Physical Evidence of Association of Camphor with Phenol and the Cresols

*By Alfred W. Francis**

The loss of the corrosive action of phenol when mixed with camphor has been known and employed in treating local surgical infections for more then forty years. Phenol-camphor mixtures produce no irritation on sound tissues and may even be used in open wounds. It is difficult to explain this observation except by assuming some combination between phenol and camphor. Yet any method of chemical analysis for phenol reveals the total percentage in the mixture. Even water in sufficient amount, decomposes the compound, if any, dissolving the phenol and causing separation of solid camphor.

The present investigation was undertaken to show physical evidence for the probable presence or absence of compound formation in mixtures of camphor with phenol and the three cresols, respectively. The latter were of particular interest because they possess some advantages in bactericidal properties over the phenol-camphor mix-

tures, and because no investigation of those systems has been published.[1]

Günther and Peiser (1) made a somewhat similar study of the phenol–camphor system. They determined the freezing curve of the system, and also the indices of refraction, densities and solubilities in water of several mixtures of phenol and camphor. Although the freezing curve revealed a complex melting at $-13.7°$ C., the flatness of its curve indicated substantial decomposition on melting; and the curve for density indicated no contraction on mixing. They concluded that no complex existed in the mixture at room temperature, but that the non-corrosive property of the phenol was due to the solvent action of the camphor phase, which permitted only a low concentration of phenol in body fluids.

The distribution of phenol between the camphor phase and water which they studied, is the most direct method of attack; and their conclusion based upon their data alone is logical. But in connection with additional data presented here, a different interpretation is probable. This is suggested by the fact that phenol has nearly the normal distribution between water and benzene,

* Arthur D. Little, Inc., Cambridge. Present address, Socony-Vacuum Oil Co., Inc., Paulsboro, N. J.
    [1] This use of cresols and camphor has been covered by U. S. Pat. 1,924,169 of J. E. Stacey and assigned to Otis Clapp and Son, Inc.

although the latter is an excellent solvent for it and is related to it in structure more closely than is camphor, which shows an abnormal affinity for phenol in equilibrium with water.

The liquefaction of camphor and phenol on mixing was observed by Buffalini (2) in 1873. The freezing curve has been studied by Wood and Scott (3) and by Kremann, Wischo and Paul (4) and partly by Leger (5) as well as by Günther and Peiser (1). Kremann, Wischo and Paul failed to find a complex crystallizing out because of the jelly-like consistency of the liquid mixtures at low temperatures. Wood and Scott found a melting temperature for the complex of $-18.6°$ C., but their curve was otherwise in fair agreement with that of Günther and Peiser.

EXPERIMENTAL

Preparation of Material.—About 500 Gm. each of phenol (Recryst.) and three cresols (Pract.) were obtained from the Eastman Kodak Company and distilled with an ordinary flask and air condenser, rejecting the first and last 50 cc. The main portion was collected over a 1.5° C. range, and this range always included the boiling point given in the International Critical Tables for the desired product, namely, 180° C. for phenol, 190.8° C. for *o*-cresol, 202.8° C. for *m*-cresol and 201.8° C. for *p*-cresol. The *m*-cresol froze completely at 11.0° to 10.8° C.,

somewhat higher than the 10° C. given in the tables The other compounds were allowed to freeze about half and were then decanted. The residual crystals showed freezing temperatures of 40.8°, 30.2° and 34.8° as compared with those in the tables—41°, 30.1° and 34.8°, respectively. Since the only probable impurities, water and the other cresols, would lower the freezing points (6) (except for *p*-cresol in *m*-cresol) the materials were considered sufficiently pure. Additional proof was shown by the bromine titrations (7) which showed the following number of moles of bromine per molecular weight:

	Calcd.	Found
Phenol	3.0	2.993
m-Cresol	3.0	3.007
o-Cresol	2.0	1.998
p-Cresol	2.0	2.006

A good grade of gum camphor was distilled rapidly without a thermometer through a short air condenser into a large evaporating dish covered by a towel to prevent excessive loss by sublimation. This crude technique was necessitated by the high melting point and hard gummy nature of the solidified liquid. The product was ground and sifted through a 20-mesh screen for convenience in making mixtures. It melted at 178.6°, which is near the figure given in International Critical Tables, 179°.

Freezing Curves.—The initial freezing temperatures of various mixtures of camphor with phenol and the cresols were determined by the visual method, using about 10 Gm. of material in test-tubes. The temperatures above $-5°$ C. were read by means of a set of short stem 50° range Anschutz thermometers graduated in fifths of degrees. The

Table I.—Initial Freezing Temperatures of Mixtures of Camphor with Phenol and the Cresols
(Percentages in Mole Per Cent of Camphor, Temperature in Degrees Centigrade)

Phenol		o-Cresol		m Cresol		p Cresol	
Per Cent	Temp.	Per Cent	Temp.	Per Cent	Temp.	Per Cent	Temp.
0	40.8	0	30.2	0	11.0	0	34.8
8.25	33.2	4.82	27.9	5.95	6	10.07	28.7
14.02	25.3	8.89	24.7	10.7	1	16.75	19.4
18.27	18.1	11.3	22.8	14.84	-4	21.45	13.3
21.39	11.3	12.27	22	17.96	-7	25.00	4.5
24.0	6.5	17.53	16	22.6	-12	27.80	-3
25.0	4	18.06	16	25	-19	28.7	-3
27.5	-4	21.7	11			30	-7
30	-10	23.1	11				
32.5	-24	25.0	7	67.7	$+35$	61.65	-4
35	-22	26.05	6	71.65	65	64.75	$+19$
42	-16	29.3	0	76.0	89	71.5	60
50	-12	30	-3	80.9	116	74.2	80
56	-12	32.95	-9	86.7	140	79.25	106
59	-14	33.3	-22^a	93.45	162	85.85	136
60.75	-17.5			100	178.6	92.1	158
62.1	-11	43.5	-19				
63.58	-1	50	-18				
65.4	$+17$	60	-19				
67.8	38	63.65	$+12$				
71.35	64	67.7	36				
75.4	86	71.6	64				
81.25	118	79.4	107				
88.81	145	85.55	138				
		92.1	159				

a Metastable.

lower range was observed with a toluene thermometer with a range from −50° to +55° C. It read 0.0° in an ice and water bath, as did the lowest Anschutz thermometer. The observations are recorded in Table I.

Figure 1 shows the phenol-camphor curve in comparison with those of Wood and Scott and of Günther and Peiser. It is slightly higher than either in most places, probably because of purer material. Günther and Peiser admitted the presence of 0.23% water in their phenol. The equimolecular complex melts at −12° C.

Figure 2 shows the curves for camphor with the three cresols. The o-cresol curve shows the existence of an equimolecular complex melting at −18°, quite analogous to that of phenol and camphor. The metastable point was found by seeding the

is nearly the same for phenol mixtures. Compare also salicylic acid-camphor complexes (8).

Densities.—Günther and Peiser (1) determined the densities of certain liquid mixtures of phenol and camphor, presumably with the idea of detecting contractions on mixing, which would be evidence of combination. If this was their object, their plot of density against *mole per cent*, which gave them a concave curve, is without significance. The plot of density should have been against per cent by *volume* in order to detect contraction by deviation from a straight line; but since the precise density for liquid camphor at room temperature (hypothetical substance) is unknown, this cannot be done. The alternative of plotting specific volume against per cent by weight is just as satisfactory for the purpose. To detect small contractions the plot should ex-
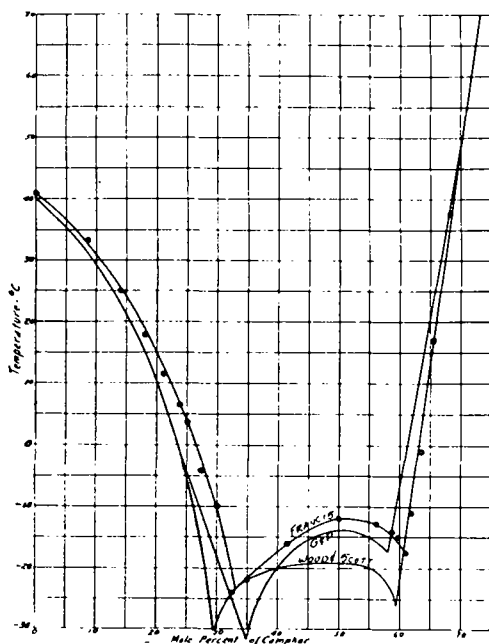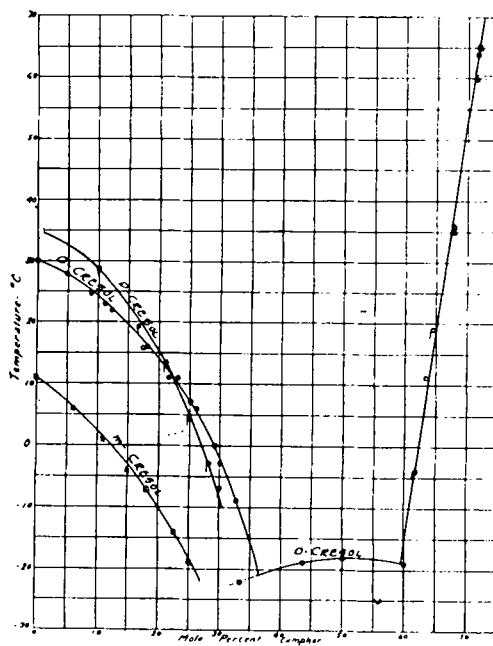

Fig. 1.— Freezing Curves Camphor-Phenol.

Fig. 2. Freezing Curves Camphor Cresols.

supercooled 33.3 mole per cent mixture with the equimolecular complex. It was not found possible to crystallize out the corresponding complexes of camphor with *m*- and *p*-cresols because of the extreme viscosity of the mixtures at temperatures below −20°. Samples of 33.3 mole per cent and of 50 mole per cent camphor with each were maintained at −30° to −40° C. for several hours with occasional scratching with a broken glass rod. They were also seeded with crystals of the o-cresol and the phenol complexes, suspecting them to be isomorphous, but the mixtures remained thick transparent jellies. Nevertheless, other evidence presented later makes the existence of these complexes in solution probable, even though they could not be crystallized. In equilibrium with solid camphor, mixtures with the three cresols give an identical freezing curve, which

tend over the maximum range of liquid mixtures available (they covered little more than half the range), and to make the range wider a higher temperature, 25° C., is preferable to their 15.8° C.

Densities of mixtures of camphor with phenol and with all three cresols are recorded in Table II. They were determined in a 2-ml. pycnometer at room temperature, 24 27° C., and corrected to 25° C. by means of the temperature coefficients (about 0.08% per degree (9)). The pycnometer was calibrated with water giving 2.0106 and 2.0127 ml. and with mercury giving 2.0099 and 2.0137 ml., mean 2.0117 ml.

The values for phenol and *p*-cresol are extrapolated. Those for all four phenols agree fairly well with those determined or estimated in the literature (9), 1.0713, 1.0440, 1.0302 and 1.0307, respectively.

Table II.—Densities of Mixtures of Camphor with Phenol and the Cresols

(Percentages in Wt. Per Cent of Camphor, Densities at 25° C. in Gm. per Ml.)

Phenol		o-Cresol		m-Cresol		p-Cresol	
(0	1.0724)	0	1.0423	0	1.0270	(0	1.0299)
22.4	1.0465	10.3	1.0311	10.2	1.0200	10.1	1.0225
22.8	1.0459	23.25	1.0213	19.6	1.0131	23.5	1.0123
32.7	1.0350	32.6	1.0130	29.2	1.0065	33.2	1.0056
40.2	1.0258	43.1	1.0047	38.45	0.9995	43.9	0.9982
41.0	1.0235	53.0	0.9952	48.4	0.9930	54.55	0.9905
44.7	1.0193	58.5	0.9902	58.4	0.9860	63.8	0.9838
56.5	1.0075	64.0	0.9855	66.4	0.9800	72.0	0.9768
61.8	1.0005	74.8	0.9766	74.6	0.9745		
70.25	0.9922						
75.4	0.9860						
76.5	0.9840						

But the densities observed by Günther and Peiser (1) are entirely inconsistent with Table II and with the value for phenol in International Critical Tables (9), being lower at 15.8° C. than those observed at 25° C.

Plots of the reciprocals or specific volumes against weight per cent were almost straight. In order to make the curvature more apparent, a derived function, $1000/d.\frac{25}{4}$—wt. per cent, is plotted against
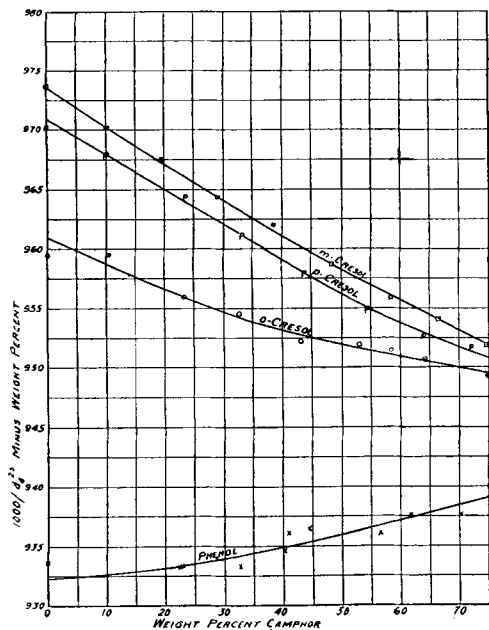

Fig. 3.—Contractions of Liquid Mixtures of Camphor with Phenol and the Cresols.

weight per cent in Fig. 3. The contraction indicated by the concavity of the curves is about 0.25% for the range covered. It would be about 0.5% for the full range, 0-100%, if available.

In view of the equivocal results of Günther and Peiser (1) on indices of refraction, this property did not seem to promise much information, and so was not used in the present investigation.

Partial Solubility in Water.—Pure phenol has a solubility in water of 8.45% at 25° C. In contact with 50 mole per cent solutions of phenol in various

solvents water contains the following percentages of phenol (10):

Solvent	Wt. Per Cent in Water
Benzene	4.53
Carbon tetrachloride	4.1
Carbon disulfide	5.2
Chloroform	4.25
Bromoform	4.84

These figures all show about half the solubility of pure phenol, indicating that the solubility is probably roughly proportional to the mole fraction unless there is some chemical combination with the solvent. In the case of camphor the partial solubilities are shown in the following table.

Table III.—Distribution of Phenol between the Camphor Phase and Water

Mole Fraction of Phenol in Camphor Phase	Wt. Per Cent of Phenol in Water Phase	
	Günther and Peiser (1)	Francis
0.35	..	0.65
0.373	0.61	..
0.421	0.79	..
0.500	1.30	1.40
0.616	2.25	..
0.649	2.82	..
0.699	3.45	..

The equimolecular mixture (38.2% by weight) shows a solubility of only 1.3% or 1.4%, less than one-third as much as would be expected from the values for other solvents. This seems to indicate that at least two-thirds of the phenol is combined
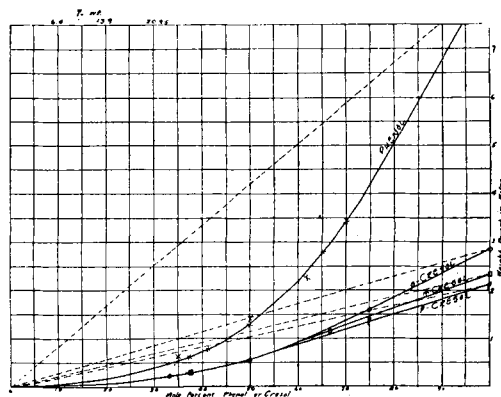

Fig. 4.—Distribution of Phenol or Cresol between Camphor Phase and Water.

in some way with the camphor. Similar tests were made with mixtures of camphor with the cresols. In each case 10 cc. of the mixture and 10 cc. of water were shaken thoroughly in a thick-walled text-tube and then centrifuged. A sample of the clear aqueous layer (in some cases the upper and in some cases the lower) was withdrawn with a pipette, weighed and titrated with bromide-bromate solution (7). Phenol and m-cresol consume three moles of bromine per mole and o- and p-cresols two each. Under the conditions of titration camphor consumes no bromine. The results are given in Table IV and Fig. 4.

Table IV.—Distribution of Cresols between the Camphor Phase and Water

Mole Fraction Cresol	Wt. Per Cent in Water		
	Ortho	Meta	Para
1.00	2.88	2.36	2.14
0.75	1.59	..	1.42
0.667	..	1.18	..
0.50	0.59	0.54	0.57
0.375	0.29	..	0.34
0.333	..	0.24	..
0.50 in benzene	1.69	1.32	1.20

As in the case of phenol, the equimolecular mixture in benzene showed in each case a solubility a little more than half that for the pure cresol; but the equimolecular mixture in camphor shows only about one-quarter as much. Apparently more than half the cresol is combined with camphor in each case.

Partial Vapor Pressures.—Another method of measuring the thermodynamic activity of one component in a mixture is by means of partial vapor pressures. This would be more nearly rigorous than that of solubility, studied in the last section; but it is usually more difficult to measure accurately. In the systems under investigation the vapor pressures of all the components at room temperature are so low that an accurate measurement of partial pressures at low temperatures is practically impossible. On the other hand, the fact that the vapor pressures of all the components are comparable and the fact that we have a simple and accurate method of analysis of mixtures (that of bromination) make such a study promising. The study was made at approximately 100° C., at which the several vapor pressures are as follows (11):

Camphor solid	20.0 mm.	o-Cresol	31.6 mm.
Camphor liquid	30.7	m-Cresol	19.05
Phenol	43.4	p-Cresol	18.3

The value for liquid camphor was computed from the equation $\log p = 7.692 - (2316/T)$ derived from the vapor pressures at higher temperatures. This value was used in the partial pressure experiments.

Two "railroad" gas bubbling tubes of Pyrex glass were modified slightly as shown in Fig. 5. Two small glass tubes were bent as in (a) and (b), respectively, so that when the two parts were connected at (c), an air stream from a calcium chloride drying tube bubbled through the first railroad tube, then through

the first narrow tube, back into the second railroad tube and out through the second narrow tube to the water pump. The railroad tubes were fastened together with a rubber band and immersed in a beaker of boiling water, while the narrow tubes served as condensers, and were immersed in ice water. Bulbs at the bottoms of the bends received the distillates. It was found necessary to have the exits from the railroad tubes below the boiling water and to have initial dips in the receiver tubes to prevent refluxing back into the railroad tubes. A small portion of the distillate was collected in these dips. Each of the four tubes was provided with a wire with a loop to permit weighing in an analytical balance.
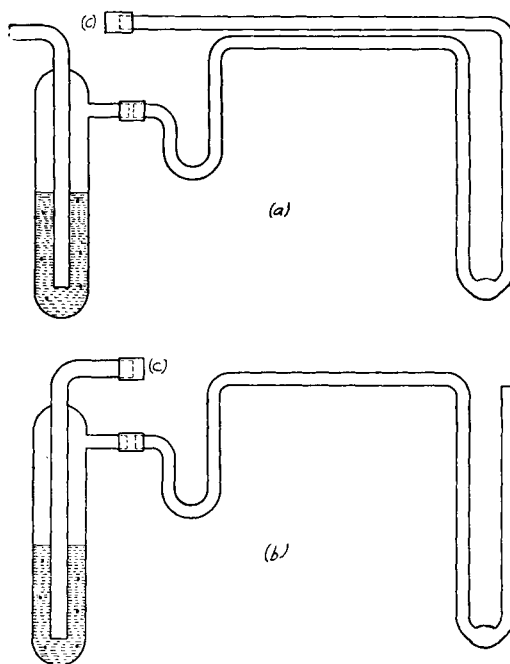

Fig. 5.—Partial Vapor-Pressure Apparatus.

In each run 10–12 cc. of the desired mixture of camphor with phenol or a cresol were put into railroad tube (b) and an equal amount of the same cresol in (a). Since exactly the same air was passed through each of the two liquids which were at exactly the same temperature (assumed to be 100° C., but which might have been slightly lower occasionally), the relative amounts of cresol or phenol vaporized and condensed from the two tubes are a fairly accurate measure of the relative partial pressures. The volume of air was not measured, so that only relative values were obtained. A run lasted about an hour and vaporized about half a gram of each liquid. This must have required about eight liters of air. Each tube was weighed before and afterward to compare the gain for the condensers with the loss from the railroad tubes. These usually checked, respectively, within 5%. The condenser tubes were then rinsed out carefully into 300-cc. Erlenmeyer flasks mostly by means of water but

using a little methanol. After being diluted to about 150 cc. the contents of the flasks were titrated with bromide-bromate (7) to determine cresol (or phenol). In the case of the (b) tubes the remainder of the condensate was considered camphor. The condensate in (a) was titrated for completeness, but was always close to 100% cresol. When a phenol-camphor mixture was used, the reference liquid was not phenol, which would solidify and plug the receiving tube, but o-cresol. All the cresols supercooled enough so as to give no trouble in this respect.

The result of a typical run was as follows:

Mixture in (b) 50 mole per cent of camphor and phenol. Reference liquid in (a) o-cresol.

	(a)	(b)
	43.6335	41.8908
	42.5605	41.2454
Distilled	1.0730	0.6454
	10.9220	8.8430
	9.8850	8.2423
Condensate	1.0370	0.6007

Analysis

1.038 Gm. = 9.6 m. moles o-cresol

$\begin{cases} 0.248 \text{ Gm.} = \\ 2.64 \text{ m. moles} \\ \quad\quad \text{phenol} \\ 0.353 \text{ Gm.} = \\ 2.32 \text{ m. moles} \\ \quad\quad \text{camphor} \end{cases}$

Vapor pressure   31.6 mm. $\begin{cases} 8.7 \text{ mm.} \\ \quad\quad \text{phenol} \\ 7.65 \text{ mm.} \\ \quad\quad \text{camphor} \end{cases}$

If Raoult's law were obeyed for this mixture the partial pressures would have been 21.7 mm. phenol and 15.35 mm. camphor (half the values for pure components). The lower observed values indicate a holding back of both components (phenol somewhat more than camphor) probably because of a less volatile complex of the two components in the mixture. To be sure, Raoult's law fails in many other cases, but I believe that where deviations are substantial, as in this case, it is partial evidence for more or less stable association of the components. In this case the greater retention of phenol than of camphor might mean a greater proportion of phenol combined, that is some C-P₂ as well as C-P. But the mixture containing 66.7 mole per cent phenol shows a considerable excess of the latter, indicating that the total composition of all the combined portion is between one-half and two-thirds phenol.

o-Cresol gives about the same result as does phenol. m- And p-cresol, however, seem to indicate nothing but compounds of camphor with two moles of cresol, since such mixtures give distillates of nearly the same composition; while the 50 mole
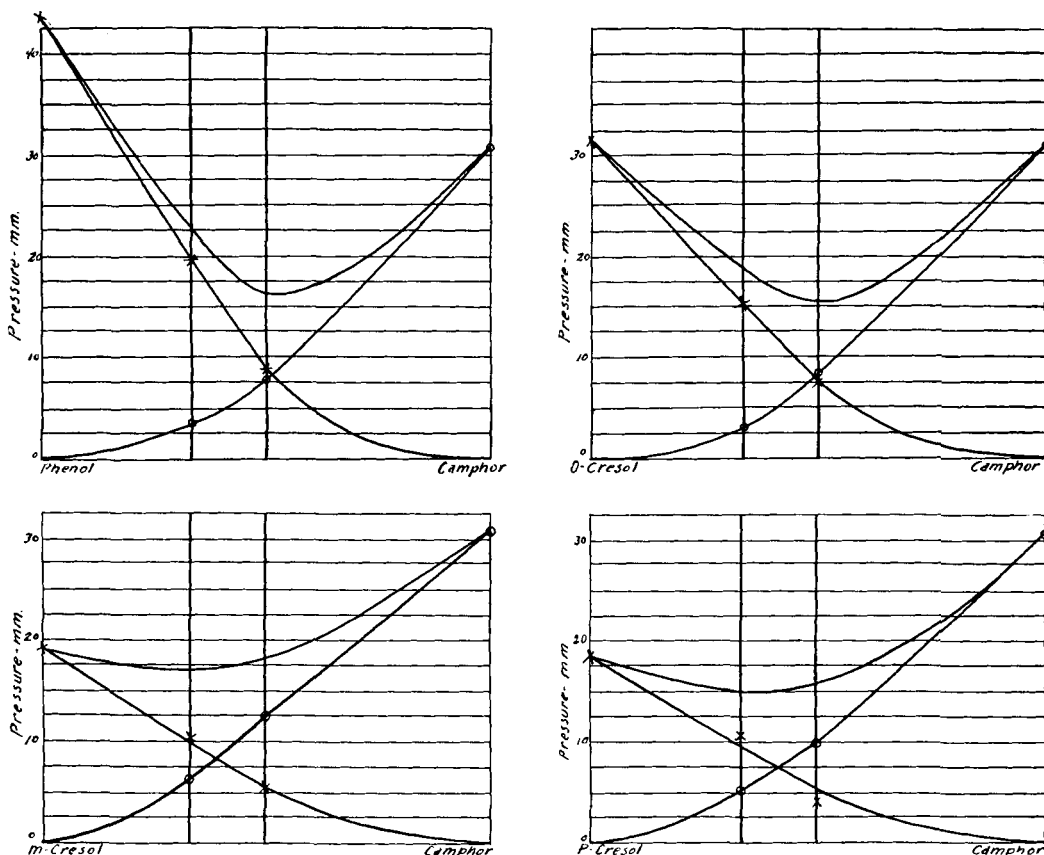

Fig. 6.—Partial Vapor Pressure at 100° C.

per cent mixtures evolve such an excess of camphor that the distillate contains a slush of camphor crystals. Additional conclusions will be discussed in relation to other observations later. A summary of the complete results is given in Table V, and also in Fig. 6.

Table V.—Partial Vapor Pressures of Camphor-Phenol and Camphor-Cresol Mixtures

Substance (Figures Are Moles)	Condensate Weight, Gm.	Milli-moles	Vapor Pressure, Mm. Observed[a]	Calcd. from Raoult's Law
o-Cresol	1.037	9.60	31.6	
1 Camphor	0.353	2.32	7.65	15.35
1 Phenol	0.248	2.64	8.7	21.7
o-Cresol	0.832	7.70	31.6	
1 Camphor	0.116	0.76	3.15	10.2
2 Phenol	0.445	4.73	19.4	28.9
o-Cresol	1.129	10.44	31.6	
1 Camphor	0.421	2.67	8.1	15.35
1 o-Cresol	0.263	2.44	7.35	15.8
o-Cresol	0.779	7.20	31.6	
1 Camphor	0.114	0.75	3.25	10.2
2 o-Cresol	0.386	3.57	15.7	21.1
m-Cresol	0.448	4.15	19.05	
1 Camphor	0.443	2.85	13.0	15.35
1 m-Cresol	0.131	1.21	5.5	9.5
m-Cresol	0.392	3.63	19.05	
1 Camphor	0.1875	1.23	6.4	10.2
2 m-Cresol	0.219	2.03	10.6	12.7
p-Cresol	0.579	5.35	18.3	
1 Camphor	0.455	2.99	10.2	15.35
1 p-Cresol	0.132	1.22	4.2	9.1
p-Cresol	0.498	4.61	18.3	
1 Camphor	0.201	1.32	5.2	10.2
2 p-Cresol	0.276	2.55	10.1	12.2

[a] For pure substances taken from International Critical Tables (11). For mixtures taken proportional to the milli-moles in the condensate.

Temperature Effects on Mixing.—If solid camphor and solid phenol are mixed adiabatically, the temperature falls about 12° C. This absorption of heat is due to the heats of fusion of the two crystalline compounds. However, an estimate of these two heats of fusion indicates that the fall in temperature should be nearly twice as great, if no reaction occurred. This was confirmed by mixing two strong solutions of camphor and phenol, respectively, in benzene. In this case there was a *rise* of over 8° since there was no heat of fusion to be absorbed. This indicates qualitatively that there is considerable chemical combination between the camphor and phenol, even in benzene solution. This method seemed a promising one for estimating the relative amounts of free and combined phenol in mixtures, and also for deciding the composition of the complex.

In the more quantitative experiments the calorimeter consisted of a small Dewar flask of 50-ml. capacity. About 15 ml. of one reagent were placed in the flask and a similar amount of the other one in a tube made from an ordinary test-tube by blowing a 9-mm. hole in the bottom and drawing it down to 9 mm. at the top, the total length being 10.5 cm. The bottom hole was closed by a tiny loose-fitting,

flat cork and the whole tube was immersed in the other reagent in the Dewar flask. When the two liquids had reached the same temperature, the cork was pushed out with the thermometer, and the tube was withdrawn over the thermometer. The mixture was stirred and the temperature read about every five seconds until the maximum was reached, usually in ten to fifteen seconds. The same Anschutz thermometer was used as was mentioned previously.

The solid components camphor and the cresols were entirely unsuited as reagents for these heat effects on mixing. A four-molar solution of camphor in benzene was chosen as one component since it was almost saturated (65.6% camphor) and was found by experiment to produce no change in temperature when further diluted with benzene in the apparatus described. The cresols are still more soluble in benzene, and because of their lower molecular weight an eight-molar solution can be made. But such a solution even in the case of m-cresol evolves heat on dilution with benzene and this would complicate studies on the heat of mixing with the camphor solution. Accordingly, four normal solutions of the cresols were used. These evolve only a trivial heat on dilution; and by having the two components of equal molality the choice of volumes for mixing and the calculations of the results were greatly simplified.

In the case of each cresol and phenol, mixtures of the two components were made in the proportion of one to one by volume and also one of camphor solution to two of cresol solution, these being the most probable proportions for combination as judged by the vapor-pressure studies. Then samples of these mixtures were used as reagents, mixing them with excess camphor solution or cresol solution or other mixtures, etc., observing the rise in temperature in each case. These were plotted in the manner shown in Fig. 7, with the molar composition of the two solutions as abscissa and the temperature rises as ordinates. When intermediate compositions were used, a dotted line was drawn connecting the tops of the ordinates obtained in making those mixtures; and the new ordinate was drawn from the appropriate point on the dotted line. This method was considered more accurate than that of making all the mixtures using the original components, because the temperature rises were much smaller and the exact curvature of the sloping sides of the curves was of importance in drawing the tangents, as indicated later. By drawing a line through the tops of all the ordinates a curve results which is presumably a function of the amount of complex present in any mixture. Tangents to the curve at the two ends show the amount of compound which would be present if there were no dissociation. A comparison in ordinate between the curve and the tangent shows the relative amount of phenol or cresol or camphor which is combined.

Strictly, the specific heats of the various mixtures should have been employed with the temperature

rises to obtain heat evolved, and this was tried. But the specific heats of all the solutions were nearly the same, and differences were further decreased by the heat capacity of the calorimeter, so that the effect upon the diagrams was almost negligible. Moreover, many assumptions were necessary in estimating these specific heats. It seemed probable that the use of temperature rises would give results as accurate as were warranted by the precision of the observations and by the assumption that the heat evolved was proportional to the amount of com-

pound formed (not quite true if more than one complex exists in one system).

The results are recorded in Table VI and Fig. 7.

All four of the curves in Fig. 7 are unsymmetrical, bulging on the side of the phenol or cresol. It was suggested that this was due to association of the phenol so that the equilibrium in solution was approximately $P_2 + 2C \rightleftarrows 2PC$, but calculation showed that this would make the curve bulge on the camphor side. The ideal cryoscopic behavior of camphor permits little probability that the bulge is
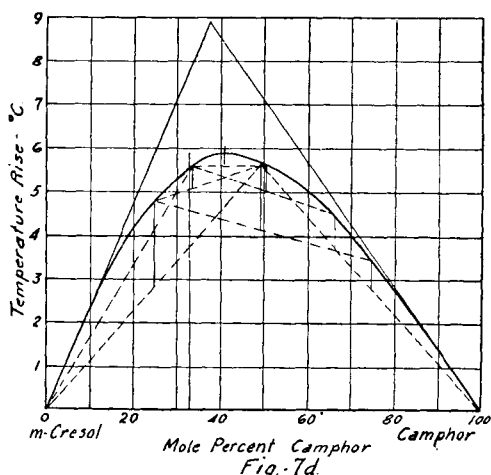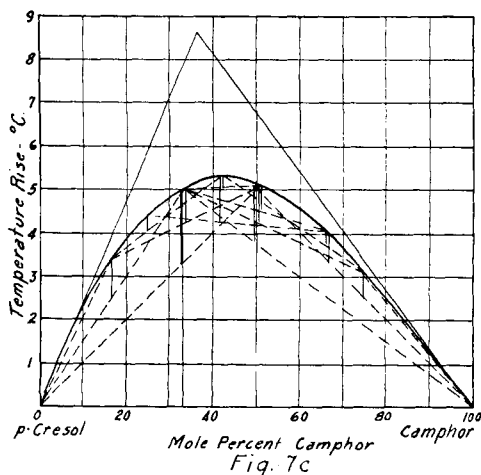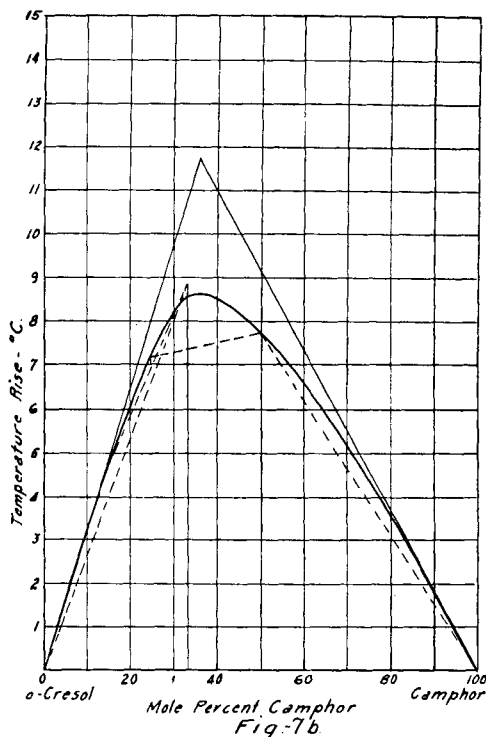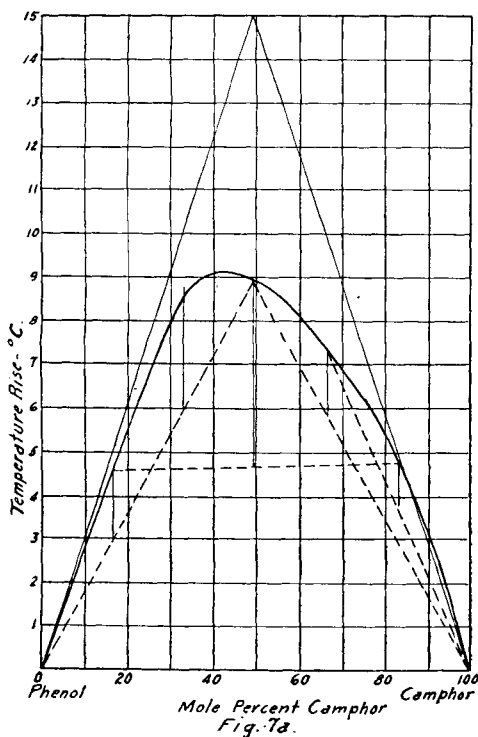
Figs. 7a–7d.—Temperature Rises on Production of Liquid Mixtures of Camphor with Phenol and the Cresols in $4N$ Benzene Solution.

Table VI.—Rises in Temperature on Producing Mixtures of Camphor with Phenol and the Cresols

Rise in degrees Centigrade
C = 4M solution of camphor in benzene
Ph = 4M solution of phenol in benzene
O = 4M solution of o-cresol in benzene
M = 4M solution of m-cresol in benzene
P = 4M solution of p-cresol in benzene
Compositions in mole per cent C

Camphor-Phenol Mixture,				Camphor-o-Cresol Mixture,		
Components		Mole Per Cent C	Rise, °C.	Components	Mole Per Cent C	Rise, ° C.
Ph	+ C	50	8.95	O + C	50	7.8
C	+ 50[a]	66.7	1.52	O + C	33.3	8.9
Ph	+ 50	33.3	2.85	C + 50	75	0.65
C	+ 66.7	83.3	1.10	O + 33.3	16.7	0.75
Ph	+ 33.3	16.7	1.60	16.7 + 33.3	25	0.75
16.7	+ 83.3[b]	50	4.50	50 + 25	33.3	1.20

Camphor-m-Cresol Mixture,				Camphor-p-Cresol Mixture,		
Components		Mole Per Cent C	Rise, ° C.	Components	Mole Per Cent C	Rise, ° C.
M	+ C	50	5.6	P + C	50	5.08
M	+ C	33	5.9	P + C	33.3	5.02
M	+ 50	25	2.0	C + 33	50	1.20
C	+ 50	75	0.7	P + 33	16.7	0.85
25	+ 75	50	1.5	17 + 50	33.3	0.75
25	+ 50	33	0.5	C + 50	75	0.68
C	+ 50	67	0.9	33 + 75	50	0.77
33.3	+ 66.7	50	0.8	50 + 33	42	0.32
33.3	+ 50	41	0.4	C + 50	67	0.85
M	+ 33.3	20	1.0	33 + 67	50	0.58
				P + 50	67	1.42
				P + 17	8	0.22
				C + 75	87	0.03
				42 + 75	67	0.34
				17 + 42	25	0.34
				25 + 67	42	0.98

[a] Under components C + 50 means that 4M camphor solution in benzene was mixed with a benzene solution containing 2M camphor + 2M phenol, or a total of 4 moles of which 50% were camphor. These were mixed to give a final mixture containing 66.7% camphor.
[b] 16.7 + 83.3 under components means that two solutions were mixed, both of which had 4 moles solute per liter benzene. In one 16.7% of the solute was camphor and in the second 83.3%, the rest being phenol. The final mixture had 50% camphor.

due to association of camphor. The remaining possibility is that in mixtures with phenols, beside the 50 mole per cent complex, there is also a 33 mole per cent (of camphor) complex. In the case of phenol the amount of this is slight since the tangents meet at almost 50 mole per cent, but the 2:1 complex seems to predominate in the case of all three cresols. This supposition may account for the failure to crystallize out a complex at low temperature, in the case of m- and p-cresol, since its freezing curve may be below the cresol curve. This possibility may be true for o-cresol also, the 1:1 complex being found merely because its composition is situated more favorably between the freezing curves of the pure components. In this connection might be mentioned the "near observation" of such a complex with phenol and camphor by Leger (5) although Wood and Scott (3) concluded this was not the case. At the low temperatures required, the mixtures are so viscous that the chance crystallization of such a complex might fail of confirmation, especially if its curve falls very close to the phenol curve, as it probably does. The present investigation also failed to find such a complex by its effect on the freezing curves.

It will be noted that the vapor-pressure method seemed to indicate that as in the case of phenol only one molecule of o-cresol is combined with camphor, while the temperature effect indicates a 2:1 complex. The difference is due probably to the difference in temperature used. The 2:1 complex may be largely dissociated at 100° C.

The curves of Fig. 7 show also that the phenol-camphor complexes have much the highest heat of formation as judged by the height of the tangent intersection, but also the highest percentage of dissociation, about 40% at the maximum point. The o-cresol complexes are only slightly dissociated, about 27% at the peak. Those of m- and p-cresol are very similar to each other, with the lowest heat of formation, and about 35% maximum dissociation. It was supposed that all these percentages would be affected somewhat by the solvent benzene, which was present when the curves were estimated, but this effect must be almost negligible, since a phenol-camphor mixture (without benzene) showed no detectable heat effect when diluted with benzene. Attempts were made to compute dissociation constants for some tentative equilibrium such as $2P + C \leftrightarrows P_2C$, but these failed to give calculated curves which agreed perfectly with the observed curves, probably because more than one complex exists in solution, and because phenol and the cresols are themselves associated to an indefinite degree.

Table VII.—Freezing Temperatures of Benzene Solutions of Camphor, Phenol, the Cresols and Some Mixtures

(Concentrations in Moles per 1000 Gm. Benzene)

| Camphor		Phenol		o-Cresol		m-Cresol		p-Cresol	
Conc.	Temp.	Conc.	Temp.	Conc.	Temp.	Conc.	Temp.	Conc.	Temp.
0	5.25	0.155	4.85	0.54	2.85	0.43	3.25	0.525	3.15
0.31	3.65	0.31	4.40	1.08	0.88	0.65	2.65	1.05	1.80
1.00	0.13	0.62	3.65	1.62	−0.25	0.85	2.05	1.58	0.80
1.52	−2.20	1.22	2.70	2.16	−1.50	1.08	1.50	2.10	0.00
		2.56	0.60	3.24	−3.60	1.29	1.05	2.63	−1.00
		3.86	−1.20	4.32	−5.60	1.51	0.60	3.15	−1.85
		5.18	−3.0	5.40	−7.60	1.72	0.20	3.68	−2.50
				6.48	−9.5	2.16	−0.20	5.1	−4.20
						3.24	−1.45	6.5	−6.0
						4.32	−2.6	7.9	−6.6
						5.40	−4.2	9.3	−8.0
						6.48	−4.9		
						7.56	−6.2		

Equimolecular mixtures.

Concentrations as if not combined, i. e., mean mol. wt. $\begin{cases} 123 \text{ for camphor-phenol} \\ 130 \text{ for camphor-cresols} \end{cases}$

Camphor-Phenol		Camphor-o-Cresol		Camphor-m-Cresol		Camphor-p-Cresol	
Conc.	Temp.	Conc.	Temp.	Conc.	Temp.	Conc.	Temp.
0.43	3.70	1.57	2.15	0.315	4.65	1.57	2.35
0.62	3.35	4.72	−2.00	0.63	3.75	3.15	0.35
0.87	2.60	6.30	−4.05	0.94	3.25	4.72	−1.60
1.30	1.60	7.86	−6.00	1.26	2.70	6.30	−3.80
1.74	0.50	9.45	−7.60	1.57	2.50	7.86	−5.60
3.48	−3.80			1.89	2.20		
				2.20	1.70		
				2.52	1.30		
				2.83	0.80		
				3.15	0.25		
				6.3	−3.55		

Although the maximum dissociation of the complexes seems to be 27% to 40%, judging from these curves, it will be noted that the equimolecular mixtures in the case of the cresols contain a much smaller proportion of free cresol, about 15, 23 and 21% of the total cresol, respectively. This means about 6% to 9% by weight in the mixture instead of 41.5% as found by chemical analysis. The equimolecular mixture of phenol and camphor contains 38.2% total phenol and about 15% free phenol.

This indicates one advantage of cresol mixtures over the phenol mixture, since they are probably less irritating. If an excess of camphor is present, as is quite common, the percentage of free cresol is still less. Thus a mixture containing 20% total m-cresol by weight (26 mole per cent) seems to contain about $1\frac{1}{2}\%$ free m-cresol.

Cryoscopic Molecular Weight Determinations.— The freezing temperatures were determined for solutions in benzene of camphor, phenol and the cresols,

Fig. 8a

Fig. 8b.

Fig 8c

Fig. 8d
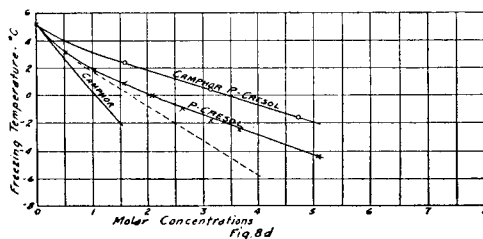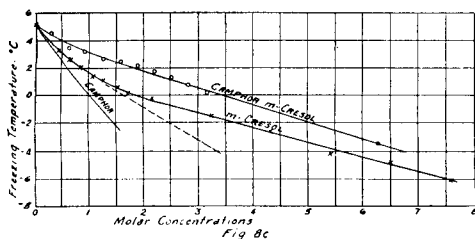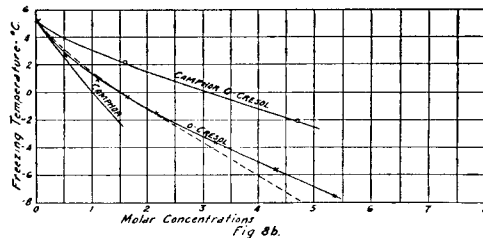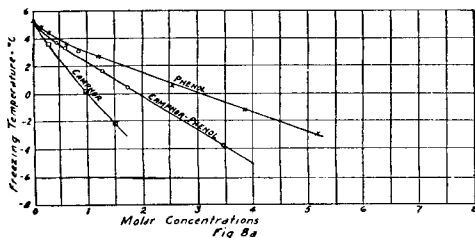
Figs. 8a–8d.—Freezing Temperatures of Benzene Solutions.

and also of equimolecular mixtures of these, in the hope of estimating the mean molecular weight of mixtures and thus giving light from still another angle upon the question of complex formation. Although camphor shows a perfectly normal effect upon the freezing point of benzene, phenol and the cresols show abnormally high molecular weights, due undoubtedly to association, even in dilute solution. Nevertheless, the depression caused by mixtures with camphor is always considerably less than the combined depression caused by its components, although greater than either alone—indicating pronounced, though not complete association of camphor with phenol and the cresols.

These results are presented in Table VII and Fig. 8.

The camphor-phenol curve is higher than the mean between those of camphor and phenol and so indicates a greater degree of combination than that of association of the phenol alone. The camphor-cresol curves are all above those of the corresponding cresols, indicating a still greater degree of combination. If the molar concentration were computed as for the combined molecule (i. e., 260 mol. wt. instead of 130), the curves (dotted lines in the figure) would fall below the cresol curves, showing incomplete combination, although in the case of o-cresol the curves become practically coincident at low concentrations, indicating nearly complete association or else an appreciable amount of molecules of still higher molecular weight such as a complex of one camphor with two o-cresol molecules.

If we compare the concentrations required to depress the freezing temperature of benzene the theoretical molar amount, 5.12°, that is, to +0.13° C., the apparent molecular weights are as follows:

Table VIII.—Apparent Molecular Weights in Benzene Solutions Freezing at +0.13° C.

Solute	Molecular Weight Observed	Molecular Weight Calcd.	Simple Moles per Complex
Camphor	152	152	1.00
Phenol	273	94	2.90
o-Cresol	156	108	1.44
m-Cresol	195	108	1.80
p-Cresol	218	108	2.015
Camphor-phenol	232	123	1.89
Camphor-o-cresol	397	130	3.05
Camphor-m-cresol	418	130	3.22
Camphor-p-cresol	433	130	3.33

The fact that the last three values are above 3.0 does not mean a higher complex than one of camphor with two of cresol, but only that most of the free cresol is also in aggregates.

Relationship between Free and Combined Metacresol.—The data given in the preceding sections show that there is certainly compound formation between camphor and phenol or cresol. In any mixture of cresol and camphor some of the cresol is free and some is combined. It is very desirable to know the relationship between them. The data in the preceding sections give us a means of calculating
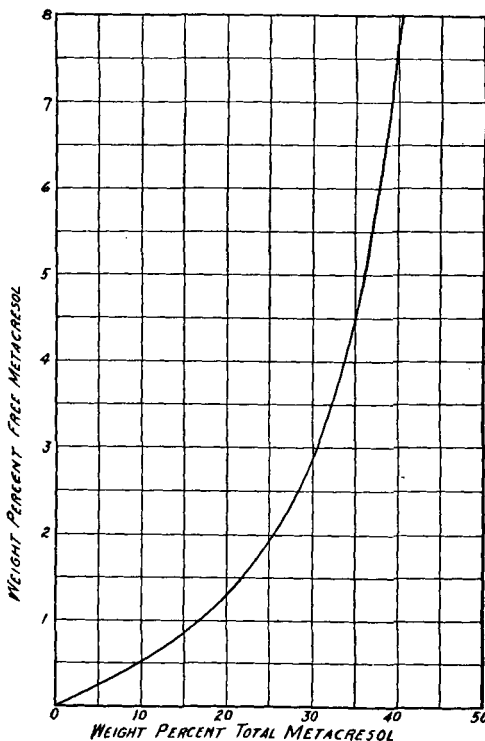

Fig. 9.—Relationship Between Free and Total Metacresol in Mixtures with Camphor.

this relationship. The precision of the calculation is not high, but is sufficient to give a good idea of the extent to which combination takes place. Table IX and the curve as shown in Fig. 9 exemplify the relation in the case of m-cresol and are based in the first place on equilibrium constants and then checked against the data obtained in other ways, particularly the curves of Fig. 7.

Table IX.—Relationship between Free and Total Metacresol in Mixtures with Camphor Expressed in Weight Per Cent

Total m-Cresol	Free m-Cresol	Total m-Cresol	Free m-Cresol
3.6	0.17	24.1	1.81
7.0	0.34	26.7	2.22
10.2	0.53	29.4	2.71
13.2	0.73	31.9	3.41
16.1	0.95	35.0	4.52
18.9	1.19	41.5	8.70
21.5	1.48		

The equimolecular constant was computed from the dissociation in the equilibrium mixture and taken as 0.046 and the mass law equation as

$$\frac{xy}{1 - (x + y)} = 0.046$$

where x = mol. fraction uncombined camphor
y = mol. fraction uncombined m-cresol

SUMMARY

Several physical properties have been studied for the systems of camphor with phenol and the three cresols, respectively. These include freezing curves, densities, partial solubilities in water, partial vapor pressures, temperature effects on mixing liquid solutions, and cryoscopic molecular weight determinations. Melting points for equimolecular complexes were found to be $-12°$ C. for camphor-phenol and $-18°$ C. for camphor-o-cresol. Complexes with the other two cresols could not be crystallized because of the high viscosity of the solutions. A convenient method of measuring partial pressures and a method of interpretation of temperature effects on mixing were devised.

Evidence derived primarily from the latter two properties, but supported also by the others, points to the existence of at least two complexes in each mixture, namely, those of one mole of camphor with one and two moles, respectively, of phenol or cresol. The former predominates in the case of phenol, but the latter in the case of all three cresols. All these complexes are partly dissociated in solution and rapidly decomposed on chemical analysis. The concentration of free cresol in an equimolecular mixture with camphor is 6% to 9%, and in a 20 weight per cent mixture with camphor the free m-cresol is about $1^1/_2\%$.

Although this investigation has been confined to the physicochemical properties of phenol-camphor and cresol-camphor mixtures, it is interesting to speculate as to the probable bearing of these properties on the known pharmacological properties of such mixtures. The low content of free phenol or cresol found probably accounts for the high toleration which wounds and tissue show to these mixtures. The fact that these are equilibrium mixtures means that they will liberate free phenol or cresol as fast as that originally present is consumed and this may explain their known antiseptic and surface anesthetic effects.

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A Method for the Quantitative Determination of Theobromine or Theobromine Salts and Phenobarbital in Mixtures

*By C. W. Bell**

Due to the introduction of many new organic drugs into medicine and the continued practice of combining two or more such drugs in a single dosage form, the analysis of medicinal preparations is a problem of increasing complexity. Occasionally as many as four active ingredients may be combined in a single dosage form and it is a very common practice to combine two organic compounds in a single dosage form. In such mixtures it is necessary to have a method for the separation and quantitative determination of each of the active constituents. Much progress has been made in this branch of pharmaceutical chemistry in the past few years but a critical survey of the literature revealed that a method for the quantitative determination of theobromine, or its salts, and phenobarbital in mixtures has not as yet been reported. In attempting to develop such a method the author was primarily concerned with the analysis of tablets containing phenobarbital and Theo-

* Control Laboratory, E. Bilhuber, Inc., Orange, N. J.