

## Contributed and Selected

### COMPARATIVE INVESTIGATION OF THE COMPOSITION OF ICHTHYOL-AMMONIUM AND SOME OF ITS SUBSTITUTES.\*

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Ichthyol-ammonium, also known as Ichthyol, is the well-known water-soluble, organic sulphur preparation of the firm Cordes, Hermanni & Co. in Hamburg. For more than 25 years it has proven a very valuable medicinal agent and it therefore need not seem surprising that during the past years a number of similar preparations have been placed upon the market, which have been advertised as "equally as effective as Ichthyol" by their manufacturers. Chemical analyses by different experts have however shown that these products, which to all appearances resemble the original, differ considerably among themselves, and particularly from Ichthyol in chemical composition.

Both physicians and pharmacists have recently complained of increased substitution of original preparations by inferior products. The following investigations were therefore conducted with a view of determining if specimens of Ichthyol obtained from different pharmacies are of uniform composition and if the better known similar preparations sufficiently resemble Ichthyol to be regarded as available, from the pharmaceutical point of view, for purposes of substitution.

Several articles have already appeared which deal with the character and composition of the preparations in question. The authors point out that the chemical analysis can only comprise the determination of the dried residue and the content of ammonium sulphate, the total ammonium and the total sulphur, since the composition of these preparations is not uniform. We are dealing with the watery solution of the ammonium salts of organic sulpho-acids, sulphones, ammonium sulphate, and small amounts of hydrocarbons poor in sulphur, which are chiefly responsible for the characteristic odor of Ichthyol.

A short resumé of previous analyses is in place. The values obtained for total sulphur are not directly comparable since the methods of Carius will frequently give too low values with preparations rich in sulphur, such as Ichthyol. The amount of sulphur combined as sulphide or not oxidized cannot be determined directly since no reliable method is at our disposal. It will be necessary to determine the amount of sulphur occurring in the form of sulpho-compounds and as sulphates and to subtract both from the total amount of sulphur present. It follows that the values obtained for sulphur occurring as sulphide are also not directly comparable.

Kothmeyer<sup>1</sup> determined the difference between Ichthyolum germanicum (Ichthyolammonium of Cordes, Hermanni & Co. of Hamburg) and the substitute

\*Translated in full from Arch. d. Pharmacie, 1912, No. 6 and 7. From the Pharmaceutical Institute of the "Herzoglichen Technischen Hochschule" in Braunschweig.

Ichthyolum austriacum (of G. Heli & Co. in Troppau, now called Petrosulfol). The German preparation (dried at 100°) yields 45% dried residue, and 21.1% of this was total sulphur. Petrosulfol yields 42-43% dry residue, with 16.3% total sulphur.

Goliner<sup>2</sup> states that the dry residue obtained from Isarol contains 17 to 19% sulphur.

G. J. Witol<sup>3</sup> investigated Petrosulfol and obtained a dry residue of 54.71%, with 16.27% sulphur.

R. Thal<sup>4</sup> carefully studied the following preparations: 1. Ichthyol of the firm Cordes, Hermanni & Co. of Hamburg; 2. Ammonium sulphoichthyolicum (now called Isarol), of the Gesellschaft fuer chemische Industrie of Basel; 3. Trasulfan of Riechold & Co. in Binningen (Switzerland); and Ammonium sulphoichthyolicum (now termed Piscarol) of Luedy & Co. in Burgdorf (Switzerland).

The author obtained the following percentages:

	1	2	3	4
Dry Residue .....	55.66	54.48	37.71	39.83
Total Ammonia .....	8.15	5.11	1.38	3.32
Total Sulphur .....	9.70	9.42	5.30	5.75
Ammonium Sulphate .....	5.72	12.94	1.93	8.05
In the organic dried substance there was:				
Ammonia .....	3.36	4.28	2.48	3.93
Total Sulphur .....	17.68	15.14	13.66	11.95
Sulphur was found:				
As Sulpho Compound .....	6.32	8.04	4.66	7.38
As Sulphide .....	11.36	7.10	9.00	4.57
Proportion of sulphonic to sulphidic sulphur: 1:1.79      1:0.88      1:1.93      1:0.62				

H. v. Hayek<sup>5</sup> compared the composition of Ichthyol with that of Ichthyinat, manufactured by von Heyden in Radebeul. The following is the result of his examination of three samples of Ichthyol and one of Ichthyinat "Heyden:—"

	Ichthyol I	Ichthyol II	Ichthyol III	Ichthyinat "Heyden"
Dry Residue .....	{ 52.69 53.06	{ 62.13 62.51	{ 55.21 54.98	{ 53.89 53.93
Ammonium Sulphate .....	{ 5.94 6.07	{ 6.77 6.92	{ 6.27 5.86	{ 5.94 6.49
Total Ammonia .....	{ 2.97 3.02 2.98	{ 3.46 3.64 3.89	{ 2.98 2.99 3.12	{ 3.48 3.33 3.58
Total Sulphur (determined from dry residue) .....	{ 17.19 17.47	{ 16.35 16.07	{ 17.01 16.39	{ 16.05 16.15
Oxidized Sulphur (determined from dry residue) .....	{ 4.89 5.19	{ 5.55 4.93	{ 4.77 4.99	{ 4.70 4.57
Non-oxidized active Sulphur (determined from dry residue) .....	{ 12.29	{ 10.97	{ 11.82	{ 11.46

The same author<sup>6</sup> also reports upon the analysis of seven samples of Ichthyol of Cordes, Hermanni & Co. in Hamburg obtained in different cities in original packages:

	ICHTHYOL.							Greatest Difference	
	No. ....	1	2	3	4	5	6		7
Dry Residue .....		54.20	54.09	53.37	53.16	51.70	54.96	53.49	3.26
Ammonia .....		2.93	2.97	2.97	2.97	3.02	3.00	3.11	0.18
Ammonium Sulphate .....		5.85	5.84	5.90	5.87	5.95	5.73	5.92	0.22
In percentages of dry residue:									
Total Sulphur .....		17.89	18.09	17.55	17.38	15.58	16.46	16.25	2.51
Oxidized Sulphur .....		3.66	3.94	4.16	3.95	4.04	3.77	4.09	0.50
Non-oxidized Sulphur .....		14.23	14.15	13.39	13.43	11.54	12.69	12.16	2.69

The author concludes that Ichthyol varies considerably in composition, probably owing to the nature of the raw material but that the fluctuations are within reasonable limits. The Ichthyol Company, Cordes, Hermanni & Co.,<sup>7</sup> replies that the fluctuations are in reality not so marked as found by v. Hayek.

F. W. Passmore<sup>8</sup> has studied the composition of a large number of organic sulphur preparations which have been recommended in the place of Ichthyol. He publishes the following percentages:

	Dry Residue at 100°	Total Ammonia	Total Sulphur	Ammonium Sulphates	Ammonium Chloride	Organic Dry Residue	Total Sulphur (in Organic (in Dry Residue)	Sulphide Sulphur in Organic in Dry Residue
Ichthyol ....	56.7	8.16	10.72	5.94	0.03	49.73	18.66	12.51
Ichthyinat ...	58.5	8.53	8.24	6.60	0.04	46.86	14.19	6.85
Ichtosan ....	58.9	2.74	8.24	1.69	0.30	51.91	15.08	6.70
Isarol ....	54.3	2.82	8.67	2.76	0.07	51.47	15.54	7.82
Lithyol ....	50.8	4.50	7.57	10.35	1.23	39.22	12.90	4.07
Petrosulfol .	60.7	2.54	10.07	trace	0.27	60.43	16.66	9.11
Piscarol ....	50.7	3.75	7.82	9.28	trace	41.42	13.44	7.27
Fossilol ....	51.9	8.15	8.57	5.65	0.09	46.16	15.60	8.67
Subitol ....	47.9	3.33	8.05	7.63	0.16	40.11	15.46	9.08

Our own analyses were made on seven samples of Ichthyol obtained from different pharmacies and the following substitutes (obtained in original packages of 0.5 or 0.25 kg.):

1. Ichthammon of F. Reichelt, limited, in Breslau.
2. Ichthium of the Factory Westend in Charlottenburg.
3. Ichthyinat of von Heyden in Radebeul.
4. Isarol of the Gesellschaft fuer chemische Industrie in Basel.
5. Petrosulfol of G. Hell & Co. in Troppau and Vienna.
6. Pisciol of Hoeckert & Michalowsky, Berlin-Rixdorf.
7. Subitol of Charles Zimmermann & Co., in London.

We determined the dry residue, the sulphur occurring as sulphate, the total sulphur, the total ammonia, and the residue remaining after incineration, according to the methods described below.

The sulphates were estimated as ammonium sulphate. The ammonia occurring as ammonium sulphate was subtracted from the total ammonia and the sulphur present as sulpho-compounds was estimated from the rest as advised by R. Thal<sup>9</sup>. The percentage of sulphides was then found by subtracting the amount of sulphur occurring as sulphates and as sulpho-compounds from the total sulphur.

The following three tables give the values found. Table I refers to the substance directly; table II to the dry residue and table III to the dry residue minus the ammonium sulphate (organic dry residue).

The determination of the dry residue was effected by heating about 5 Gm. of the preparation in a water-drying oven until the loss of weight after several hours drying did not exceed 0.2 percent. It was not considered desirable to heat to constant weight because on drying, other volatile compounds besides water are gradually driven off.

TABLE I.

In Percentages:	Dry Residue	Total Sulphur	Sulphur as Sulphate	Sulphonic Sulphur	Sulphidic Sulphur	Total Ammonia	Ammonium Sulphate	Ash
Ichthyol	56.84	11.27	1.515	2.65	7.105	3.02	6.25	0.074
of Cordes,	No. 1.....	56.84	10.91	1.451	2.71	6.749	2.98	5.98
Hermann	No. 2.....	55.86	11.055	1.50	2.69	6.865	3.02	6.19
& Co. ob-	No. 3.....	55.98	10.74	1.45	2.66	6.63	2.955	5.98
tained from	No. 4.....	53.99	10.855	1.511	2.54	6.804	2.95	6.23
different	No. 5.....	55.53	11.02	1.48	2.71	6.83	3.01	6.10
pharmacies	No. 6.....	56.16	11.32	1.465	2.76	7.095	3.02	6.01
"Reichelt"	No. 7.....	66.16	10.375	0.355	3.96	6.06	2.48	1.46
Ichthammon	.....	54.80	8.08	1.537	5.04	1.503	4.81	6.34
Ichthium	.....	51.86	8.13	1.743	2.917	3.47	3.40	7.19
Ichthyinat	.....	55.41	7.49	1.251	2.98	3.259	2.915	5.16
Isarol	.....	52.24	9.22	trace	4.56	4.66	2.42	traces
Petrosulfol	.....	57.45	8.04	0.925	4.18	2.985	3.21	3.82
Pisciol (a)	.....	51.10	8.33	0.97	4.25	3.11	3.29	4.00
Pisciol (b)	.....	52.70	8.43	1.35	3.14	3.94	8.10	5.67
Subitol	.....	54.85						0.09

TABLE II.

In percentages of dry residue:		Total Sulphur	Sulphur as Sulphate	Sulphonic Sulphur	Sulphidic Sulphur	Total Ammonia	Ammonium Sulphate
Ichthyol	No. 1.....	19.83	2.67	4.66	12.50	5.31	11.01
of Cordes,	No. 2.....	19.53	2.60	4.85	12.08	5.33	10.72
Hermann	No. 3.....	19.74	2.68	4.80	12.26	5.43	11.06
& Co. ob-	No. 4.....	19.90	2.69	4.93	12.28	5.47	11.10
tained from	No. 5.....	19.55	2.72	4.58	12.24	5.31	11.22
different	No. 6.....	19.62	2.64	4.82	12.16	5.36	10.89
pharmacies	No. 7.....	20.15	2.61	4.91	12.63	5.38	10.77
Ichthammon	"Reichelt".....	18.93	0.65	7.22	11.06	4.53	2.67
Ichthium	.....	15.58	2.96	9.72	2.90	8.31	12.22
Ichthyinat	.....	14.67	3.15	5.26	6.26	6.14	12.79
Isarol	.....	14.35	2.40	5.70	6.25	5.58	9.88
Petrosulfol	.....	16.05	traces	7.94	8.11	4.21	traces
Piscioli (a)	.....	15.73	1.81	8.18	5.74	6.28	7.48
Piscioli (b)	.....	15.80	1.84	8.06	5.90	6.24	7.59
Subitol	.....	15.51	2.48	5.78	7.25	5.70	10.25

TABLE III.

In percentages of organic dry residue:		Total Sulphur	Sulphonic Sulphur	Sulphidic Sulphur
Ichthyol	No. 1.....	19.28	5.24	14.04
of Cordes,	No. 2.....	18.96	5.43	13.53
Hermann	No. 3.....	19.18	5.40	13.78
& Co. ob-	No. 4.....	19.36	5.55	13.81
tained from	No. 5.....	18.95	5.16	13.79
different	No. 6.....	19.06	5.41	13.65
pharmacies	No. 7.....	19.66	5.50	14.16
Ichthammon	"Reichelt".....	18.78	7.42	11.36
Ichthium	.....	14.38	11.07	3.31
Ichthyinat	.....	13.21	6.03	7.18
Isarol	.....	13.26	6.32	6.94
Petrosulfol	.....	16.05	7.94	8.11
Piscioli (mean of a and b)	.....	15.08	8.78	6.30
Subitol	.....	14.52	6.44	8.08

The determination of total sulphur in organic sulphur preparations according to the method of Carius presents difficulties since heating the substance in sealed tubes under pressure at 300° for several hours will not always suffice for complete oxidation. This is particularly the case where much sulphur is present as in Ichthyol. W. Hinterskirch<sup>10</sup> has obtained reliable results with this method only when he employed less than 0.3 of the preparation or if, after releasing the pressure and again sealing the tube, the heating was repeated for several hours on the following day. The method of Carius is laborious and long-winded and requires a furnace. Hinterskirch (l. c.) has therefore recommended a method thoroughly tested by him, and involving the use of sodium peroxide as oxidizing agent. The authors, however, find that oxidation with pure sodium peroxide is accompanied by violent explosions, while if potassium carbonate is used as diluent, considerable sulphur may be lost. The amount of water present also plays a role. Definite proportions must therefore be used, and the heating must be conducted in a special way, else the results will not agree with those obtained by the method of Carius.

The method of Hinterskirch therefore hardly presents advantages over the method of Carius. It is not easy to carry out, hence that a chemist not an expert is not apt to get accurate results.

The following experiments were carried out to discover a practical method. At first, the substance to be investigated was fused with sodium carbonate and saltpeter in a tube sealed at one end. About 0.8 grammes Ichthyol were dried in the drying chamber at about 100° with 5 grammes of a mixture of 1 part saltpeter and 7 parts anhydrous sodium carbonate. The dried mass was thoroughly rubbed up with the soda-saltpeter mixture and then filled into a tube of potash glass, sealed at one end. Traces of Ichthyol remaining in the dish were removed by further portions of the mixture until the tube contained about 40 grammes in all. The tube was then heated, beginning at the open end, in a combustion furnace up

to red heat. The escape of bluish vapors with peculiar odor could not be avoided. After cooling, the tube was broken and its contents dissolved in water. The solution was acidified with hydrochloric acid and evaporated to dryness to allow of the separation of silicic acid. The residue was taken up with hot water containing hydrochloric acid. In the filtrate, the sulphuric acid was precipitated in the usual way as barium sulphate. The figures obtained, however, were too low, hence this method was not considered suitable for the determination of sulphur in Ichthyol. It is probable that during the heating, volatile sulphur compounds escape undecomposed. The oxidation of the sulphur in a closed tube is therefore a more reliable procedure.

The reason why the determination of the total sulphur according to the method of Carius often gives too low figures is probably to be explained by the fact that the sulpho-acids will to a certain degree resist oxidation with nitric acid. Hinterskirch (l. c.) found that the results will be too low by 1.5 to 2% even if the heating is continued for several hours at 300°. In order to convert all the sulphur contained in Ichthyol into sulphuric acid, the following method was employed: About 0.3 to 0.5 gramme Ichthyol was heated with about 4 cc. fuming nitric acid for about 9 hours in a sealed tube. The temperature was slowly raised up to 260 to 275 and kept there about 6 hours. After opening the tube, the fluid was washed into a porcelain dish, rendered alkaline with 8 grammes sodium carbonate, and evaporated to dryness. The dried mass was then placed in a large nickel crucible with tightly fitting cover. The crucible is fitted into the opening of an asbestos plate held in a slanting position, so as to avoid the effect of the gas during heating. The crucible is heated with a moderately sized flame until the mass is uniformly molten. After cooling, the contents of the crucible are dissolved in water and acidified with hydrochloric acid. The sulphuric acid was then determined in the usual way as barium sulphate. The following figures were obtained with one sample Ichthyol by this method:

0.4860 g substance gave 0.3525 g BaSO<sub>4</sub>, equals 11.14% S.  
 0.3560 g substance gave 0.2825 g BaSO<sub>4</sub>, equals 10.90% S.  
 With a second sample:  
 0.3450 g substance gave 0.2675 g BaSO<sub>4</sub>, equals 10.65% S.

When the preparation was oxidized according to Carius and the sulphuric acid precipitated directly in the usual way, the following figures were obtained with the same samples:

SAMPLE I.  
 0.3895 g substance gave 0.3155 g BaSO<sub>4</sub>, equals 11.12% S.  
 0.3240 g substance gave 0.2595 g BaSO<sub>4</sub>, equals 10.99% S.  
 SAMPLE II.  
 0.3250 g substance gave 0.2540 g BaSO<sub>4</sub>, equals 10.74% S.

The same method was employed in determining the sulphur in the following preparations: Ichthium, Ichthynat, Isarol and Subitol, with the following results:

	After oxidation with nitric acid, evaporated with sodium carbonate and fused	Directly precipitated after oxidation with nitric acid.
Ichthium .....	7.92%	8.06%, 8.08%
Ichthynat .....	8.03%, 7.96%	8.13%
Isarol .....	7.45%, 7.48%	7.49%
Subitol .....	8.40%	8.46%

It follows that the method of Carius is very serviceable in determining the total amount of Sulphur in Ichthyol and similar organic sulphur preparations if 0.3 to 0.5 g. of the substance are heated with about 4 cc. fuming nitric acid for about 9 hours up to 260° to 275°.

Double determinations of the amount of total sulphur in other samples of Ichthyol and its substitutes gave figures which agreed very well, thus 10.92 and 10.90%, 10.84 and 10.87%, 11.37 and 11.27%, 9.50 and 9.47%. This is another proof of the value of the Carius method.

When the substance was heated in the tube up to 300° almost all the tubes cracked. In the few cases where the high pressure was resisted, the amount of sulphur was not found any higher. A temperature of 300° is therefore not necessary. A temperature of 260° to 275° will suffice if the heating is continued for 9 hours and at least 4 cc. fuming nitric acid are employed.

The method of Thal may also be used in determining the total sulphur; it has the advantage of not requiring a furnace. About 1 gm. Ichthyol is evaporated twice with 20 cc. fuming nitric acid each time. The syrupy residue is then mixed with 5 grams of a mixture of 4 parts anhydrous sodium carbonate and 3 parts saltpeter and fused. The solution of the fused mass is acidulated with hydrochloric acid and evaporated to dryness so as to separate off the silicic acid. In the filtrate of the solution of the residue, the sulphuric acid is determined in the usual way. The following figures were obtained for Ichthyol No. 3, a nickel crucible being used:

0.7850 g substance gave 0.6245 g BaSO<sub>4</sub>, equals 10.93% S.  
 0.8995 g substance gave 0.7080 g BaSO<sub>4</sub>, equals 10.81% S.  
 0.9880 g substance gave 0.7895 g BaSO<sub>4</sub>, equals 10.85% S.

With the method of Carius, 11.055% S were found. The figures obtained thus agree fairly well with those of the method of Carius. The following modification is however recommended since there often will be slight explosion if care is not exercised in heating the residue which has been oxidized with nitric acid, with the sodium carbonate and saltpeter. This is due to the presence of large amounts of not yet oxidized organic matter. It is thus possible that portions of the fused mass may be lost by being ejected from the crucible.

"About 0.5 gm. Ichthyol is evaporated three times with 10 cc. fuming nitric acid each time, and the thick residue is rubbed up with 5 gm. of a mixture of 4 parts anhydrous sodium carbonate and 3 parts saltpeter. As much as possible of this mass is transferred into a capacious nickel crucible, and a few drops of water are used to wash out all remnants from the dish. After drying, the mass is carefully fused. The fused mass is taken up with hot water and filtered. The filtrate is then acidulated with hydrochloric acid and the sulphuric acid precipitated in the usual way as barium sulphate."

The following figures were obtained:

0.4455 g Ichthyol No. 3 gave 0.3600 g BaSO<sub>4</sub>, equals 11.10% S.

With the method of Carius an average of 11.055% was obtained.

The amount of sulphur occurring as sulphate could easily be determined by the method of Thal (l. c.). In this sulphoichthyolic acid is precipitated by the addition of fresh white of egg and concentrated hydrochloric acid; the sulphuric acid present in the filtrate is then determined without heating with chloride of barium. Not more than 4 gm. of the preparation are dissolved in about 300 cc. of water. The white of a medium-sized egg, stirred up in about 100 cc. water is then added, and finally 5 cc. 25% hydrochloric acid with enough water to make 500 cc. After shaking, the whole is filtered. The sulphuric acid is determined without heating in 200 cc. of the filtrate by weighing as barium sulphate in the usual manner.

The amount of sulphonic sulphur present could only be determined as suggested by Thal (l. c.). Thal deducts the ammonia occurring as ammonium sulphate from the total ammonia. In the remainder, the sulphonic sulphur is calculated by allowing 17 parts of ammonia to 32 sulphur.

There is no practical method for determining the sulphonic sulphur directly. v. Hayek<sup>11</sup> recommends the following procedure for determining the total oxidized sulphur (sulphur occurring as sulphate and as sulpho-compounds): The solution of Ichthyol is acidulated slightly with hydrochloric acid and then precipitated with barium chloride. After having been washed, the precipitate is heated to red heat. According to this author, the sulphoichthyolic acid is precipitated quantitatively as barium sulphoichthyolate. The amount of barium sulphate remaining after heating is supposed to correspond to the oxidized sulphur occurring as sulphate and as sulpho-compounds.

The following experiments will show that the conclusions of v. Hayek are not correct and that only part of the sulphonic sulphur can be weighed in this way as barium sulphate. If organic sulpho-acids are heated under pressure with hydrochloric acid, the sulpho-acid group will be converted more or less completely into sulphuric acid. 1 gm. Ichthyol No. 3 was heated under pressure for some time up to 200° to 210° with 5 cc. fuming hydrochloric acid and 10 cc. water in a sealed tube. The contents of the tube were then diluted with water and filtered. In the filtrate, the sulphuric acid was then precipitated in the usual way as barium sulphate. Depending upon the length of time of heating, the following results were obtained:

on heating for six hours:

1.1300 g Ichthyol gave 0.3260 g BaSO<sub>4</sub>, equals 3.95% S.  
0.8270 g Ichthyol gave 0.2410 g BaSO<sub>4</sub>, equals 4.00% S.

on heating for twelve hours:

1.1630 g Ichthyol gave 0.3400 g BaSO<sub>4</sub>, equals 4.01% S.

If the amount of sulphur occurring as sulphate (Ichthyol No. 3 contains 1.5% sulphate sulphur) is subtracted, this would leave 2.5% sulphonic sulphur if the separation of the sulpho-acid group occurs quantitatively.

With Petrosulfol, which only contains sulphates in traces, the following figures were obtained on heating for six hours:

0.9957 g substance gave 0.2245 g BaSO<sub>4</sub>, equals 3.1% S.

Since sulphates are almost completely absent, the sulphur found by this method in Petrosulfol must occur as sulpho-compound.

By the method of determining oxidized sulphur according to v. Hayek the following figures were obtained for both preparations:

ICHTHYOL No. 3.

0.6219 g substance gave 0.0915 g BaSO<sub>4</sub>, equals 2.02% S.  
0.6219 g substance gave 0.0955 g BaSO<sub>4</sub>, equals 2.11% S.  
The average is 2.065% S.

PETROSULFOL.

0.7451 g substance gave 0.0605 g BaSO<sub>4</sub>, equals 1.12% S.  
0.7451 g substance gave 0.0615 g BaSO<sub>4</sub>, equals 1.14% S.  
The average is 1.13% S.

The amount of sulphonic sulphur can be determined by the following calculation: The amount of sulphur found in the form of sulphate is subtracted from the above results and the remainder multiplied by 2, since one atom of barium corresponds to two atoms of sulphur (as sulpho-acid). With Ichthyol 3 we get the following figures:  $2.065 - 1.5 = 0.565 \times 2 = 1.13\%$ ; with Petrosulfol:  $1.13 \times 2 = 2.26\%$  sulphonic sulphur. These amounts are considerably lower than those

obtained by us by decomposition with hydrochloric acid. Further experiments showed that sulphonic sulphur cannot always be completely converted into sulphuric acid, and the results often lack uniformity. The above experiments show that Ichthyol contains at least 2.5% sulphur in the form of sulpho-compounds and Petrosulfol at least 3.1%. The real figures are probably still higher since, according to Thal's calculation from the amount of ammonia present, 2.69 and 4.56% will be obtained.

It follows that the figures published by v. Hayek<sup>12</sup> for the amount of oxidized sulphur in Ichthyol and Ichthyinat must be too low.

It has been shown by further experiments that the decomposition of the sulpho-acids present in organic sulphur preparations is not complete if the substance is heated with hydrochloric acid to 200° to 210°. With Ichthyol 1 and Ichthium, results agreeing fairly well when calculated from the ammonia content were obtained:

	Decomposition with Hydrochloric Acid	Determined from the Ammonia Content
Ichthyol I.....	2.560 resp. 2.450%	2.65%
Ichthium .....	5.083 resp. 4.903%	5.04%

In the remaining experiments, the results obtained were however considerably lower. When two determinations were made, they did not agree sufficiently. In the case of Subitol, less sulphuric acid was found after heating with hydrochloric acid than by the direct method by the addition of egg albumin and hydrochloric acid. The reason for this could not be determined. From all this it follows that the sulphur combined as sulpho-compounds cannot be recovered quantitatively as sulphuric acid by heating with hydrochloric acid to 200° to 210°. It is therefore necessary that the amount be calculated from the ammonia content.

In order to determine the amount of sulphur present as sulphide, the amount corresponding to sulphates and sulpho-compounds must be subtracted from the total sulphur. A direct method has not yet been discovered.

The total ammonia is determined by distillation as follows: 5 gm. of the preparation are dissolved in about 150 cc. water and distilled after the addition of 10 cc. 50% soda lye and a few granules of zinc. With the aid of a cooler, the distillate is caught in N/2 hydrochloric acid. The excess of acid is titrated with N/2 soda lye, methyl orange being used as indicator. The same figures were obtained where duplicate determinations were made.

The ash was determined by incinerating 5 gm. of the preparation in a platinum crucible at a dull red heat, in every instance, the ash had a brownish red color and consisted chiefly of ferric oxide.

If the analyses of the different preparations be compared, it will be found that uniform figures were obtained with the different samples of Ichthyol except for the amount of dry residue (as high as 2.85% difference, probably to be explained by a loss of water by evaporation after the bottle has been opened in the pharmacies). The greatest variation calculated for dry residue was: For total sulphur, 0.6%; for sulphate sulphur, 0.12%; for sulphonic sulphur, 0.35%; for sulphidic sulphur, 0.55%; for the total ammonia, 0.16%, and for ammonium sulphate 0.50%. Greater uniformity in the preparation of so complex a substance is hardly possible.

Differences in the analyses of various samples of Ichthyol as reported by v. Hayek were not confirmed by us. Inasmuch, as the figures obtained by v. Hayek



for total ammonia and ammonium sulphate agreed among themselves and with our values, it is not likely that the difference in the contents of total sulphur and hence also in sulphidic sulphur will really be so marked as this author states (2.51 and 2.69%). It is more logical to assume that the author's estimation of total sulphur in the sulphur-rich Ichthyol has always and to a varying degree been too low.

The fact that the Ichthyol substitutes vary so much in their composition among each other and also as compared with Ichthyol is probably to be explained by the use of crude oils differing in composition and containing only small amounts of sulphur as sulphides. The action of all these preparations undoubtedly depends upon their content of sulphides. Unna has given special attention to the study of Ichthyol as a water-soluble, organic sulphur preparation. When he first recommended Ichthyol therapeutically he drew attention to the fact that the preparation possesses characteristic properties, and that these are due to the large amounts of sulphur in firm chemical union found in the crude Seefeld oil, and which occur in the finished product chiefly as sulphides.

Whether the processes to which the oil are subjected play an important role is less easy to answer. The present patent concerning the separation of sulpho-ichthyolic acid does not give us sufficient information. Since, however, the substitutes differ so considerably from the original preparation, it seems likely that the special methods of manufacturing these preparations are also of some importance.

From the stand-point of both the physician and the pharmacist it is therefore proper that each preparation should have its distinctive name (Ichthammon, Ichthium, Ichthyinat, Isarol, etc.) Our experiments have shown such variations in composition that it would be improper to designate these substitutes "Ichthyol" or "Ammonium ichthyolate," or to regard them as identical with the original Ichthyol.

Ichthyol is a very popular remedy and it would seem but proper to add it to the list of drugs official in the Pharmacopoeia. On the other hand, the preparation cannot be so characterized that its identity and uniformity will always be assured. The description of the Italian Pharmacopoeia, edition 1902, and of the British Pharmaceutical Codex, edition 1911, will not suffice to properly identify so complex a drug. The Italian Pharmacopoeia requires neither a qualitative nor a quantitative analysis of sulphur, and the British Pharmaceutical Codex merely states that an oil containing about 10% sulphur is furnished by the bituminous slate. Our investigations have however shown that the amount of sulphur and the way in which it is chemically combined varies with each preparation. In view of the inadequate directions for testing these preparations it is therefore improper to regard them as identical.

- (1) *Wien. klin. Rundschau*, 1898.
- (2) *Therap. Monatshefte*, 1903, 151.
- (3) *Pharmaceut. Zentralh.*, 1904, 198.
- (4) *Apoth. Ztg.*, 1906, 431.
- (5) *Wien. klin. Rundsch.*, 1907, Nos. 7 and 8.
- (6) *Pharm. Ztg.*, 1907, p. 952.
- (7) *Pharm. Ztg.*, 1907, p. 994.
- (8) *Midland Drugg. and Pharm. Rev.*, 1910, 44, 154.
- (9) *Apoth. Ztg.*, 1904, 431.
- (10) *Zeitsch. analyt. chem.*, 1907, 241.
- (11) *Wien. klin. Rundschau*, 1907, Nos. 7 and 8.
- (12) *Wien. klin. Rundschau*, 1907, Nos. 7 and 8, and *Pharm. Ztg.*, 1907, 952.