil divide themselves in this extract in much the same manner as in the original, and that the dihydroxy phenol is removed by ether along with carvacrol. A different concentration of alkali might yield a product in which a better separation has been effected. Also, there is only a very slight concentration of the methoxyl constituents by this process. However, this separation should be undertaken on other samples of oils to ascertain the conditions under which a better concentration and separation may be obtained.

The Residual Phenol Oil of M. Punctata.—Another method of concentration of the methoxyl constituents of Monarda oils was available. From previous lots of oil from *M. punctata* which had been used for large scale production of thymol, a quantity of phenol oil remained which no longer yielded thymol by freezing. This non-crystalline portion was of a dark brown or nearly black color and rather viscous. The total quantity represented a small percentage of the

original phenols and it was analyzed for methoxyl value, yielding 1.06 p. c. and 1.02 p. c., respectively, in two determinations.

This oil was then subjected to further treatment in which it was first fractionated at reduced pressure, whereupon a mobile distillate and a black, brittle tar remained. The first fractionation was made at 36 mm. up to 180° and was divided as follows:

Temperature.	Yield.
Up to 135°	...
135–140°	140 Gm.
140–145°	206 Gm.
145–160°	222 Gm.
160–180°	134 Gm.
Total,	702 Gm.

The second fractionation was made at 18 mm. and of the above oil 636 Gm. were recovered. Other similar fractions were added and there were obtained about 1.5 kg. all of which was fractionated at 19 mm. and resolved for the largest part into a single fraction with a slight "Vorlauf" and a very high boiling residue distilling off at 2 to 3 mm.

Fraction.	Pressure.	Quantity.	Methoxy.
Up to 120°	19 mm.	....	....
120 to 125°	19 mm.	1062 Gm.	0.21 p. c.
125 to 135°	19 mm.	110 Gm.	0.38 p. c.
135° and up	19 mm.	140 Gm.	0.55 p. c.

The distillate obtained by fractionation at 2.5 to 3.5 mm. was very viscous and of a brownish color with a slight fluorescence. As the thymol obtained originally from the oil was purified from petroleum ether, the residual petroleum hydrocarbons may be responsible for this fluorescence. The viscous distillate gradually solidified and dilution with heptane up to three volumes resulted in the deposition of crystals in large quantity easily proven to be hydrothymoquinone. These fractions have the smoky odor characteristic of the higher polyhydroxy phenols.

These results seem to indicate that here, too, there is only a very slight difference in concentration of methoxyl constituents by this process. In fact, all of the fractions contained less than the original oil and there appears to be an actual loss. Examination of the tar remaining did not account for this loss.

Monarda Tar.—In practically every operation upon Monarda oils a black, brittle tar is obtained which resists almost all attempts to resolve it into its constituents or to obtain crystalline derivatives. This may represent the quinhydrones which are capable of forming in the oil and to which the red color of the oil is attributed, and also the black color of the tar.

Nitric acid of specific gravity 1.2 reacts vigorously with the tar and on long-continued boiling oxidizes it almost completely. Chromic acid mixture also reacts vigorously on warming to the boiling point. Neither yielded anything that looked hopeful as a means of identifying constituents of the original tar.

Along with other portions of Monarda oils the methoxyl value was determined on this tar also. A brittle tar, representing the residue of an oil after fractionation of the non-crystalline phenols at 36 mm. up to 180°, gave the follow-

ing methoxyl values, using also a modified method with acetic anhydride as a solvent for comparison.

Tar.	Methoxy.
I	1.48 p. c. direct
II	0.62 p. c. direct
III	0.61 p. c. direct
IV	0.68 p. c. acetic anhydride

A fraction of oil distilled from these residues which deposited crystals of hydrothymoquinone was analyzed, giving 0.82 p. c. methoxyl.

When carvacrol from Monarda oil was extracted from alkaline solution by means of ether, the alkaline solution on acidification gave a phenol mixture which was distilled at 2 to 3 mm. and in this case also a tar resulted which was hard and friable. This was analyzed, using acetic anhydride as a solvent, giving 1.17 p. c. and 0.95 p. c., respectively, as the results of two determinations.

The most promising method of investigation seemed to be by fractionation of the tar at as low temperatures as possible. The tar itself had previously been fractionated at 35 mm. up to a temperature of 180° when decomposition had begun to take place. These residues were accordingly fractionated at as low a pressure as possible.

The following data were obtained on two runs:

I. 279 grammes of tar were taken.

Time.	Temperature.	Pressure.	Wt. of distillate.
3:45	118°	15 mm.	...
4:12	124°	15 mm.	...
4:16	124°	14 mm.	115 Gm.
4:30	134°	16 mm.	31 Gm.
4:37	144°	16 mm.	12 Gm.
		Total,	158 Gm.

II. 160 grammes tar were added and again fractionated.

3:13	120°	17 mm.	11 Gm.
3:20	124°	18 mm.	..
3:28	126°	18 mm.	..
3:34	133°	18 mm.	50 Gm.
3:40	144°	18 mm.	29 Gm.
		Total,	90 Gm.

Of 440 Gm., 250 Gm. were recovered at 18 mm. Distillation was continued at 3 mm. with the aid of a mechanical pump.

Temperature.	Pressure.	Wt. of distillate.	Temperature.	Pressure.	Wt. of distillate.
101°	3.0 mm.	..	144°	3 mm.	34 Gm.
102°	3.5 mm.	..	158°	3 mm.	..
113°	3.5 mm.	..	168°	3 mm.	..
116°	3.5 mm.	84 Gm.	184°	3 mm.	25 Gm.
131°	2.5 mm.	..			

The portion (34 Gm.) gradually solidified spontaneously and was easily proved to consist principally of hydrothymoquinone, melting at 141° after crystallization from hot water. The last fraction was exceedingly viscous. All three deposited crystals when diluted with heptane up to three volumes. Beyond

that a tarry layer began to separate. Thus about one-third of the tar consists of hydrothymoquinone which can be separated by fractionation and, if necessary, by precipitation with heptane.

This result suggested the possibility of obtaining derivatives of hydrothymoquinone directly from the tar, a thing that had not been previously accomplished.

2.5 Gm. tar were treated with 4.0 Gm. phenyl isocyanate in 20 Cc. solvent* and boiled for 35 minutes at this time. The contents became granular and apparently crystalline after standing for ten days. The flask was reheated. This product was taken up in alcohol, after separation from petroleum, and an oil obtained which deposited some crystals on standing. The alcoholic solution was evaporated and dirt removed as well as possible. The product melted at 237 to 238° and gave the same result after an attempted recrystallization from alcohol. It was by no means colorless yet. An analysis by Dumas' method gave this result:

0.1313 Gm. gave 15.2 Cc. N_2 at 23° and 709 mm., or 12.55 p. c., whereas hydrothymoquinone diphenylurethane contains but 6.93 p. c. The amount of material was too small for further study.

The separation of hydrothymoquinone in quantity from the mother liquid of thymol obtained from *Monarda punctata* on a large scale supports the view that the tar consists in no small part of phenoquinones or quinhydrones, or both. Its isolation in the manner described above suggests the further study of these tar residues for the ketones with which the phenols from the quinhydrones or phenoquinones are assumed to be combined.

BIBLIOGRAPHY.

1. Erlenmeyer, Buchners, *Neues Repert. d. Pharm.*, 23, 1, 1873.
2. Sigel, *Ann.*, 170, 345, 1873.
3. Semmler, *Ber.*, 41, 509, 1908.
4. Miller, *Bull. Univ. Wis.*, No. 693, 49, 1914.
5. Dilipine, *C. R.*, 150, 106, 1910.
6. Pickles, *J. C. S.*, 93, 867, 1908.
7. Zeisel, *Monatsh.*, 6, 989, 1885.
8. Gregor, *Ibid.*, 19, 116, 1892.

THE CAPSICUM MONOGRAPH IN U. S. P. X.

BY E. N. GATHERCOAL AND R. E. TERRY.

The revision of the monograph of Capsicum hinges largely on the desirability of excluding all commercial forms of Cayenne pepper except true African chillies.

That African chillies are the most pungent is generally conceded. J. M. Francis states that the degree of pungency is approximately as follows: Mombassa chillies 50,000 to 100,000, Zanzibar chillies 40,000 to 50,000, Japanese chillies 20,000 to 30,000. Pungency is apparently the only pharmacologic property desired of capsicum as a medicine, hence it is desirable that medicinal capsicum be of the highest pungency and fairly uniform in this property.

* Petroleum boiling at 180–200°.