[CONTRIBUTION FROM THE LABORATORY OF THE SYNTHETIC DRUG COMPANY, LTD.]

EXAMINATION OF NEOARSPHENAMINE. II. THE CONSTITUTION OF THE FRENCH DRUGS

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In a previous paper¹ the nature of American neoarsphenamines, but not of the European preparations, was indicated. The composition of some of the latter compounds is dealt with briefly below.

Some of these products, it is true, are similar to the American ones, but others, notably those of French origin, consist entirely of doubly substituted arsphenamines, the formation of which may be illustrated as follows:

The most noticeable physical characteristic of the French compounds is that, unlike the neoarsphenamines, which are soluble in neutral and alkaline solution alone, they dissolve unchanged in weakly acid media as well.² The former darken and decompose at relatively higher temperatures, are less affected by atmospheric oxygen, and are of lower toxicity, but also of lower trypanocidal activity, than the neoarsphenamines. Otherwise the two kinds of drug much resemble each other, for example, in their ion reactions, solubilities and behavior on any sort of drastic treatment. The separation of the individual compounds in a pure state is rendered somewhat difficult by a tendency towards decomposition, so that up to the present, the identification of these has depended on analysis of samples as they stood.

In connection with the recognition of such compounds, the iodometric

¹ Macallum, *THIS JOURNAL*, **43**, 643 (1921).

² Including sulfuric acid,--sparing solubility in this reagent being the usual test for arseno compounds [Ehrlich, *Ber.*, **44**, 1263 (1911)]. Consequently, it seemed a question whether such products were not substituted at the arseno as well as the amino groups. However, as soluble derivatives like these could not be made from arsenobenzene, or its intermediates, the writer concluded that the preparations were, after all, merely N,N'-di-substituted derivatives of arsphenamine.

The series includes also less definite neutral complexes which are more readily decomposed than the above by mineral acids with the almost complete regeneration of arsphenamine salts. The latter are taken to be molecular compounds, but the distinction between these and the others is not very well marked.

method described in the first communication has been extended for analysis of the methylene-bisulfite group, which appears to rank in importance with the sulfoxylate in these preparations. The development consists essentially in making use of the oxidation figures obtained when a preparation is treated with iodine successively in acid and alkaline solution, and from these deriving the group configuration by the aid of the elementary analysis.

In the following table are shown the iodine requirements found to hold for the principal reducing groups in such compounds.

TABLE I
IODINE REQUIREMENTS FOR PRINCIPAL GROUPS

Group formula	Group name	Molecular iodine acid solution <i>M</i>	Requirements in alkaline solution <i>M</i>
--CH ₂ OSONa	-methylene-sulfoxylate	4 ^a	6
--CH ₂ OSO ₂ Na	-methylene-bisulfite	0 ^a	4
arsphenamine base	7.755 ^b (c. g. $K \times 8M$)	15.02 ^b ($k' \times 16 M$)

^a Reinking, *Ber.*, **39**, 1069 (1905).

^b The oxidation and substitution of "606" by iodine under the conditions described in this paper are not quite quantitative. Thus a sample of the pure drug gave the following titration figures.

Cc. of 0.1 <i>N</i> iodine required by 1 g. of powder in		
	Acid solution	Alkaline solution
Found	165	310
	160.5	315
	160.5	316.5
Av.	162	313.8
Calc. for As:31.3%	167.1 (8 <i>M</i>)	334.2 (16 <i>M</i>)

Sulfoxylate and formaldehyde bisulfite are more completely oxidized, however.
Formaldehyde sulfoxylate (m. p. 64–5°, uncorr.)

Cc. of 0.1 <i>N</i> iodine required by 1 g. of substance in		
	Acid solution	Alkaline solution
Found:	257.5	390
Calc. for HOCH ₂ OSONa.2H ₂ O:	259.5 (4 <i>M</i>)	394.5 (6 <i>M</i>)

Formaldehyde bisulfite (m. p. 78–9°, uncorr.)

Found:	2.5	259
Calc. for HOCH ₂ OSO ₂ Na.H ₂ O:	0	263 (4 <i>M</i>)

Analytical Procedure

The complete oxidation analysis may be carried out in the following steps in order to conform to the technique indicated in the original paper.

Partial Reducing Power.—Two-tenths g. of powder is dissolved in 10 cc. of distilled water in a 500cc. flask, acidified with 25 cc. of 0.5 *N* sulfuric acid, immediately treated with 50 cc. of 0.1 *N* iodine, and titrated back with thiosulfate and starch after 3 minutes' shaking. The cc. of iodine required multiplied by 5 gives the partial reducing power of 1 g. of powder.

Total Reducing Power.—One-tenth g. of powder is dissolved in 50 cc. of water and immediately treated with 100 cc. of 0.1 *N* iodine solution. After 3 minutes' shaking, 10 cc. of 2 *N* sodium hydroxide solution is added and the mixture shaken again for 3 minutes, when it is diluted with 50 cc. of water, acidified with 10.5 cc. of 2 *N* sulfuric acid and titrated back with thiosulfate solution, using, finally, starch. The cc. of iodine required multiplied by 10 is the total reducing power per gram of powder.

Arsenic.—The percentage of arsenic determined by Lehmann's method is multiplied by 5.172 (or 775.5/149.9) to give the cc. of iodine reduced by the arseno or arsenide radical in 1 g. of powder. When this amount would exceed the partial reducing power found, the presence of oxygenated arsenic groups is indicated.

Arsphenamine.—The percentage of arsenic times 10.02 (or 1502/149.9) equals the total cc. required by the group.

Sulfoxylate.—The iodine used by any sulfoxylate present is found by subtracting that required by the arsenic from the partial reducing power. This divided by 3.960 (or 400/101) gives the percentage of sulfoxylate (as $-\text{CH}_2\text{OSONa}$). The total iodine requirement of the sulfoxylate is 1.5 times the preceding number.

Bisulfite.—The iodine absorbed in the oxidation of any methylene-bisulfite in the preparation is found by subtracting from the total reducing power the added total iodine requirements from the arsphenamine and sulfoxylate groups, according to the following example, which shows the titer of a well-known drug.³

Calculation of Sulfoxylate.—

Cc. of 0.1 <i>N</i> iodine per g. of powder	
Partial reducing power, (1) 125.4 (2) 116,	av. 120.7
Iodine required by arsenide radical, calc. (20.22×5.172)	104.5
Partial iodine requirement of sulfoxylate	16.2
whence sulfoxylate $(16.2/3.96) = 4.09\%$ and the total requirement of the sulfoxylate	24.3

Calculation of Bisulfite.—

Total reducing power (1) 331; (2) 341.5; (3) 317;	av. 329.8
Total iodine required by arsphenamine group (20.22×10.2) or	206.2
Total iodine requirement of sulfoxylate	24.3
	230.5
Difference	99.3

This iodine requirement divided by 3.41 (or 400/117) gives the percentage of methylene-bisulfite (as $-\text{CH}_2\text{OSO}_2\text{Na}$). Thus in the above, this group was found to be present to the extent of 29.12%.

Determination of the Sulfur Groups.—The computation of results obtained by oxidation and elementary analysis is illustrated by tabulating the figures obtained with the same preparation.

³ It should be mentioned that the errors here are greater than have been noticed in subsequent titrations. The most nearly uniform results are obtained when solution is effected in an indifferent atmosphere.

TABLE II

ANALYSIS

Element or Group	Av. % found	Molecular proportions	
As.....	20.22	2 ^a	
N.....	4.3	2.274	
Cl.....	0	0	
S.....	11.43	2.64	
Na.....	7.52	2.422	2.422
Sulfone (presumably).....		0.218	
Sulfoxylate ($-\text{CH}_2\text{OSONa}$)...	4.09 ^b	0.30	
Bisulfite ($-\text{CH}_2\text{OSO}_2\text{Na}$)....	30.17	1.9108	
Total.....			2.210
Sulfonate ($-\text{SO}_3\text{Na}$).....			0.212

^a The cryoscopic depression of 0.26° found for the 2.95% water solution corresponds to a molecular weight of 209.9 g. Calc. for pure $\text{C}_{14}\text{H}_{14}\text{O}_8\text{N}_2\text{As}_2\text{Na}_2$: 598.2 g. Ionization is naturally a factor here. Arspphenamine itself under similar conditions gives low molecular weights.

^b Free sodium sulfite (Na_2SO_3 or NaHSO_3) if present in small amounts would not readily be distinguishable from sulfoxylate.

The Commercial Products

Rather more variation has been observed in European than in American products, no two makes of the former being alike; variation has been found, too, in different lots of the same make of drug. The makers' claims as to the constitution of a number of these preparations have not been substantiated by analysis. Graphic structures that are ascribed by the writer to several French compounds are shown below:

^a This was found to differ entirely from lot to lot.

In confirming the composition of products like the above by synthetic methods, it has been found that not more than 2 sulfur groups could be introduced into their structures except where one was non-reducing, such as the sulfonic group, and this was assumed to have migrated to the nucleus after a manner already known.⁴ Of the sulfur groups, the substituting activity of the sulfoxylate was seen to be the most marked, the

⁴ King, *J. Chem. Soc.*, 119, 1415 (1921).

formation of bisulfite derivatives often being of a secondary nature.

The following are examples of true neoarsphenamines.

The toxicological and therapeutic actions of the French drugs are compared with those of other arsphenamine preparations in the appended table. The figures show the results obtained in this laboratory with representative commercial samples, using mice infected with trypanosoma equiperdum.

TABLE III
RELATIVE DOSES

Preparations	As %	Curative dose G. per k.	Tolerated dose G. per k.
Arsphenamines.....	30	0.0075-0.0125	0.15-0.19
Sodium arsphenamines.....	20	0.015 -0.025	0.25-0.3
Neoarsphenamines.....	20	0.0225-0.04	0.3 -0.4
French neo mixtures.....	20	0.04 -0.06	0.4 -0.5

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A SYNTHESIS OF BETA-CHLORO-ALLYL CHLORIDE

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The interesting properties possessed by compounds containing the allyl group ($\text{CH}_2\text{:CH.CH}_2$) have invited chemical investigation, even during the earlier periods in the development of organic chemistry. In addition to synthetic applications, it has been shown, particularly during the last decade, that the allyl residue possesses interesting properties from a pharmacological standpoint. In consideration of the importance of allyl compounds it is therefore surprising that so little attention has been paid β -chloro-allyl chloride, $\text{CHCl:CH.CH}_2\text{Cl}$. This may be attributed in part to the fact that the literature contains no procedure for its successful preparation. Its non-availability, as well as the necessity for utilizing it in some investigations in progress in this laboratory, led the writers to develop a synthesis which afford its preparation on a practical scale.

¹ This paper is constructed from a dissertation presented by Edwin J. Fischer to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy.