[CONTRIBUTION FROM THE LABORATORIES OF THE UPJOHN COMPANY]

TOXICITY OF NEO-ARSPHENAMINE

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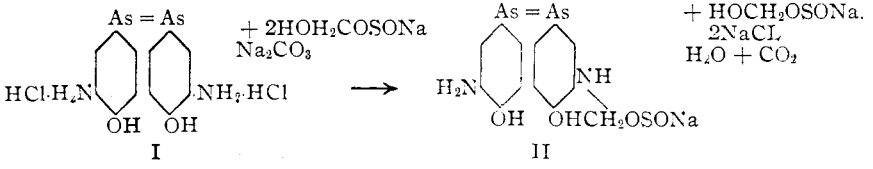
The basic patent[1] of Korndorfer and Reuter describes the production of a neutral solution of a derivative (II) of arsphenamine (I) derived by condensation with sodium formaldehyde sulfoxylate.



The first motive for this preparation was the hope that this solution would be more easily prepared than that of the phenolate made by treating (I) with an excess of sodium hydroxide. As a matter of fact, the solution is much more difficult to produce and is unstable, but is found in practice to be much less toxic.

In order to make this much less toxic derivative available clinically it was necessary to produce a dry powder, and this proved a matter of considerable difficulty. So readily is it oxidized that it is not advisable to increase the manipulations for the purpose of purification of the intensely soluble derivative. The commercial product is a pharmaceutical mixture of the reaction products containing 18–20% arsenic rather than a chemical individual of 32% arsenic.

The pharmacological examinations (with rats) at the Hygienic Laboratory[2] showed that while imported neo-arsphenamine was at first being tested at 90 mg./kg., the standard minimum tolerated dose which rats should survive should be increased to 180 mg./kg. This was later increased to 200 mg./kg. It may be doubted if the neo-arsphenamine first imported into this country was examined in this respect, for with the first year of work the toxicity of this drug was greatly decreased.

Schamberg, Kolmer and Raiziss[3] showed that for commercial neo-arsphenamine the maximum tolerated dose varied from 180 to 300 mg./kg. or more (rat), the average tolerance being 254 mg./kg. Of 24 samples examined 5 were tolerated in doses above 300 mg./kg. In the recorded table only two rats are used for this test. Later these experimenters[4] reported the average of a large number of lots of neo-arsphenamine to be

[1] Korndorfer and Reuter, U. S. pat. 1,053,300 (1913). Reissue No. 13,848 (1914).

[2] *Hygienic Lab. Bull.*, **113**, (1918): 3 samples passed tests at 100, 175 and 150 mg./kg.

[3] Schamberg, Kolmer and Raiziss, *Am. J. Med. Sci.*, **160**, 197 (1920).

[4] Schamberg, Raiziss and Kolmer, *J. Am. Med. Assoc.*, **78**, 6, 402 (1922).

280 mg./kg. Roth[5] reports a sample which was tolerated in doses of 420 mg./kg. and had an arsenic content of 19.5%. Another sample (18.8% arsenic) from the same source was tolerated in doses of 280 mg./kg. There is, therefore, a great variability in the toxicity of various products when studied by this method. We may add that we do not believe that these figures convey any clinical significance unless they fall below 200 mg./kg.

What is the cause of this variability? In the first place, the difference in arsenic content has an influence. A sample containing 20% of arsenic and borne at 280 mg./kg. would be tolerated at 310 mg./kg. had it contained only 18%. Second, there is a variability in the tolerance of the albino rats used. This may amount to 100 mg./kg., as we will show in the experimental part. Third, Raiziss and Falkov[6] have indicated that the analyses of various samples show the presence of considerable quantities of the dimethylene sulfinic acid derivative. In the "neo" derivative having Formula II the ratio of arsenic to sulfur should be 2:1, while if two groups were substituted it would of course be 2 : 2. A finding of 2 : 1.4 as found in several samples would indicate a mixture of 60% of the mono-, with 40% of the disubstituted arsenical. In view of the well-known decrease in toxicity produced by replacing an amino hydrogen by an acidic radical (*e. g.*, acetanilide from aniline) it would appear that this consideration may be of importance in the variability. Macallum[7] on the contrary reports that "analysis of best preparations has indicated that it is not possible to form products of sulfoxylate:arsenic ratio exactly 1:2, but that products closely approximating to this are quite practicable." Furthermore, neither of these papers contains toxicity determinations of the material analyzed.

What appeared at first to be another important factor in producing variability in neo-arsphenamine was the toxicity of the original arsenical. Arsphenamine itself is not used for the commercial production of neo-arsphenamine. This is prepared from the base which is dissolved in the requisite amount of hydrochloric acid. The base is readily oxidized upon exposure, and the variable nature will be disclosed by the toxicological examination of the hydrochloride. This preparation is, however, produced in rather remarkably uniform quality. Schamberg, Kolmer and Raiziss[3] examined 22 samples which were tolerated in doses varying from 90 mg./kg. to above 120 mg./kg. The average tolerated dose was 0.105 g. per kg. The government requirement of 100 mg./kg. is a high requirement, and in fact is probably not always passed in production. In our opinion the 90 mg./kg. requirement is a more reasonable one. Christiansen[8]

[5] Roth, *U. S. Pub. Health Repts.*, **35**, No. 38, 2208 (1920). *Arch. Derm. Syph.*, **2**, 300 (1920).

[6] Raiziss and Falkov, *J. Biol. Chem.*, **46**, 209 (1921).

[7] Macallum, THIS JOURNAL, **43**, 643 (1921).

[8] Christiansen, *ibid.*, **43**, 2204 (1921).

reports a finding of 110 mg./kg. as the average. This drug as marketed is quite stable and uniform and white rats react to it acutely in a most definite manner. We have shown that using arsphenamine varying in toxicity from 90 mg./kg. to 130 mg./kg. there is no corresponding variation in the toxicity of the resulting neo-arsphenamine.

According to King[9] the variable sulfur found in arsphenamine is partly sulfate and partly 3,3′-diamino-4,4′-dihydroxy-5-sulfo-arsenobenzene hydrochloride. It is reported as being more toxic than arsphenamine (mice). This "nuclear" sulfur would of course introduce a second factor into the ratio of arsenic to sulfur in the "neo" derivative. This factor can be demonstrated by distinguishing between sulfoxylic sulfur, and nuclear sulfur (the sum being total sulfur). While sulfonation always results to a slight extent in the production of arsphenamine, this side action is more pronounced in the production of neo-arsphenamine.

In our experimental work, two sets of experiments were conducted: small scale experiments, in which the mechanical factors such as filtration and desiccation were eliminated; and semi-commercial (50–100 tubes) experiments in which we could compare the errors involved in various mechanical procedure.

In this paper the former control experiments are reported, and it will be observed that when the rats used for testing are normal and when mechanical errors are avoided neo-arsphenamine is quite a constant product and is tolerated in doses of 320 to 355 mg./kg. for 20–18% material. In another paper we will take up briefly the second series of experiments, and the chief source of variability.

Experimental

Market Conditions.—Our laboratory results agree with those mentioned above. We made a special endeavor to find a sample comparable to the high test sample reported by Roth. We followed the official method and excluded unfit rats by means of weight curve. We find that 360 mg./kg. is a maximum figure. This product was, therefore, one in which commercial production is perfected under ideal conditions. We report a typical series of results.

TABLE I

TOLERATED DOSES IN MG./KG. OF COMMERCIAL SAMPLES

Sample	% As	200	240	280	320	360	400	M. T. D. mg./kg.
A	19.0				+----			280
B	18.7		+++	+++	+++	++++-	----	360
C	18.9	+++	+++		---			280
D	20.2			+++	+++++	+++++	+---	360
E	19.0		+----	+---	---			200
F	18.5				+++++			320
G	18.5				6L; 2D			320

+ Lived. - Died.

[9] King, *J. Chem. Soc.*, **119**, 1107, 1416 (1921).

The variability as indicated ranges from 200 to 360 mg./kg. The test on "E" is inaccurate due to change in test animals. This is a serious matter, because the determination of such a value as the maximum tolerated dose is sufficiently defective even when the same stock is used.

Standardization of White Albino Rats.—In any pharmacological work it is important to ascertain results by comparison. Thus in assaying digitalis, crystalline ouabain forms a basis for comparison. In pituitary work histamine is used. In this work the test animals offer an element of variability which hitherto has not been rigidly controlled.[10]

The dimensions of the error which may result by making the same test on different rats are indicated below.

TABLE II

VARIATION IN RESISTANCE TO SAME DOSES IN MG./KG.

Sample	200	240	280	300	320	360	Discrepancy
M 138	$13^{+}; 0^{-}$	$12^{+}; 0^{-}$	$10^{+}; 1^{-}$	+++++			Over 100 mg./kg.
Ditto[a]	$10^{-}; 0^{+}$						
M 168	+-+-+	+++++	+----				About 40 mg./kg.
Ditto	+----						
H 187[b]			+----		--+++	-----	About 40 mg./kg.
Ditto			+++++		+----	$5^{+}, 5^{-}$	

[a] Run independently by another pharmacologist. With different rats the tests at 200 mg./kg. were satisfactory.

[b] Control rats of this batch sacrificed and autopsied showed heavy infection with B. bronchosepticus which lowered their resistance.

On the other hand, it is true that while the test animals vary they are quite uniform in most cases. Roth[11] suggests the possibility of seasonal variation in the resistance of rats, stating that they are perhaps more resistant to neo-arsphenamine during the summer than during the winter. It does not appear that an accurate estimate of the factor of deterioration can be made unless the test animals are standardized, *i. e.*, unless the tests at different dates are made comparatively against a standard.

At the present time it is impossible to accept a sample of neo-arsphenamine as a control. Not to speak of deteriorative possibilities, there are unavoidable variations in arsenical content. The work of Raiziss proves the possibility of other chemical variations. Furthermore, the real object of the official test is to limit the oxidation of the product through mechanical errors in manufacture. Hence it appeared to us that a suitable standard would be a 4% solution of neo-arsphenamine (20% arsenic) prepared from analyzed arsphenamine in such a way that all manipulative errors are eliminated. By using the conditions of the experiment on p. 1154 a solution results which when injected is tolerated in doses of 320 mg./kg. This we consider a standard. In our work we have discarded all rats in

[10] See Hooper, Kolls and Wright, *J. Pharmacol.*, **18,** 141 (1921).

[11] Roth, *U. S. Pub. Health Repts.*, **36,** No. 41, 2538 (1921).

which more than one death in 5 tests resulted at 280 mg./kg. (see, *e. g.*, H-187, Table II).

Maximum Tolerated Dose of Neo-arsphenamine.—This was determined by use of the apparatus in Fig. 1. The object was to prepare in the calibrated 100cc. flask A, a 4% solution of neo-arsphenamine (20% of arsenic).

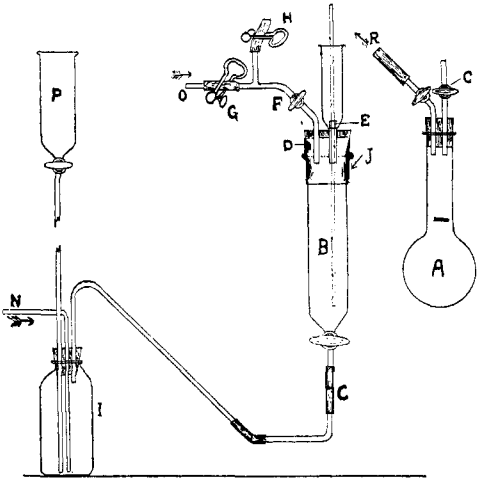


Fig. 1.—Apparatus for preparation of standard solutions.

The 50cc. cylindrical separatory funnel B is the reaction chamber. Into this is placed the methyl alcohol, and the lower orifice C is connected with oxygen-free nitrogen gas under a pressure of 8 cm. of mercury. This gas is led through the hydrosulfite wash bottle I fitted with the safety tube P which is also used in the regulation of the pressure of the nitrogen. Thus the chamber is swept out and the mixture agitated. The cylinder carries a 2-hole stopper D which is flexibly connected by means of elastic rubber band tubing J such as is used for Gooch crucibles. One of the openings bears a cut 25cc. pipet into which is inserted a close fitting glass rod bearing a piece of rubber tubing E which serves to make a tight joint when necessary. The other opening in the stopper bears a stopcock F, which connects through G with a gasometer of nitrogen, and with an outlet at H. All the nitrogen is carefully washed with an alkaline hydrosulfite solution. As there is occasionally a trace of air in compressed nitrogen, and since the same is more frequently true for carbonic acid, this requires attention.

The apparatus and tubes are swept out with nitrogen gas. Then F is left open and H is opened but G is closed. The weighed arsphenamine (2.581 g. for 31% material) is dusted into the pipet, the glass rod removed for the time being and the material dissolved in the agitated methyl alcohol. The pipet is brushed out and rinsed with a few drops of methyl alcohol and dried and the rod fitted loosely into place. By slipping along the rubber tubing the rod can be used to break up any gummy masses of the hydrochloride which may form.

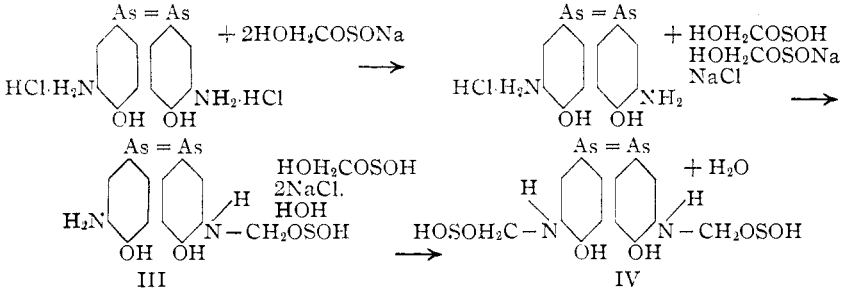
Long standing at this point causes the separation from the alcohol of the sulfur-containing impurities, so when solution is completed, H is closed and G opened and the cylinder is placed in a thermostat at 25°. The calculated quantity (1.95 cc. of 100% solution) of analytically pure[12] sulfoxylate is added, allowed to drop in by releasing H, and a few drops of water are used to rinse the tube. E is fitted tightly into position and the reaction proceeds. The calculated quantity of 10% sodium carbonate solution is finally added at E and allowed to run in by opening H.

The nitrogen is turned off at C and the reaction cylinder after removal from the thermostat is connected with the nitrogen-filled bulb A which is wired on. A is evacuated (through R) to 10–15 mm. and, after closing E and H and opening G, the solution

[12] Heyl and Greer, *Am. J. Pharm.*, **94**, 80 (1922).

of the neo-arsphenamine is drawn into A, nitrogen gas from the gasometer through O displacing it. Most of the methyl alcohol is lost by evaporation, while the cylinder is quantitatively rinsed with air-free water added at E with the exclusion of all air. This is readily and perfectly accomplished by keeping G and F open and opening H only when it is desired to allow liquid to flow at E. It is convenient to use the rod as a policeman. Finally, the brilliantly clear solution is made up exactly to the mark, a layer of toluene run over it and it is ready for the toxicological tests.

With this apparatus we now varied a number of conditions and observed the effect on toxicity. It is stated in the patent literature[13] that if one uses an alcoholic medium instead of an aqueous one there is a decreased toxicity. Another variation consists in operating with the precipitating base rather than the hydrochloride. When working in alcoholic solution the reaction involved two dissolved substances, *i. e.*, hydrochloride and the sulfoxylate. The latter functions in two ways. First, it liberated the amino group, which promptly reacts with the sulfoxylic acid and the free "neo" acid with one sulfoxylic group (III) is almost immediately precipitated.



As this acid (III) is insoluble in alcohol and in water, this factor controls the reaction and a fairly uniform product is formed. The product is quantitatively precipitated in less than 5 minutes and greatly increasing the time does not conspicuously alter the pharmacological or chemical findings.

In view of the discovery of Raiziss and Falkov[6] of a considerable admixture of the dimethylenesulfinate derivative in some samples, we endeavored to form this material by raising temperature, or increasing time, or increasing volume of medium, the idea being to render the precipitate at first formed somewhat more soluble and thus assist in the introduction of the second group, giving the disubstituted derivative (IV).

These changes immediately complicate the product with by-products. These do not appear to consist entirely of the dimethylene-sulfinate derivative. Instead, the sulfur enters the ring.

Since the aqueous alkaline medium favors the solution of the reaction product, several experiments were run in which the sulfoxylate had ample opportunity to react beyond the first stage but this did not favorably affect the product.

[13] Ger. pat. 260,235, **1913**. Compare Ger. pat. 245,756, **1912**.

The following table of reactions in methyl alcohol indicates the fact that the reaction is practically completed in 10 minutes. When the temperature is raised even to 35° for 30 minutes discoloration and increased toxicity result.

TABLE III

METHYL ALCOHOLIC SOLUTION-ACID SOLUTION

		Condition of reaction				Doses: mg./kg.			
Expt.	Arsphenamine	Temp. °C.	Vol. Cc.	Time Min.	As %	280	320	360	400
H-166	A-1	25	15	10	19.8	+++++	++++-		
H-179	171	25	15	10	19.6	+++++	++++-	+++--	+---
H-185	M	25	15	10	20.1	+++++	++++-	5L:5D	
H-191	M	25	45	10	20.1	+++++	+++--	+----	
H-196	M	35	15	10	19.8	+++++	+++++	+++--	
H-197	M	35	30	30	17.0		-----	-----	
H-182	171	50	15	10	19.7			++---	+----
H-198	M	25	20	20	19.7	+++++	+++++	+---	

Found: Maximum Toxicity = 320 mg./kg.

The reaction was carried out once (Expt. 195) by dissolving the hydrochloride in 15 cc. of alcohol, precipitating the base with the calculated quantity of sodium carbonate solution (10%), adding the sulfoxylate and allowing the reaction to proceed, testing it at 30-minute intervals for complete solubility in dil. carbonate solution. After 3 hours the reaction had not gone to completion. The toxicity of this preparation was not determined.

In aqueous solution the following experiments were run.

TABLE IV

AQUEOUS SOLUTION

		Condition of reaction				Doses: mg./kg.			
Expt.	Arsphenamine	Temp. °C.	Vol. Cc.	Time Min.	As %	280	320	360	400
H-193	M	25	45	10-30[a]	20.3	++++-	++++-	-----	
H-138	138	25	15(50% alc.)	20	18.7	++++-	++++-		
H-199	M	25	25	60	19.2	++++-	-----	----+	

[a] After running the reaction for 10 minutes the calculated quantity of 10% sodium carbonate solution was added, after which a clear solution resulted in 25 minutes. The reaction was discontinued after 30 minutes.

The chief object of the experiments in aqueous solution was to learn whether the dimethylene-sulfinic acid derivative was produced in greater amount and how this affected the toxicity of the preparation. This might be expected to be less toxic. All the runs in both alcoholic and aqueous medium were subjected to the following analytical control.

Analyses of the Products Tested Above.—For this purpose 3 samples

of the solution of 5, 5 and 25 cc., respectively, were removed. Duplicate estimations of the arsenic were made by the Lehman method. For a 20% neo-arsphenamine 0.04 g. of arsenic (10.67 cc. of 0.1 *N* sodium thiosulfate solution) is required.

The 25cc. sample diluted to 70 cc. was cooled to 0° and precipitated with a slight excess of 2 *N* hydrochloric acid and then centrifuged. The precipitated neo-acid was washed thrice with 70 cc. of water at 0° acidulated with 2 cc. of 2 *N* hydrochloric acid, then centrifuged to obtain a sharp separation. The resulting free acid was dissolved in a slight excess of 2 *N* sodium hydroxide solution and made up to 50 cc. This was divided into 3 parts of 10, 20 and 20 cc., respectively. Ten cc. was used for the arsenic determination in the precipitated neo-acid. One of the 20cc. aliquot portions was used for the determination of total sulfur by the regular sodium peroxide fusion method. The other portion was used for the determination of all the sulfur except nuclear (sulfoxylate sulfur) by the method given by Raiziss and Falkov.[6] This involves oxidation with an excess of iodine solution and precipitation of barium sulfate.

The difference between total sulfur and sulfur by the iodine oxidation method may be taken as sulfur which has been introduced into the ring as a sulfonic acid derivative or united with the arsenic as an organic arsenic sulfide. The calculations are reported in terms of atomic ratios. Theory for the pure monomethylene-sulfinic acid derivative requires 2 arsenic : 1 sulfur. The findings are as follows.

TABLE V

DISTRIBUTION OF SULFUR

	Sulfur in original arsphenamine			Condensation				Sulfur distribution in neo-arsphenamine		
Sample	Total S	S by iodine	Nuclear S	Solvent	Time Cc.	Min.	Temp. °C.	Total S	Neo.[b] S	Nuclear S
H-166	0.15	0.04	0.11	CH_3OH.	15	10	25	1.15	1.06	0.09
H-179	0.15	0.07	0.08	CH_3OH.	15	10	25	1.18	1.04	0.14
H-185	0.10	0.08	0.02	CH_3OH.	15	10	25	1.27	1.18	0.09
								1.26	1.12	0.14
H-191	0.10	0.08	0.02	CH_3OH.	45	10	25	1.21	1.15	0.06
H-196	0.10	0.08	0.02	CH_3OH.	15	10	35	1.34	1.19	0.15
H-197	0.10	0.08	0.02	CH_3OH.	30	30	35	1.37	1.23	0.14
H-182	0.15	0.07	0.08	CH_3OH.	15	10	50	1.39	1.17	0.22
H-198	0.10	0.08	0.02	CH_3OH.	20	20	25	1.39	1.25	0.14
H-193	0.10	0.08	0.02	HOH	15	10–30[a]	25	1.18	1.04	0.14
H-199	0.10	0.08	0.02	HOH	25	60	25	1.30	1.16	0.14

[a] See Table IV.

[b] Neo-sulfoxylic sulfur.

These results show that when this reaction is carried out at 25° for ten minutes a relatively pure mono derivative is formed (4 to 15% of the di derivative being formed). When the time is doubled 25% of the

di compound is formed. Varying the dilution seemed to have no appreciable effect on the introduction of the methylenesulfinic acid group. Increasing the temperature 10° resulted in an increase in the di derivative (about 4%). A further increase up to 50° gave no greater percentage of the di compound. Increasing the time from 10 to 30 minutes at 35° gave a slight increase in the substitution (about 4%). When this reaction was carried out at higher temperature and longer times a secondary decomposition took place with more of the sulfur entering the nucleus, a marked coloration of the solution and a somewhat higher toxicity.

Influence of Toxicity of Intermediate Base on Toxicity of Resultant Neo-arsphenamine

We recognize the stability of arsphenamine, particularly in acid solution, but the base itself is more prone to oxidation. It would appear probable that this factor might have a final influence, particularly as neo-arsphenamine is prepared from base rather than hydrochloride. Since this work was originally outlined to study the last part of the preparation, (*i. e.*, the condensation of sodium formaldehyde sulfoxylate), only standardized hydrochlorides were used instead of the unstandardized base. It will be admitted that any irregularities in base production will be accentuated in the corresponding hydrochlorides, because it involves one further manipulation (*i. e.*, precipitation and desiccation of the product). In using hydrochlorides of various toxicities we have been astonished to find that a variability of 40 mg./kg. in the starting material has been without conspicuous influence upon the neo-arsphenamine solutions prepared therefrom.

The following determinations will show the nature of the starting material used in the above described experiments.

TABLE VI

TOXICITY OF ARSPHENAMINE USED

Doses: mg./kg.

Sample	As %	90	100	110	120	130
A-1	31.3	+++++	3L; 7D	++---		
171	30.8			+++++	+++++	+++--
M	32.1		++++-	+----	-----	

By comparing this table with Table III, it will be observed that a 19.6% of drug (H-179) made from the hydrochloride passing the tests at 130 mg./kg. makes a distinct failure at 400 mg./kg.; whereas the sample H-185 made from M which while just passing 100 mg./kg., gives an equally good neo derivative. Even A-1, failing to pass at 100 mg./kg. gives a neo derivative of standard tolerance.

One reason for this uniformity is probably found in the fact that the free sulfoxylic acid present in the reaction mixture in large amounts

must tend to eradicate traces of oxidation products, for the free acid is quite unstable, breaking down easily.

$$CH_2OH.OSOH + O \longrightarrow HCHO + H_2O + SO_2.$$

The Lethal Activity of Neo-arsphenamine.—The characteristic delayed effects which result in the official tests, make it advisable to extend the period during which the rats are under observation to 7 days. This is in marked contrast to the acute poisoning due to arsphenamine, for which the period of observation is but 2 days. Roth[14] has plotted a curve showing this difference between the drugs. With commercial arsphenamine the maximum number of deaths occurs on the first day, whereas the fourth day is the critical day for neo-arsphenamine poisoning.

In testing solutions of freshly prepared high test neo-arsphenamine, we find that toxic doses behave very similarly to arsphenamine itself. The acute lethal effect is at a maximum in 24 hours as is shown by the solid line curve in Fig. 2.

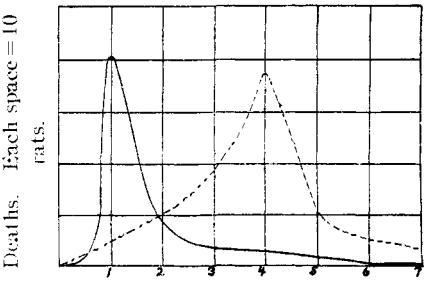


Fig. 2.—Difference in the death rate of rats after poisoning with solutions of freshly prepared, high test neo-arsphenamine and with the solid commercial product.

The findings of Roth[14] for the death rate of rats treated with commercial neo-arsphenamine (dry powder) is given by the broken line.

It would appear that when the mono derivative is prepared in pure condition and when traces of oxidation products are excluded, the toxic action of higher doses is acute. It should be noted in passing, where high test products such as B and D (p. 1152) are being tested a similar acute death rate frequently results.

Summary

1. The toxicity of commercial samples of neo-arsphenamine ranges from 200 to 360 mg./kg.

2. In determining the toxicity of neo-arsphenamine the variability of the test rats is a very important factor. Examples were given where 40 to 100 mg./kg. difference was obtained by the same test made on different animals.

3. A method is suggested which can be used for the standardization of the neo-arsphenamine test rats.

4. The toxicity of the arsphenamine (90–130) is shown to have a negligible effect on the toxicity of the neo-arsphenamine derived from it. In the condensation of arsphenamine to neo-arsphenamine the influence

[14] Roth, *Arch. Derm. Syph.*, **2**, 295 (1920). See also Ref. 10.

is shown of the change of solvents, dilution, time, and temperature on the toxicity, introduction of the methylene-sulfinate group and sulfur distribution.

5. A curve is given showing the acute lethal activity of a freshly prepared solution of neo-arsphenamine.

6. The introduction of a methylene-sulfinic acid group in the arsphenamine increases the tolerated dose of the arsenical from 110 mg./kg. to about 320 mg./kg. (20% of arsenic). Introduction of the second group was complicated with side reactions giving a higher toxicity.

In conclusion we wish to thank Dr. Frederick W. Heyl at whose suggestion this work was carried out.

KALAMAZOO, MICHIGAN

NEW BOOKS

Within the Atom. A Popular View of Electrons and Quanta. By JOHN MILLS. D. van Nostrand Company, N. Y., 1921. xiii + 215 pp. 36 figs. 13 × 19.5 cms. Price, $2.00 net.

The rapid advance that has been made in the past decade or two in the investigation of the structure of the atom, and which is still in full progress, has attracted the interest not only of scientists but also of the general reading public. Mr. Mills in undertaking the extremely difficult task of presenting the experimental results and theoretical conclusions of the subject in a form that will be popularly comprehended, has gone to unusual lengths in excluding everything of mathematical nature and in introducing elaborate illustrations drawn from everyday life. The result is a very readable book which appears to serve its purpose acceptably. While no attempt is made to furnish references to the literature, the reader is familiarized with the names of the principal investigators in the various fields considered.

The author has rather wisely disregarded historical order and with the assumption of some knowledge of a few of the fundamentals of physics and chemistry begins with the presentation of the electronic structure of the atom, and passes successively to isotopes, radioactive phenomena, conduction of electricity through gases, and general electronics. Atomic numbers are introduced through a consideration of X-radiation, the quantum theory through photo-electric effects; the structure of crystals as revealed by X-rays is simply and clearly presented. The final chapter is devoted to the consideration of energy and its availability. In an appendix several pages are given to an elementary exposition of the use of the decimal exponential system of writing numbers, which though undoubtedly necessary, is a rather sad commentary on our common school methods of teaching mathematics. The appendix contains definitions, magnitudes, and discussions of various units and terms employed