cal nature of the compound without sacrificing something of this ensemble of physical-chemical properties which determine its efficacy.

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PREPARATION OF NEOARSPHENAMINE[1]

BY FREDERICK W. HEYL AND GEORGE E. MILLER.

With the progress of clinical experience with the arseno compounds the attention of the medical profession is becoming centered upon neoarsphenamine for the reason that with it fewer untoward reactions are experienced, and because it is less toxic and may be readily administered in practice.

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[1] Received for publication April 24, 1922.

Neoarsphenamine (sodium 3 : 3′ diamino-4 : 4′ dihydroxyarseno-benzene-N-methylene sulphinate) is the practical solution of the idea of Ehrlich for producing an acidic arseno derivative which would furnish a neutral water-soluble sodium salt. In Ehrlich's[1] work this thought stimulated the production of sodium arseno-phenyl glycinate, but this drug has been entirely supplanted by neoarsphenamine.

This product is unusually sensitive to oxidation. Roth,[2] in an article written for the purpose of improving the clinical technic used in preparing solutions for injection, showed that shaking aqueous solutions of neoarsphenamine in air for 30 to 60 seconds greatly increased the toxicity of the solution. A preparation for which the original tolerance was maximum, when shaken one minute, now failed to pass sharply the test at the minimum legally allowable. In other words the physician in one minute can oxidize the product to such an extent that he completely nullifies the advantages gained by the elaborate technique of the chemist.

In producing this substance it is impossible to consider the isolation of a pure compound, and the end product is the precipitated reaction mixture which, however, contains the arseno compound quite uniformly. The problem therefore consists in so altering the manipulations as to produce a mixture of the required arsenic content and of as low toxicity as possible.

The preparation falls into four steps:

(1) The preparation of the arseno-base.
(2) The condensation with sodium formaldehyde sulphoxylate.
(3) The precipitation, filtration and desiccation of the product.
(4) Ampuling.

The most important of these steps is 3. The ampuling is next in importance.

The preparation of the arseno base has been discussed[3] in the literature. Although too much stress is perhaps placed on the corresponding clinical significance of too great refinements in the rat test, it is a fact that carefully prepared hydrochlorides vary from 90 mg./Kg. to above 130 mg./Kg. These variations produce no practical differences in the resultant neoarsphenamine. With an aberrant sample of arseno base, the hydrochloride of which is tolerated above 130 mg./Kg. it is possible to produce a preparation passing at 360 mg./Kg. but we have observed samples prepared from average base (barely passing the test at 100 mg./Kg.) from which a "neo" derivative was prepared, which when injected at 360 mg./Kg. was tolerated by 50% of the test animals. In our opinion, therefore, the preparation of the base in the first step does not materially affect the toxicity of the final product.

The intermediate free sulphinic acid which precipitates almost immediately from solution when sodium formaldehyde sulphoxylate is dropped into the solution of the hydrochloride is remarkably uniform in composition. We conduct this reaction at 25–27° for 15 minutes. Elevating temperature or increasing time introduces the element of variability which can be observed in the undesirable deepening of the color, and in altering the composition of the drug.

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[1] *Ber.*, 42, 36, 1909.

[2] *Pub. Health Reports*, 35, 2208, 1920.

[3] Ehrlich and Bertheim, *B.*, 45, 756, 1912; Kober, *J. A. C. S.*, 41, 442, 1919; Christiansen, *Ibid.*, 43, 2202, 1920; King, *J. C. S.*, 119, 1107, 1921.

We come now to the technically difficult mechanical part of the preparation. These difficulties have been surmounted on the commercial scale, as is evidenced by the fact that the average sample to-day is tolerated by the rat in doses of 250 mg./Kg. whereas for the first importations this test was set at 90 mg./Kg. The problem consists in precipitating, filtering, and drying the enormously soluble reaction products without oxidation. A suitable apparatus for this is described in the experimental part, along with a description of the sealing and preservation of the drug in ampuls.

The work in this laboratory has been carried out starting with 25 or 50 Gm. of crystalline analytically pure nitro-oxyphenyl-arsonic acid. In this paper the apparatus is described for the smaller scale, making the directions suitable for laboratory instructions.

The results are summarized at the end of the paper.

EXPERIMENTAL.

1. Reduction of Nitro-Oxyphenyl-Arsonic Acid.

Into a separate wide-mouth 3-liter bottle, equipped with stirrer and set up in a water-bath, are placed 1500 cc distilled water. To this are added 65 Gm. crystallized magnesium chloride and then 375 Gm. sodium hydrosulphite (80%). To this is added a cold solution of 25 Gm. pure nitro-oxyphenyl-arsonic acid in 86 cc 2 *N* sodium hydroxide but diluted to 420 cc with water. We have added this rather rapidly (5 minutes), with stirring. The mixture is warmed to 30–35°, and following Kober's directions the dirt from the hydrosulphite is filtered off, through asbestos at A, collecting in the suction flask B.

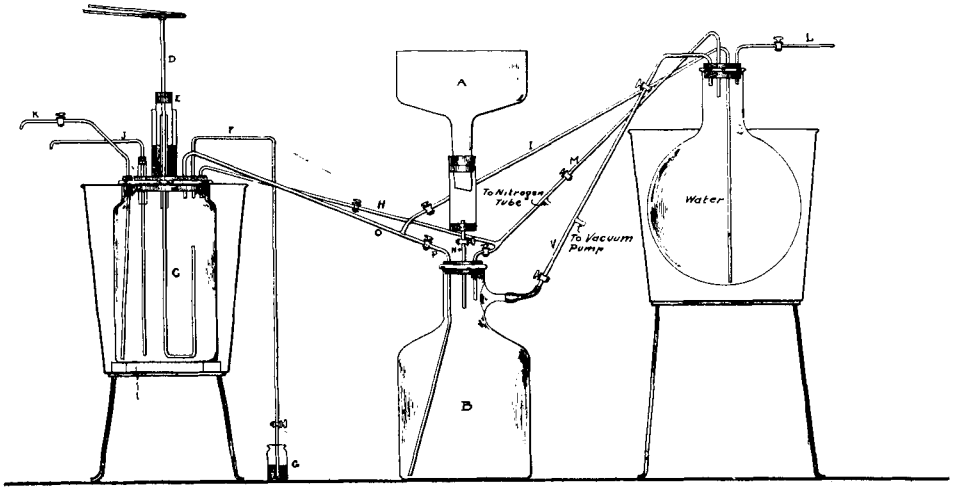


Fig. 1.—Reducer for Arseno-base.

Fig. 1 is a diagrammatic representation of an ideal reducer. The reducing chamber C carries a stirrer, D, with a large ($3^1/_2$") mercury seal at E. A safety tube, F, passes into a small mercury seal, G. The reaction mixture or air-free water can be blown in through O or I, respectively. J is a movable syphon for removing rinse water when washing the precipitated base by decantation, while K is the outlet for the precipitated base.

Beginning the preparation, the water flask is filled by opening L, closing M, I, and applying the vacuum at V. When filled, L is closed, the bath is heated and all air expelled by applying the vacuum. The bath is cooled and M opened to nitrogen.

All the rest of the apparatus is filled with water from A, it being necessary to blow it over into C through O, and this is all displaced by nitrogen which enters under pressure. The pressure from the tank is regulated so as to be related to the mercury trap at G.

It is into the apparatus thus prepared that the reaction mixture is filtered. A loss in yield is caused by delaying this step. By manipulating N, the asbestos can be washed out. The clear fluid is promptly blown into C and with a good arrangement not more than 5 cc is lost. The bath at C is at 45°. The stirrer is started, after raising J, and the reaction completed under nitrogen (H). The temperature is elevated to 55° in 10–15 minutes and then carried on for about two hours at this temperature. At the end of this time the stirrer is stopped and the base allowed to settle. The water from the bath is withdrawn. As soon as the base has settled out, the tube J is properly lowered and the supernatant fluid carefully blown off by closing the safety at F.

Thereupon after raising J, cold air-free water is blown in by opening F, and using I. The base is again allowed to settle, and the supernatant fluid blown off. This is repeated, and finally about 1 liter of water added. The base is thoroughly stirred and the suspension blown out at K, either into the filter (Fig. 2) or into a carbon dioxide filled separatory funnel. Where a permanent apparatus is not desired, this step can be simplified by taking the apparatus apart each time and inserting a wash-bottle arrangement which will work by gravity. For filtration of the base, with the exclusion of oxygen, we have found it convenient to combine filtration and desiccation in one operation, thus avoiding exposure. In most of our experiments the base was finally allowed to subside in a separatory funnel which was attached with the filter at A.

The cast iron filter and desiccator is shaped almost exactly like a large Frühling and Schultz desiccator. It carries two windows on the lid, and also in inlet tube B, carrying a ground-in stopcock at C. For filtering base we used one which was plated with German silver. The cast iron shell also carries a lower orifice, D, large enough to fit a No. 12 or No. 13 rubber stopper, E, and is controlled with a stopcock at F.

The shell also carries a gauge, G, and stopcock at H. This connects with the vacuum pump and a tank of air-free nitrogen or carbon dioxide. A shelf at I, I carries a lead-lined trough for drying agents and these are also placed in suitable vessels on the floor of the desiccator. K is a receiver for the filtrate.

The day before using this apparatus the Büchner is set in place (using a coarse alundum plate, or filter paper). Calcium chloride chiefly, with sulphuric acid and phosphoric anhydride are used for desiccation, and the cover is clamped evenly over the gasket L by means of six eye bolts, M. The chamber is evacuated to about 30 mm., and the bolts tightened down. This vacuum must hold until the next day, whereupon the chamber is filled with the inert gas. This is easily done by use of a Bishop and Babcock gas regulator at about 3 pounds pressure.

The connection at A being made, a vacuum is again prepared, evacuating the connections, and the apparatus is flooded with inert gas. H is then closed, a partial vacuum drawn by opening F, and the base is allowed to run into the funnel and filtration completed by opening F in a regulated way.

When finally a high vacuum is attained, F is closed and F and H connected with the pump for about two hours. After standing over night the quantities here used are dry. The apparatus is then flooded with carbon dioxide, and the base dropped into a weighed bottle. The yield in 40 runs varied from 13.4 Gm. to 16.0 Gm., averaging 15.1 Gm.

This arseno base contains 38.3% As.

$(C_6H_3(NH_2)\ (OH)As)_2$: Calc., As = 41.0

$(C_6H_3(NH_2)\ (OH)As)_2 \cdot 1^1/_2H_2O$: Calc., As = 38.2

The product is, however, probably a monohydrate (39.06% As), containing enough of the sulphonic acid derivative to lower the arsenic content. Theory therefore requires a yield of 18.25 Gm. The above yield is 83% of theory.

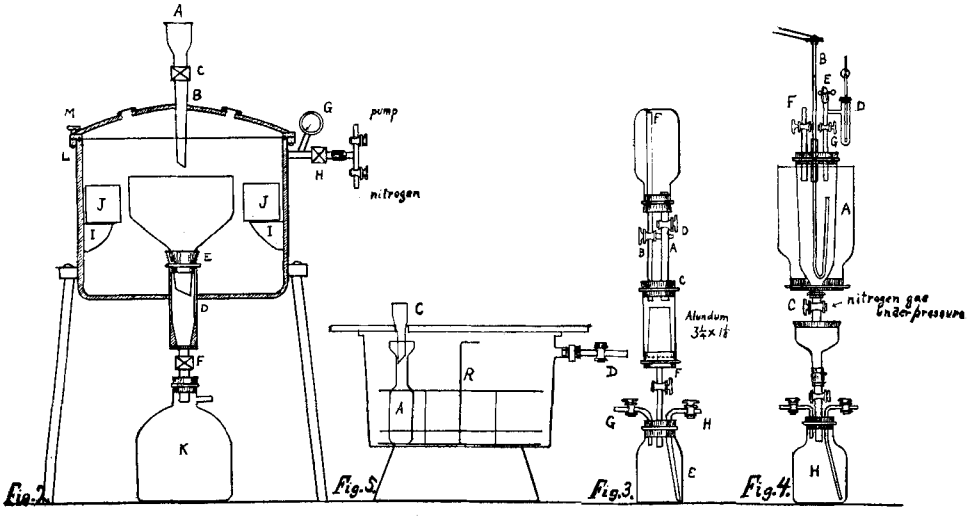
2. *Preparation of Arsphenamine.*

The base in part was converted into the hydrochloride. The solution of the hydrochloride was prepared in a 250-cc centrifuge bottle in which the base had been weighed. Upon it was poured a quantity of chilled methyl alcohol and a calculated quantity of 2 *N* methyl alcoholic hydrochloric acid. The mixture is kept cool in an ice bath and 3 Gm. charcoal are added and the whole is vigorously shaken under carbon dioxide until solution is complete. The solution is filtered through an alundum thimble (R. A. 360)* as described in principle by Kober.

The following table gives the reagents with various yields used in this series.

Base (Gm.)	13.5	14.0	14.5	15.0	15.5
2 *N* alcoholic HCl (cc)	36.9	38.3	39.6	41.0	42.4
Methyl alcohol (cc)	63.1	61.7	60.4	59.0	57.6

In the preparation of the hydrochloride the filtration (Fig. 3) is conducted by inserting the stopper bearing two tubes, A and B, into the bottle, flooding with CO_2 and then inverting and tightening the two-holed stopper C into the filter tube. B



Apparatus for preparing, filtering and ampuling neoarsphenamine solution.

Fig. 2.—Filter and desiccator for 8″ funnel; Fig. 3.—Anerobic filtration of hydrochloride; Fig. 4.—For preparing "Neo" solution; Fig. 5.—Ampuling neoarsphenamine.

is a three-way stopcock. A bottle, E, is connected at the lower opening F. The apparatus is evacuated to 15 mm. and then flooded with CO_2 from a gasometer connected at B. The gas is then passed up into the top bottle and the solution filtered, CO_2 running in at the top as the fluid recedes. When the filtration is complete the upper bottle is removed, a small funnel put at F and 20 cc absolute methyl alcohol allowed to drop into the filter. The gasometer was then connected with F or B and the fluid drawn through.

By closing F, applying gas under pressure at G, this solution is slowly blown into the precipitating ether through H. For this purpose 1200 cc chilled absolute ether are poured into a 2-liter separatory funnel provided with a stirrer. Also carbon dioxide under pressure is bubbled up through the lower orifice to displace air. The alcoholic solution (0°) is dropped in during 5 minutes and the agitation completed in 3–5 minutes more. The stopped stirrer is raised from the fluid and

* This was washed and burned out in a muffle furnace each time.

CO_2 is stopped from below, while the preparation is well protected from air by the layer of supernatant ether.

The separatory funnel is now attached to the cast iron filter and desiccator. The top of the separator may be connected with a CO_2 gasometer, but this probably offers no advantages.

For this filtration the Büchner is supplied with a porous alundum plate (cemented in with a silica cement) over which a hardened filter paper is laid. The desiccator is charged with paraffin, $CaCl_2$, H_2SO_4 and P_2O_5. This filtration requires only a small part of the fluid to be run through as the precipitated arsphenamine separates readily. The precipitate is washed with 150 cc absolute ether, and dried for two days.

In this work the material was removed to a weighed dish and dried to constant weight *in vacuo* over P_2O_5, before ampuling.

The yields and toxicological findings are summarized in Table I.

The following are the results of 9 runs.

TABLE I.—ARSPHENAMINE DOSES IN EXPERIMENTS. MG./KG.

Sample.	% As.	Yield.	90.	100.	110.	120.	130.	M. T. D.
173	31.5	15 Gm.	.....	.....	+++++	+----	.....	110
174	31.0	17	+++++	++++-	+----	.....	.....	100
175	30.8	....	+++++	+++++	-----	.....	.....	100
181	30.2	13.5	.....	+++++	++---	.....	.....	100
182	31.1	15.8	.....	.....	+++++	++---	.....	120
183	31.3	15.7	.....	++++-	++---	++-	++-	100
A 1	31.4	16.2	+++++	3L; 7D	++---	.....	.....	90
A 2	31.2	16.2	+++++	++++-	+----	++---	.....	100
171	30.8	15.5	.....	.....	+++++	+++++	+++--	130

Average tolerance = 105 mg./Kg.

These results indicate the significance of the 100 mg./Kg. test which is officially required. It is for all practical purposes a maximum value.

We experimented with Kober's method for precipitating the hydrochloride.[1] The method was followed precisely. The product is entirely different in its physical properties. It requires boiling water for solution.

TABLE II.—ARSPHENAMINE TESTS. MG./KG.

Sample.	% As.	Yield.	100.	110.	120.	135.
8	....	15 Gm.	13L; 2D	.....	.....	.....
9	....	14	5L;	.....	.....	.....
12	30.6	15	.....	.....	++++-	.....
10	31.2	12	.....	+++++	7L; 3D	+----

Estimated average, about 120 mg./Kg.

Although only a few experiments were conducted we are inclined to agree that the use of hydrochloric acid as a precipitant favorably affects the results of the rat test. Since the appearance of Hunt's[2] paper we felt that the continued agitation with hot water might have been a favorable influence in these tests. We find that it may increase the tolerance of an ether-precipitated sample by 10 mg./Kg. We note that the British Medical Research Committee[3] believe that the varying toxicity of different samples is related to differences in the physical properties of the product, which determine the state of physical dispersion in which the free base comes out of solution when the alkaline solution is injected intravenously.

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[1] *Loc. cit.*

[2] *J. A. M. A.*, 76, 854, 1921.

[3] Reports upon the Manufacture of Salvarsan and Its Substitutes, 1919.

We tested in duplicate two samples made by ether precipitation by making the acid solution with (*a*) cold water, (*b*) with hot water and agitation. These were neutralized as soon as dissolved and injected at 120 and 110 mg./ Kg., respectively, with the following results:

Sample 173 { hot ++++−
cold +−−−−−

Sample 174 { hot +++−−
cold +−−−−

3. Preparation of Neoarsphenamine.

After this preliminary work we directed our attention to the production of a series of preparations of neoarsphenamine, using for the most part the filtered methyl alcoholic solution as the starting material for the condensation.

The condensation was carried out in the apparatus sketched in Fig. 4. The percolating cylinder A, fitted with a rapidly revolving stirrer, B, is flooded for some time with carbon dioxide or nitrogen gas from the 3-way stopcock C. This gas leaves through the trap at D and E, and when all the air is displaced the solution of the hydrochloride is let in at F. The jacket keeps this solution at 25–27°. It is agitated by the gas from below and the stirrer is started later.

This is followed by a solution of freshly recrystallized pure sodium sulphoxylate. Of this 11.6 Gm. are used for 14.0 Gm. base, and 12.4 Gm. where the yield of base is 15.5 Gm. The sulphoxylate is dissolved in a minimum quantity of water at about 50° C. This requires about 12 cc water. F is closed and the reaction allowed to run 15 minutes.

At the end of this time 10 cc water are added and this is followed gradually by the calculated quantity of 20% sodium carbonate solution (20.3 cc for 14 Gm. base to 22.5 cc for 15.5 Gm. base). This operation is a critical part of the preparation. It is necessary to keep the volume of water used small enough to facilitate the subsequent precipitation of the fluid, and yet large enough to dissolve the sulphinic acid. The above figures, although small and favoring the subsequent precipitation, usually yield a clear solution.

The stopcock F is now connected with a gasometer and the pressure is great enough to force the hydrosulphite liquor up the tube in D, and the fluid is filtered through asbestos into the flask H, which has been previously evacuated, after preliminary filling with CO_2.

The solution is now dropped with stirring into an ice-cold mixture (850 cc + 700 cc) of absolute alcohol (99%) and absolute ether, in an atmosphere of CO_2. The product precipitates quantitatively and the filtration is conducted as has been previously described for arsphenamine. The drying was carried out for 2–3 days and the product was passed through a No. 40 mesh sieve and dried to constant weight *in vacuo* over P_2O_5. This we consider of importance, as it desiccates the precipitated excess of sodium formaldehyde sulphoxylate and thus prevents the subsequent production of garlic-like odors and dampening of the product. This might be a factor in subsequent deterioration.

The product was transferred to large constricted test-tubes (2) which were evacuated to 15 mm. and filled with CO_2 and sealed.

From these test-tubes the product was ampuled as follows:

An 8″ Scheibler tubulated vacuum desiccator was equipped with a flat plate glass top which had an aperture bearing a No. 5 rubber stopper. This was equipped with a copper rack, R, holding 36 ampuls (A) (see Fig. 5). The rack is filled with sterilized ampuls, the aperture C closed and a vacuum drawn. This is filled with carbon dioxide. A constant positive pressure of the gas is forced in at D and the ampuls filled with weighed amounts, shifting the plate as

required. The cork is replaced, the filled ampuls again evacuated and refilled afresh with CO_2, and then maintaining a constant positive pressure of the gas the ampuls are lifted out one by one through C and sealed. We use soft glass ampuls to reduce possible exposure. The desiccator is charged with calcium chloride, and the gas used is air-free and dried through sulphuric acid.

In seventeen experiments under the vicissitudes of laboratory production the yields varied from 18 to 26 Gm. with an average of 23.5 Gm. or 75% of the theory calculated from arseno base. The arsenic content was controlled by dilution with sodium chloride C. P. when necessary. It varied from 18.0 to 18.7%. The average was 18.45% As. The M. L. D. varied from 200 mg./Kg. (2) to 300+ mg./Kg. (4) with an average of 255 mg./Kg. Since the maximum tolerated dose[1] is 346 mg./Kg. the discrepancy is about 90 mg./Kg.

In runs made under highly satisfactory conditions, involving a perfect desiccator, the maximum appeared to be more closely approached. These are listed in Table III.

TABLE III.—NEOARSPHENAMINE EXPERIMENTS. DOSES IN MG./KG.

Sample.	% As.	Yield.	240.	280.	320.	M. T. D.
177	18.5	23 Gm.	++++−	++++−	.....	280+
178	18.5	22	.....	++++−	.....	280+
183	18.4	18	.....	7L; 1D	6L; 1D	320+
185	18.5	21	.....	.....	++++−	320+
189	18.5	24	.....	+++++	−−−−−	280

Here an average of 300 mg./Kg. approaches within 46 mg./Kg. of a maximum value. While the average tolerance above mentioned of 255 mg./Kg. is somewhat disappointingly low, it should be pointed out that a series such as those given in Table III represents perfect technical smoothness with a quite difficult set of operations.

We carried out a few further experiments with the thought of cutting the time factor down to a minimum of 8 hours. This introduced other difficulties and is probably not feasible on larger scale. It is the better laboratory method for student work. To accomplish this purpose the base which separated by sedimentation was transferred to a 250-cc bottle and centrifuged instead of being filtered. The bottle was filled to the neck, covered, and the wet base, which occupies 65 cc, was obtained directly, about 1 P.M. The excess water was blown out with CO_2 and the base was taken up in 75 cc ice-cold methyl alcohol and solution was effected by the addition of 5.5 cc concentrated HCl. This solution was bone-coaled and filtered as before and the reaction conducted as described above, using a longer time for the condensation, 20–25 minutes.

With the additional water here present, it is necessary to precipitate the reaction mixture with a large volume (1800 cc) of absolute alcohol at 0–5° C. After sedimentation the product is filtered in the usual manner. Samples were diluted when necessary by the addition of the calculated quantity of C. P. sodium chloride.

The variations here are greater than in the method first described because of the great solubility of the product and the increased quantity of water. The toxicity is slightly decreased by this technique:

[1] Hart and Payne, *J. A. C. S.*, 44, 1922.

TABLE IV.—NEOARSPHENAMINE EXPERIMENTS. DOSES IN MG./KG.

Sample.	Yield.	% As.	200.	240.	280.	320.	M. T. D.
128	19 Gm.	18.2	+++++	+++++	+++++	+++++	320+
136	17	18.6	+++++	++−−−	.....	.....	200
138	20	18.5	.....	.....	++++−	+++−−	300+
141*	25	18.1	+++++	+++++	+++++	+++++	320+

Average tolerance = 285 mg./Kg.

* Failed at 360 mg./Kg.

All preparations on this small scale were very dry.

A determination of loss on drying at 78° in CO_2 gave volatile matter = 1.2%.

SUMMARY.

1. Two laboratory methods are described in detail for the preparation of neoarsphenamine.

2. The nature and dimensions of the variation in its toxicity action are compared with values previously reported.

3. Toward average samples, prepared by these processes, the rat shows a tolerance of 255 mg./Kg. Under particularly favorable manipulation this value approaches more closely to the maximum.

4. The increase in toxicity which results in the final steps amounts to 90 mg./Kg. for the average sample, but with perfected conditions we have approached within 45 mg./Kg. (*i. e.* M. T. D. = 320+ mg./Kg.).

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SOLUBILITY OF PHENOL IN LIQUID PARAFFIN.

Jules Cofman-Nicoresti reports experiments on the solubility of phenol in liquid paraffin, in the *Pharmaceutical Journal and Pharmacist* of April 29, 1922, p. 349. The conclusions the contributor draws from the experiments are as follows:

"1. The solubility of phenol in liquid paraffin at 15° C. is not above 1 percent.

"2. The quantity of phenol, exceeding 1 percent, dissolved in liquid paraffin by means of heat will, when cool, separate in a liquid, oily layer, which layer will occupy the lower part of the solution."

Further references made in the article are reprinted:

"Boemingham (*Exper. Cancer.*, December 8, 1921; see *P. J.*, Vol. 108, p. 298) points out the dangers of using liquid paraffin as a substitute for glycerin in phenol solutions. He mentions a case in which a young physician prescribed as ear-drops, for a boy of ten, suffering from earache, liquid phenol in liquid paraffin. A glass dropper was used to administer the drops; the pure phenol collected in the tip of the dropper and was injected in the child's ear, with the result that half the tympanic membrane was destroyed and the external meatus and the auricle very badly corroded.

"A similar case came before the law courts in a North town about two years ago. A prescription for ear-drops containing 6.2 percent of pure phenol in liquid paraffin had been dispensed by a pharmacist. The patient, after using half of the solution in the bottle (1 oz. bottle), complained of pains in his ears, and suspecting that the prescription had been wrongly dispensed, sent it to an analyst, who found 10.3 percent of phenol in the solution.

"An action was taken against the chemist for wrongly dispensing the prescription, and, in spite of the chemist's defense, the jury, apparently impressed by the analytical evidence, found for the plaintiff, giving heavy damages against the chemist with the result that the unfortunate pharmacist was sent to the bankruptcy court."