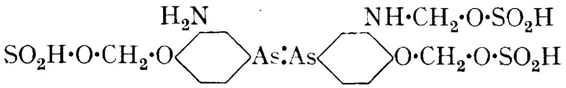
183. *The Constitution of Sulpharsphenamine. Part II. A New Interpretation.*

By W. J. C. Dyke and Harold King.

In a previous communication (J., 1933, 1003) we showed that commercial sulpharsphenamines agreed in composition with a trimethylenesulphurous acid derivative of salvarsan base, and formulated sulpharsphenamine as the sodium salt of **3** : 3′-diamino-4 : 4′-dihydroxyarsenobenzene-*OO′N*-trimethylenesulphurous acid (I).



(I.)

The main reasons which led to this formulation were as follows. Newbery and Phillips (J., 1928, 116) treated the hydrochlorides of a series of anilines and *o*-, *m*-, and *p*-aminophenol derivatives in aqueous solution with two molecular proportions of formaldehyde, followed after a minute's interval by two molecular proportions of sodium hydrogen sulphite. The total sulphur, by a fusion method, and the amount of sulphur oxidised to sulphate under Elvove's conditions (iodine in alkaline solution) were then determined: out of nineteen substances examined, only six showed a deficiency in sulphur oxidisable to sulphate by alkaline iodine and these six were all *o*-aminophenol derivatives. In five of these six cases the atomic ratio of " unoxidised " sulphur to nitrogen approximated to unity. It was not possible to alter this ratio by taking excess of the reagents, for, when arsphenamine was treated with four, six, or eight proportions each of formaldehyde and sodium hydrogen sulphite, the ratio of " unoxidised " sulphur to nitrogen was again unity. In other words, *o*-aminophenol derivatives have the specific property of fixing one sulphur-containing group in such a way that it is not oxidised to sulphate by alkaline iodine.

We showed conclusively that the methylenesulphite groups of commercial sulpharsphenamines were part of the molecular structure. By our distillation method of estimating methylenesulphurous acid radicals, three were found to be present, and of these three, approximately one only was oxidised to sulphate by Elvove's method. Since we showed that crystalline mono-*N*-methylenesulphites of anilines and anilinearsonic acids gave a quantitative yield of sulphate by Elvove's method, it was a reasonable deduction that in the trimethylenesulphite, sulpharsphenamine, the methylenesulphite groups which do not appear as sulphate on oxidation with alkaline iodine are present as *O*-methylenesulphite groups. Such an interpretation was supported by the results of hydrolysis by hydrochloric acid at 0°, a monomethylenesulphite being precipitated in which the whole of the sulphur could be oxidised to sulphate by alkaline iodine.

We realised, however, that our interpretation of the results was open to criticism, for no *O*-methylenesulphites of phenolic substances were known and our own attempts to prepare such failed, and in addition it was very surprising that *O*-methylenesulphite groups, in contradistinction to *N*-methylenesulphite groups, should not be oxidised to sulphate by Elvove's method. No alternative explanation could, however, be devised which would reconcile the results of Newbery and Phillips with our own.

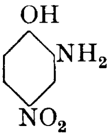
In development of our programme of study of the correlation of the therapeutic properties with degree and type of substitution in the group of methylenesulphoxylate and methylenesulphite derivatives of arsphenamine base we attempted to prepare a fully substituted *OO'NN'*-tetramethylenesulphite of salvarsan base by the action of six molecular proportions of formaldehyde followed by six molecular proportions of sodium hydrogen sulphite. The solid product was a typical sulpharsphenamine and on analysis it yielded the following results, which are expressed as atomic ratios. In the second row are the results of the analysis of the product precipitated from an aqueous solution of this sulpharsphenamine by glacial acetic acid, a reagent which allows of the separation of any inorganic salts present.

TABLE I.

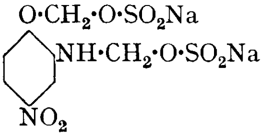
	As.	Total S.	Oxidised S (Elvove).	Unoxidised S.	CH_2O.
Original product	2	3·6	0·43	3·2	3·3
After $CH_3·CO_2H$	2	3·3	0·54	2·8	3·2

This table shows that there are more than three combined methylenesulphite radicals in the product and of these, almost three escape oxidation to sulphate by Elvove's method. On the basis of the views we have developed, these three groups should be attached to phenolic hydroxyl groups, of which only two are available. This result is typical of several such products obtained with a high degree of substitution and it necessitated a critical re-examination of the problem of the constitution of sulpharsphenamine.

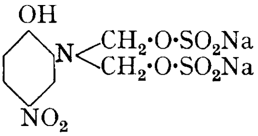
In our earlier communication we recorded unsuccessful attempts made to prepare crystalline methylenesulphites of *o*-aminophenol derivatives which would show the Elvove anomaly. We have now isolated three crystalline dimethylenesulphites of suitable *o*-aminophenol derivatives. When 4-nitro-2-aminophenol (II) in hydrochloric acid solution is treated with four molecular proportions of formaldehyde for 60 seconds, followed by four molecular proportions of freshly prepared sodium hydrogen sulphite, a clear solution is obtained from which, after removal of the sulphur dioxide by aspiration and subsequent neutralisation, a very soluble crystalline *dimethylenesulphite* of 4-*nitro*-2-*aminophenol* can be isolated by fractional crystallisation but with considerable difficulty. By making use, however, of a chance observation that this dimethylenesulphite reacts with another molecule of sodium hydroxide to yield a *trisodium* derivative which crystallises well from solutions rich in methyl alcohol, it was possible to isolate from the original reaction mixture a pure substance $C_8H_7O_9N_2S_2Na_3,2H_2O,1\frac{1}{2}MeOH$, in 87% yield. A portion of the methyl alcohol is retained on drying at 120° and is essential for crystallisation of this salt, since



(II.)



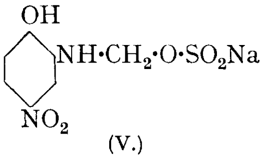
(III.)



(IV.)

no crystallisation occurs with other alcohols. When this trisodium salt is neutralised with one equivalent of hydrochloric acid, the previously mentioned dimethylenesulphite of

4-nitro-2-aminophenol can be isolated in 84% yield. There are only two possible formulæ, (III) and (IV), for such a dimethylenesulphite, and the observation that it can form a tri-sodium salt is in favour of formula (IV). This constitution is substantiated by a comparison of the results of electrometric titration (see Fig.) of this dimethylenesulphite with those obtained with the corresponding *mono*-N-*methylenesulphite* of 4-*nitro*-2-*aminophenol* (V) by means of the glass electrode. For this determination we are indebted to our colleague, Dr. W. J. Elford.



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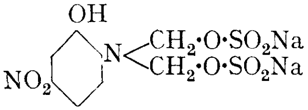

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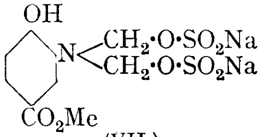
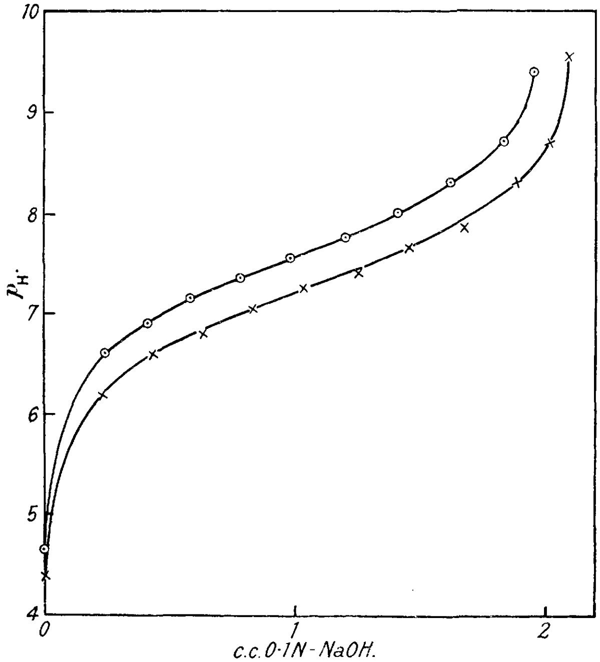


(VII.)

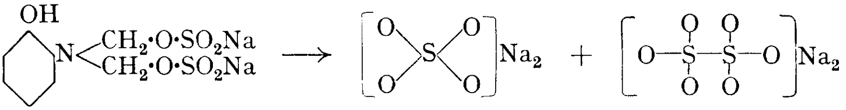
From 5-nitro-2-aminophenol hydrochloride and from 4-carbomethoxy-2-aminophenol hydrochloride by condensation with formaldehyde and sodium hydrogen sulphite in succession it has been found possible, but again with considerable difficulty, to isolate both the *mono*-N-*methylenesulphites* and the *di*-NN-*methylenesulphites* (VI) and (VII) respectively in the crystalline state. Since (VII) was a colourless substance, it could be titrated with 0·1*N*-alkali and thymolphthalein; it consumed approximately one equivalent of alkali —an observation also in support of the assigned structure.



Upper curve : sodium 5-*nitro*-2-*hydroxyanilino*-N-*methylenesulphite* (0·0594 *g. in* 5 *c.c.*).
Lower curve : disodium 5-*nitro*-2-*hydroxyanilino*-NN-*dimethylenesulphite* (0·0902 *g. in* 5 *c.c.*)

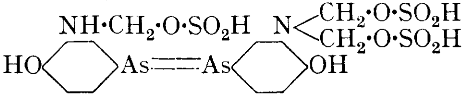
Crystalline dimethylenesulphite derivatives of substituted *o*-aminophenols of known constitution now being available, a close study was made of the applicability of Elvove's method of oxidation to these substances. 2-Hydroxy-5-nitroanilino-*NN*-dimethylenesulphite (IV), when oxidised by alkaline iodine, gave erratic results, for out of a total of 14·2% of sulphur found by distillation and estimated as barium sulphate, the amount found by Elvove's method ranged between 6·9 and 9·2% and thus bore no stoicheiometric relation to the total sulphur or the nitrogen content of the parent substance. The *NN*-dimethylenesulphites (VI) and (VII) gave 61 and 64% respectively of their sulphur as sulphate under Elvove's conditions.

The striking observation that the sulphur in a mono-*N*-methylenesulphite should behave in a different way from that in an *NN*-dimethylenesulphite made it necessary to inquire into the fate of the sulphur which escaped oxidation to sulphate. For this purpose the highly substituted experimental sulpharsphenamine (p. 806) proved very suitable, since only 12% of its sulphur appears as sulphate on oxidation with alkaline iodine. On examination of the acid filtrate after quantitative separation of barium sulphate it was found that, if more hydrochloric acid was added and the solution was boiled down for ½ hour, there was no visible precipitate, but if boiled down still further for an additional 1·5 hours there was a copious separation of barium sulphate. If to the original acid filtrate of a control experiment the same amount of hydrochloric acid was added, followed by a quantity of sulpharsphenamine equal to the starting material and the solution boiled, then within 10 minutes there was a marked appearance of barium sulphate and after 30 minutes' boiling 65% of the sulphur introduced had appeared as sulphate. These experiments demonstrate that the " unoxidised " sulphur under the Elvove conditions cannot be present as sulphite or methylenesulphite, but must be present in a form which on prolonged digestion with mineral acid yields sulphate. The only explanation which covers the observations is that the missing sulphur is present as dithionate. The analytical detection of dithionates usually depends on the formation of sulphur dioxide and sulphuric acid without separation of any elementary sulphur when a solution is boiled with moderately strong mineral acid. The detection of sulphurous acid is not possible in our solutions owing to the presence of oxidising agents, but the way in which barium sulphate appears is exactly paralleled by control dithionate solutions containing barium ions. We also find that dithionate is not converted into sulphate by alkaline iodine. It is generally agreed that the sulphur atoms in dithionates are linked together and we suggest that it is the proximity of the two methylenesulphite groups which favours dithionate formation. The action of alkaline iodine on these *NN*-dimethylenesulphites of *o*-aminophenols is therefore a dual action, a portion of the sulphur being oxidised to sulphate and a portion to dithionate.



It is a remarkable observation that in the case of a highly substituted sulpharsphenamine as much as 88% of the methylenesulphite groups should appear as dithionate, a reaction which has no counterpart in inorganic chemistry where dithionate formation from sulphites and iodine plays but a minor rôle (Mellor, " A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. X, 579; compare, however, Sokoloff and Maltschewsky, *J. Russ. Phys. Chem. Ges.*, 1881, **1**, 169).

On our present view commercial sulpharsphenamine conforming to B.P. 1932 corresponds approximately to a sodium salt of 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene-*NNN′*-trimethylenesulphurous acid (VIII)



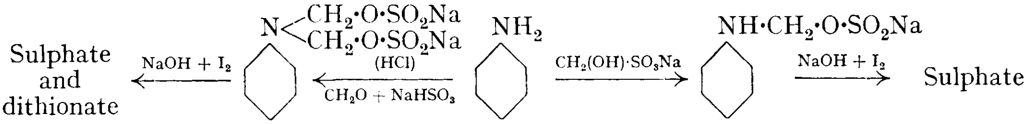
(VIII.)

and the whole of our experimental observations both in this communication and in our previous one are in agreement with this structure. In particular the observation that 4-nitro-2-aminophenol hydrochloride, when allowed to react in succession with four molecular proportions of formaldehyde and sodium hydrogen sulphite, gives at least an 87% yield of an *NN*-dimethylenesulphite is an indication that the main attack in such circumstances falls on the amino-groups, and the same probably applies to arsphenamine when subjected to the same treatment.

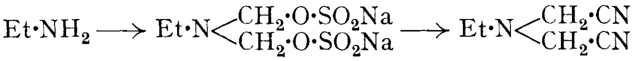
There remained only one outstanding difficulty, that of explaining why the Elvove phenomenon according to Newbery and Phillips's experimental results should be confined to *o*-aminophenol derivatives. This necessitated a repetition of the work of Newbery and Phillips on aniline, *o*-anisidine, *o*-aminophenol, *p*-aminophenol, 4-amino-2-hydroxyphenylarsonic acid, and arsphenamine, with the result that we failed to substantiate their findings. On the contrary we find that anilines in general, when treated in acid solution with two molecular proportions of formaldehyde, followed by sodium hydrogen sulphite, yield a solution in which the whole of the sulphur can be estimated by our distillation method for methylenesulphite groups, but when examined by Elvove's alkaline iodine method show a marked deficiency in the amount of sulphur found as sulphate. In fact, aniline, *o*-anisidine, *o*-aminophenol and *p*-aminophenol show a deficiency of sulphur appearing as sulphate amounting to somewhere between 0·5 and 1·1 atoms of sulphur. Furthermore the ratio of " unoxidised " sulphur, that is, sulphur not appearing as sulphate, to nitrogen in the case of arsphenamine does increase with increasing proportions of formaldehyde and sodium hydrogen sulphite and may be considerably more than unity. The Elvove phenomenon is thus not a specific property of *o*-aminophenol derivatives but of anilines in general.

It follows that it should be possible to isolate *NN*-dimethylenesulphites of anilines containing no hydroxyl groups by the action of formaldehyde and sodium hydrogen sulphite in succession on their hydrochlorides. This we have been able to accomplish quite readily in the only case so far examined, namely, *m*-nitroaniline. As might now be expected, *disodium* 3-*nitroanilino*-NN-*dimethylenesulphite* shows the Elvove phenomenon in striking fashion.

In conclusion, the results recorded in our previous communication and those just described enable us to say that anilines in general, when condensed with preformed sodium formaldehydebisulphite, form almost exclusively mono-*N*-methylenesulphites in which the whole of the sulphur can be found as sulphate when oxidised by alkaline iodine; but if their hydrochlorides are treated at room temperature with excess of formaldehyde, followed by sodium hydrogen sulphite, the product is mainly the *NN*-dimethylenesulphite in which only a portion of the sulphur can be oxidised to sulphate by alkaline iodine.



It is possible that these observations, which have led to the discovery of a new class of compounds, may have important technical application. It is of interest that with an aliphatic amine a dimethylenesulphite may be formed by the action of preformed formaldehydebisulphite, for Knoevenagel and Mercklin (*Ber.*, 1904, **37**, 4093) record the isolation of a 73% yield of ethyliminobisacetonitrile by treating ethylamine with sodium formaldehydebisulphite, followed by potassium cyanide. The reaction may be represented in this way :



$$\mathrm{Et{\cdot}NH_2} \longrightarrow \mathrm{Et{\cdot}N}{<}\begin{matrix}\mathrm{CH_2{\cdot}O{\cdot}SO_2Na}\\ \mathrm{CH_2{\cdot}O{\cdot}SO_2Na}\end{matrix} \longrightarrow \mathrm{Et{\cdot}N}{<}\begin{matrix}\mathrm{CH_2{\cdot}CN}\\ \mathrm{CH_2{\cdot}CN}\end{matrix}$$

A study of the action of potassium cyanide and other reagents on the *NN*-dimethylenesulphites of anilines should lead to results of interest.

EXPERIMENTAL.

Sodium 5-*Nitro*-2-*hydroxyanilino*-N-*methylenesulphite* (V).—4-Nitro-2-aminophenol (4·6 g.) was condensed with sodium formaldehydebisulphite (9 g., 2 mols.) in water (20 c.c.) at 70—75° for 30 minutes, and the resulting deep red solution concentrated over sulphuric acid in a vacuum until crystallisation set in. The product (8·6 g.), twice recrystallised from 0·7 part of water, separated in orange-red feathery needles. From two preparations different *hydrates* were obtained, one having $2\frac{1}{2}$ molecules of water [Found : S(Elvove), 10·2; S(volatile), 10·4; CH_2O, 9·3; H_2O at 120°, 13·6. $C_7H_7O_6N_2SNa,2\frac{1}{2}H_2O$ requires S, 10·2; CH_2O, 9·5; H_2O, 14·3%] and the other $1\frac{1}{2}$ molecules of water of crystallisation [Found : Na, 7·7; S(Elvove), 10·6, 10·5; H_2O at 120°, 9·3. $C_7H_7O_6N_2SNa,1\frac{1}{2}H_2O$ requires Na, 7·7; S, 10·8; H_2O, 9·1%].

Disodium 5-*Nitro*-2-*hydroxyanilino*-NN-*dimethylenesulphite* (IV).—4-Nitro-2-aminophenol (10 g.) in 2*N*-hydrochloric acid (32·5 c.c., 1 mol.) was treated with 40% aqueous formaldehyde (20 c.c., 4 mols.) for 1 minute; a gummy solid then separated in quantity. On addition of sodium hydrogen sulphite solution (4 mols.), freshly prepared by saturating an aqueous solution of 13·8 g. of anhydrous sodium carbonate in water (55 c.c.) with sulphur dioxide, a clear solution was obtained in a few minutes. Excess of sulphur dioxide having been removed by aspiration, the solution was neutralised with 50% sodium hydroxide solution and filtered, and 50% sodium hydroxide solution (5·2 c.c., 1 mol.) added (total volume now 115 c.c.), followed by warm methyl alcohol (120 c.c.). The orange-red needles obtained (24·8 g.) were collected after 24 hours and washed with 50 c.c. of 80% methyl alcohol. The filtrate and washings on further dilution with pure methyl alcohol gave a further 3·15 g. The product was *trisodium* 5-*nitro*-2-*hydroxyanilino*-NN-*dimethylenesulphite* free from chloride, sulphite, or sulphate. It can be recrystallised with very little loss by solution in an equal weight of warm water and addition of 5 vols. of warm methyl alcohol [Found: Na, 14·2; S(volatile), 13·2; S(Elvove), 6·45, 6·15; OMe, 7·9, 8·1; CH_2O, 11·5; loss at 120°, 10·7. $C_8H_7O_9N_2S_2Na_3,2H_2O,1\frac{1}{2}CH_3{\cdot}OH$ requires Na, 14·0; S, 13·0; OMe, 9·4; CH_2O, 12·2; loss of $2H_2O,\frac{1}{2}CH_3{\cdot}OH$, 10·6%. Found for solid dried at 120°: OMe, 4·9, 5·3, 5·2. $C_8H_7O_9N_2S_2Na_3,CH_3{\cdot}OH$ requires OMe, 7·0%].

For conversion into the disodium salt the trisodium salt (19·7 g.) was treated with *N*-hydrochloric acid (37·5 c.c.) until the solution was neutral to litmus. The clear solution was evaporated in a vacuum over sulphuric acid until there was a copious crystallisation, then warmed to dissolve all salts, and allowed to crystallise at 0°. The *disodium* salt separated in clusters of large bold orange prisms (12·8 g.). It contained a trace of chloride, removable by recrystallisation from 0·6 part of warm water. Owing to the difficulty of removing larger quantities of sodium chloride when present it is preferable to recover the trisodium salt by the methyl alcohol method described above. In this way from the mother-liquors of the disodium salt a crop of pure trisodium salt (3·0 g.) was recovered, making the yield of disodium salt on trisodium salt used, 84% [Found: Na, 9·9; S(volatile), 14·4; S(Elvove), 7·0, 7·5; loss at 120°, 13·4. $C_8H_8O_9N_2S_2Na_2,3\frac{1}{2}H_2O$ requires Na, 10·2; S, 14·3; H_2O, 14·0%].

Disodium 5-nitro-2-hydroxyanilino-*NN*-dimethylenesulphite has also been isolated without making use of the trisodium salt. By laborious fractional crystallisation of the neutralised solution obtained from 4-nitro-2-aminophenol monohydrate (10·3 g.) condensed as previously described, the disodium salt (1·5 g.) was obtained as small, pale orange-yellow prisms [Found: C,* 21·5, 21·5; H,* 3·5, 3·6; N*, 6·1, 6·3; Na, 10·0; S(volatile), 14·3; S(Elvove), 7·9; CH_2O, 12·5; H_2O at 120°, 13·4. Calc.: C, 21·4; H, 3·4; N, 6·2; Na, 10·2; S, 14·3; CH_2O, 13·4; H_2O, 14·0%].

*Sodium 4-nitro-2-hydroxyanilino-*N*-methylenesulphite* (6·75 g.), prepared by the condensation of 5-nitro-2-aminophenol (3·1 g.) with sodium formaldehydebisulphite (6 g., 2 mols.) in water (10 c.c.) at 100° for 30 minutes and subsequent concentration in a vacuum, crystallised from water (5 c.c.) in rectangular, pale orange-brown prisms (4·9 g.) of a *trihydrate* [Found: Na, 7·1; S(volatile), 10·1; S(Elvove), 9·7; CH_2O, 8·8; H_2O at 120°, 15·0. $C_7H_7O_6N_2SNa,3H_2O$ requires Na, 7·1; S, 9·9; CH_2O, 9·2; H_2O, 16·7%].

*Disodium 4-Nitro-2-hydroxyanilino-*NN*-dimethylenesulphite* (VI).—Addition of 40% formalin (18 c.c., 4 mols.) to a solution of 5-nitro-2-aminophenol (9·3 g.) in *N*-hydrochloric acid (120 c.c., 2 mols.) caused an immediate formation of a yellow precipitate. After 30 seconds, 35% sodium hydrogen sulphite solution (68 c.c., 4 mols.) was added and, on shaking, the precipitate completely dissolved. After removal of free sulphur dioxide by aspiration the solution was neutralised, concentrated to a small volume under reduced pressure at 50°, and kept at 0°. Sodium chloride separated first and after filtration the red liquor was concentrated to a syrup, which gradually deposited crystalline material (24·9 g.). After several recrystallisations each time from 0·3 part of water the pure NN-*dimethylenesulphite* (1 g.) was obtained [Found: N, 6·4; Na, 10·9; S(volatile), 14·95; S(Elvove), 10·1; CH_2O, 13·3; H_2O at 120°, 5·8. $C_8H_8O_9N_2S_2Na_2,2\frac{1}{2}H_2O$ requires N, 6·5; Na, 10·7; S, 14·9; CH_2O, 13·9; loss of $1\frac{1}{2}H_2O$, 6·3%]. This salt crystallises in golden rectangular plates from water, in which it is many more times more soluble than the corresponding mono-*N*-methylenesulphite and is therefore freed from other salts only with great difficulty. The original mother-liquor deposited small crops, 3·1 g. in all, of a substance which on recrystallisation from water gave pure sodium 4-nitro-2-hydroxyanilino-*N*-methylenesulphite trihydrate identical with that described above [Found: S(volatile), 10·2; CH_2O, 9·0. Calc.: S, 9·9; CH_2O, 9·2%].

*Disodium 2-Hydroxy-5-carbomethoxyanilino-*NN*-dimethylenesulphite* (VII).—To a solution of methyl 3-amino-4-hydroxybenzoate (10 g.) in *N*-hydrochloric acid (60 c.c., 1 mol.), 40% formalin (18 c.c., 4 mols.) was added, followed in 40 seconds by 35% aqueous sodium hydrogen sulphite (70 c.c., 4 mols.). The yellow precipitate dissolved on shaking and the free sulphur dioxide was removed by aspiration. The neutralised solution was filtered, and concentrated to a thick syrup in a vacuum. After removal of some sodium chloride, the syrup deposited crystals (24·5 g.), which on recrystallisation from water (10 c.c.) gave a small crop (1·3 g.) which crystallised from water (0·6 c.c.) in characteristic elongated plates (0·6 g.) of sodium 2-hydroxy-5-carbomethoxyanilino-*N*-methylenesulphite (J., 1934, 1715) [Found: S(volatile), 10·2; CH_2O, 8·9. Calc.: S, 10·0; CH_2O, 9·4%]. From the first recrystallisation mother-liquor after removal of further quantities of the mono-*N*-methylenesulphite a larger crop (7·8 g.) was obtained. In two recrystallisations from 0·3 part of water the required NN-*dimethylenesulphite dihydrate* was obtained in extremely fine, colourless, hair-like needles [Found: N, 3·1; Na, 10·7; S(volatile),

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* Micro-analyses.

14·9; S(Elvove), 9·1; CH_2O, 12·85; H_2O at 120°, 8·5. $C_{10}H_{11}O_9NS_2Na_2,2H_2O$ requires N, 3·2; Na, 10·6; S, 14·7; CH_2O, 13·8; H_2O, 8·3%]. On titration with thymolphthalein as indicator, 0·1 g. required 2·20 c.c. of 0·1*N*-sodium hydroxide, the calculated value for one phenolic group being 2·30 c.c. For comparison 0·1 g. of the mono-*N*-methylenesulphite required 3·13 c.c. of 0·1*N*-sodium hydroxide, corresponding to complete neutralisation of the phenolic group, the calculated value being 3·13 c.c.

Sodium 3-*Nitroanilino*-N-*methylenesulphite.*—*m*-Nitroaniline (3·5 g.), sodium formaldehyde-bisulphite (7·5 g.), and water (20 c.c.) were gently boiled together until solution was effected and then kept at 90° for 1 hour. The condensation product (5·5 g.) crystallised readily. It was twice recrystallised from 2 parts of water and separated as a *dihydrate* crystallising in dense clusters of small yellow plates [Found: Na, 7·7; S(volatile), 11·0; S(Elvove), 11·2; CH_2O, 10·0; H_2O at 120°, 12·1. $C_7H_7O_5N_2SNa,2H_2O$ requires Na, 7·9; S, 11·0; CH_2O, 10·3; H_2O, 12·4%].

Disodium 3-*Nitroanilino*-NN-*dimethylenesulphite.*—A solution of *m*-nitroaniline (6·9 g.) in *N*-hydrochloric acid (57 c.c.) was treated with 40% formalin (11·25 c.c., 3 mols.), immediate precipitation of a yellow solid occurring. After 60 seconds a solution of sodium hydrogen sulphite (3 mols.) prepared from anhydrous sodium carbonate (8 g.) in water (30 c.c.) was added; after a short time the precipitate dissolved. Free sulphur dioxide was removed, and the solution neutralised to litmus. On concentration a crop (17·2 g.) of a reddish-yellow crystalline solid was obtained containing some sodium chloride. The latter can be removed by several recrystallisations from water, but more readily by dissolving the crude solid in 0·5 part of warm water and adding 9 parts of methyl alcohol. On keeping, the NN-*dimethylenesulphite* crystallised in long silky yellow needles containing one molecule of methyl alcohol of crystallisation which is only partly lost at 120° [Found: N, 6·9; Na, 11·3; S(volatile), 15·7; S(Elvove), 8·3; CH_2O, 14·1; OMe, 6·2; loss at 120°, 3·3. $C_8H_8O_8N_2S_2Na_2,MeOH$ requires N, 7·0; Na, 11·4; S, 15·9; CH_2O, 14·9; OMe, 7·7%]. Further quantities can be isolated from the aqueous methyl-alcoholic mother-liquor by careful addition of dry ether.

Highly Substituted Sulpharsphenamines.—In the following preparations the method of Christiansen (*J. Amer. Chem. Soc.*, 1923, **45**, 2184) was followed, 3·66 g. of the same stock of arsphenamine base being employed in each case. After condensation the products were precipitated by 5 vols. of alcohol. Products B and C were preparations which had been reprecipitated in the same way. The products were in each case typical sulpharsphenamines showing the phenomenon of delayed precipitation by excess of mineral acid. The analytical data and atomic ratios are recorded in the following table:

							Atomic Ratios.				
Prepn.	CH_2O and $NaHSO_3$ equiv.	As, %.	Volatile S, %.	Elvove S, %.	Free SO_4'' S, %.	CH_2O, %.	As :	Volatile S :	Oxidised S :	Unoxidised S by diff. :	CH_2O
A	4	19·3	12·1	2·8	0·25	11·2	2 :	2·9 :	0·6 :	2·3 :	2·9
B	6	18·1	14·0	1·9	0·3	12·0	2 :	3·6 :	0·4 :	3·2 :	3·3
C	8	19·1	12·6	2·2	0·4	11·4	2 :	3·1 :	0·45 :	2·65 :	3·0

Preparation B was dissolved in water (2 g. in 5 c.c.), and the solution cooled in ice. With rapid stirring, glacial acetic acid (40 c.c.) was added, and the precipitate collected, washed with acetic acid and then alcohol. The product (1·8 g.), dried in a high vacuum, was a pale yellow powder easily soluble in water [Found: As, 17·2; S(volatile), 12·2; S(Elvove), 2·0; CH_2O, 11·1, whence As : S(volatile) : S(oxidised) : S(unoxidised, by diff.) : CH_2O = 2 : 3·3 : 0·5 : 2·8 : 3·2]. This experiment shows that practically the whole of the sulphur in preparation B is in the form of combined methylenesulphite groups and that about 88% is not found as sulphate on oxidation with alkaline iodine.

It is instructive to compare the analyses of preparations A, B and C with those given for commercial sulpharsphenamines (J., 1933, 1005).

Elvove's Oxidative Method of Analysis and its Limitations.—In the original directions given by Elvove (*U.S. Pub. Health Rep.*, 1925, **40**, 1235) an aqueous solution of the substance (0·1 g.) is treated with 0·1*N*-iodine (50 c.c.), followed by *N*-sodium hydroxide (20 c.c.). After 5 minutes the excess of iodine is liberated by addition of *N*-hydrochloric acid (21 c.c.) and then removed by the addition of sufficient 0·05*M*-sodium arsenite. Another 5 c.c. of *N*-acid are added, and the sulphate in the solution then estimated as barium sulphate.

Elvove employed the reaction for the analysis of neoarsphenamine and sulpharsphenamine. In the former case all the sulphur except the so-called nuclear sulphur, but in the latter only a portion, was oxidised to sulphate. Elvove expressed the opinion that in the latter case it was only uncombined sodium formaldehydebisulphite which had its sulphur oxidised to sulphate

In our previous communication we showed that this view was incorrect, since mono-*N*-methylenesulphites of various substituted anilines give up the whole of their sulphur as sulphate.

In our attempts to clear up the anomaly discovered by Elvove in the case of sulpharsphenamine we examined the Elvove conditions closely and tried the effect of varying the numerous factors involved. Although Elvove found that 5 minutes was sufficiently long in the case of sulpharsphenamine for the alkaline iodine to exert its maximum effect, our experience with pure crystalline *p*-aminophenylarsono-*N*-methylenesulphurous acid (J., **1933**, 1009) leads us to believe that as a general process for *N*-methylenesulphites 5 minutes' oxidation is insufficient, but that after 1 hour oxidation is complete [Found : S(Elvove conditions, 5 mins. oxidation), 8·3, 6·9; S(1 hour's oxidation), 10·4. Calc., 10·3%]. In all our analyses, therefore, the alkaline iodine has been allowed to react for 1 hour.

In the case of the sulpharsphenamines where the Elvove anomaly appears, the effect of varying the conditions was very instructive. Using preparation A recorded above, where the proportion of sulphur appearing on oxidation as sulphate is very small, we obtained the following results : Ordinary Elvove quantities, 1 hour at 20°, S, 2·8%; 16 hours at 20°, S, 2·9%; 16 hours at 37°, S, 2·9%. If, however, the substance was kept, with 20 c.c. of *N*-sodium hydroxide only, for 16 hours at 20°, and then for 1 hour after the addition of 50 c.c. of 0·1*N*-iodine, almost all the sulphur appeared as sulphate [Found : S, 11·7%, by distillation method 12·1%]. Another preparation of a sulpharsphenamine gave with the ordinary Elvove quantities, time 1 hour, S, 3·1; 3·3%. When the quantity of iodine was increased to 60 c.c. and oxidation carried out for 16 hours, the sulphur found as sulphate was 2·9%, and when the quantity of iodine and alkali was doubled and the time of oxidation 16 hours the sulphur found as sulphate was 3·5%.

For sulpharsphenamines, therefore, the Elvove method gives consistent results independent of time, quantity of reagents or temperature, but *N*-alkali alone, given sufficient time, hydrolyses practically the whole of the combined methylenesulphite groups, which ensures their conversion into sulphate.

When the Elvove method was applied to the analysis of crystalline disodium 5-nitro-2-hydroxyanilino-*NN*-dimethylenesulphite (IV), erratic results varying between S, 6·9 and S, 9·2% were obtained by the same method as had always given reproducible results with sulpharsphenamines. The trisodium salt derived from it also showed a similar behaviour; *e.g.*, the total sulphur found by distillation had the approximately constant values 13·2, 13·1, 13·4, and 13·3 after successive crystallisations of the trisodium salt from aqueous methyl alcohol, but the Elvove figures were respectively 9·6, 6·7, 8·3, 9·3. A search was made for the factors or conditions which might produce extreme values, but without success. The action may be an uncontrollable catalytic effect or may be connected with the complex mechanism involved in the action of alkaline iodine on dimethylenesulphites.

Observations on the Mechanism of the Elvove Reaction.—A sample of sulpharsphenamine (B), analysed in duplicate by the Elvove method, gave the values (I) S, 2·15%; (II) S, 2·2% out of a total sulphur content of 14·0%. To the filtrates 3*N*-hydrochloric acid (10 c.c.) was added in each case. In addition, to filtrate (I), 0·1032 g. of fresh sulpharsphenamine was added. Both solutions were then boiled and within 10 minutes there was a marked appearance of barium sulphate in (I). The boiling was continued for 30 minutes, during which there was no visible appearance of a precipitate in (II). At this stage the barium sulphate in (I) was removed and weighed; it corresponded to 65% of the sulphur of the second amount of sulpharsphenamine added. The liquor (II), after being boiled for 2 hours to a small volume, was filtered; the extra barium sulphate now present represented S, 5·6%. These results show that the sulphur not found by Elvove's method cannot be present as unoxidised methylenesulphite groups, since they would be readily oxidised in the acid oxidising solution. The results are, however, consistent with the view that during the alkaline iodine oxidation dithionate is formed, which is slowly transformed in the boiling acid solution with deposition of barium sulphate. A pure specimen of barium dithionate on treatment by Elvove's method showed no formation of barium sulphate and on digestion with mineral acid slowly generated barium sulphate in the same way as the sulpharsphenamine solutions under parallel conditions.

Since it has been shown that a sulpharsphenamine exposed to the quantity of alkali used in the Elvove method for 16 hours but without the iodine gives up practically all its sulphur as sulphate on completion of the Elvove conditions, it seems to follow that the action of alkaline iodine on an *NN*-dimethylenesulphite is partly hydrolytic. Any sulphite liberated by hydrolysis is, however, straightway exclusively oxidised to sulphate. At the same time there is a direct attack of the alkaline iodine on the intact dimethylenesulphite leading to oxidative union of the sulphur atoms, followed by hydrolysis and appearance of the sulphur as dithionate.

Analytical Examination of the Reaction between Aniline Hydrochlorides and Formaldehyde, followed by Sodium Hydrogen Sulphite.—The experimental conditions laid down by Newbery and Phillips were followed as closely as possible. The aniline (0·002 g.-mol.) was dissolved in *N*-hydrochloric acid (2 c.c., 1 equiv.), and the solution made up to 5 c.c. with water. 4% Formalin (3 c.c., 2 equivs.) was added, and after 1 minute a freshly prepared solution of sodium hydrogen sulphite (2 equivs.) prepared from anhydrous sodium carbonate (0·212 g.) in water (4 c.c.) by saturation with sulphur dioxide. By this means errors due to sulphate which is always present in commercial sodium hydrogen sulphite are avoided. The amount of free sulphur dioxide is a variable factor, but it has been controlled and shown to be immaterial by results obtained with a pure sample of sodium hydrogen sulphite. For di-acid bases the quantities of hydrochloric acid, formaldehyde, and sodium hydrogen sulphite were doubled. After 30 minutes the solution was made up to 200 c.c., and aliquot parts taken for the following analyses.

Nitrogen determinations were carried out in duplicate by the Kjeldahl method on 50 c.c. of the solution. Elvove sulphur: 25 C.c. of the solution were treated with 50 c.c. of 0·1*N*-iodine, followed by 20 c.c. of *N*-sodium hydroxide. After 1 hour the solution was acidified with 21 c.c. of *N*-hydrochloric acid, excess of iodine removed by addition of sufficient 0·05*M*-sodium arsenite, a further 5 c.c. of *N*-acid added, and the sulphate precipitated as barium sulphate in the usual manner. A duplicate analysis was carried out in which the iodine and sodium hydroxide were added in the reverse order. In all cases the results by both procedures were almost identical and mean values have been used in the table. Volatile sulphur: This was determined on 25 c.c. of the solution by our previously described method. For clarity, atomic ratios only are given in the following table.

Substance.	Equiv. CH_2O and $NaHSO_3$.	Atomic Ratios. N		Volatile S		Elvove S		Unoxidised S
Aniline	2*	1	:	2·2	:	1·5	:	0·7
	2*†	1	:	2·0	:	1·1	:	0·9
	4	1	:	3·4	:	2·6	:	0·8
2-Aminophenol	2*	1	:	2·4	:	1·3	:	1·1
	4	1	:	4·1	:	2·8	:	1·3
4-Aminophenol	2*	1	:	2·5	:	1·9	:	0·6
2-Anisidine	2	1	:	1·7	:	1·3	:	0·4
	2*	1	:	2·5	:	1·9	:	0·6
	2*	1	:	1·7	:	1·3	:	0·4
	4	1	:	3·6	:	2·9	:	0·7
4-Amino-2-hydroxyphenylarsonic acid	2*	1	:	1·8	:	1·7	:	0·1
3 : 3′-Diamino-4 : 4′-dihydroxyarsenobenzene	4*	1	:	1·9	:	1·1	:	0·8
	6*	1	:	3·3	:	2·0	:	1·3
	8*	1	:	4·4	:	3·0	:	1·4

* The concentrations are exactly the same as those of Newbery and Phillips. In all other cases the concentration is greater.

† In this case freshly prepared pure solid sodium hydrogen sulphite was used.

A control on the reliability of the results was obtained by mixing the reagents in correct amount and order without using any aniline. The weights of barium sulphate found in 25 c.c. portions of the solution were (Elvove) 0·1530 g., 0·1535 g., and (volatile) 0·1504 g.

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