LXXIX.—*Lead Subacetate Solution ("Goulard's Extract") and its Reaction with Phenols.*

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During experiments on the production of easily isolable lead organic compounds with a view to their possible use as therapeutic agents, it has been necessary to investigate the precipitates which phenols produce with the aqueous solution of lead subacetate known in pharmacy as Goulard's extract.

This solution is referred to under that name in the 1898 and 1914 editions of the British Pharmacopœia, although the method of preparing it, by boiling 250 g. of lead acetate and 175 g. of powdered lead oxide with water, filtering the solution from the considerable residue, and making up the cooled filtrate to 1 litre, was described in all editions of the Pharmacopœia from 1867 to 1898 inclusive. In the editions of 1867, 1874, and 1885, a formula was given for the lead subacetate, but no formula was given in the later editions. Although the essential properties of the solution appear to be the same as formerly, the method of making Goulard's extract in the 1914 edition is different from that previously described and is set forth in the experimental portion of the present paper. It has now been possible to prove that the composition of the solute is $Pb(OH)_2,Pb(O_2C{\cdot}CH_3)_2$ or $Pb(OH)(O_2C{\cdot}CH_3)$, agreeing with the formula $Pb_2O(C_2H_3O_2)_2$ given in the 1885 edition. If, instead of taking the above quantities of lead acetate and lead oxide—which are in approximately equivalent proportion—three times the amount of lead oxide is taken, the composition of the solute is $2Pb(OH)_2,Pb(O_2C{\cdot}CH_3)_2$, thus confirming the existence in solution of the two definitely established basic acetates of lead. Further, a volumetric method of standardisation of Goulard's extract is shown to be possible and an improvement on that described in the Pharmacopœia.

It appears that Medley (*Pharm. J.*, 1926, 149) was the first to point out that an aqueous solution of phenol yields a precipitate with a solution of lead subacetate but not with a solution of lead acetate. Medley stated that the fine white powder was readily soluble in alcohol (50%), acetone, benzene, chloroform, ether, and dilute acetic acid. He concluded that the precipitate was lead phenoxide, $(C_6H_5{\cdot}O)_2Pb$, and if this were so, it would be identical with the compound prepared by dissolving lead oxide in hot phenol (Calvert, J., 1865, **18**, 69). Further, he found that twelve other phenols reacted similarly; in only one case (pyrogallol) was the precipitate insoluble in acetic acid and in the majority of cases the precipitate was soluble in chloroform.

In the present paper, three typical compounds are described in detail, *viz.*, the precipitates produced with phenol, *o*-nitrophenol, and *o*-bromophenol. Others have been investigated, but not so completely, since it has been found that, although the precipitates as soon as they are formed and while still in contact with the solution may be soluble in organic solvents, they cease to be soluble to anything like the desired extent after separation, washing, and drying at the ordinary temperature. The formation of these precipitates is apparently general, but the sparing solubility in water of many phenols renders the experimental difficulties somewhat greater than might be anticipated.

The composition of these precipitates appears to be $Pb(OR)_2,Pb(OH)(O_2C{\cdot}CH_3)$, where $R =$ an aryl or substituted aryl group. These formulæ have been determined by careful analyses, but, unfortunately, molecular-weight determinations have not been found practicable. The presence of the acetic acid residue was always detected by the usual test. The only previously described compounds with which these substances can be compared are the sparingly soluble compounds, $Pb(OH)(O{\cdot}C_6H_4{\cdot}NO_2)$, prepared by Post and Mehrtens (*Ber.*, 1875, **8**, 1552) by mixing dilute aqueous solutions of lead acetate and the potassium salts of *o*-, *m*-, and *p*-nitrophenols.

EXPERIMENTAL.

The Solute in Goulard's Extract.—The Liquor Plumbi Subacetatis Fortis (Strong Solution of Lead Subacetate—Goulard's Extract) is made (British Pharmacopœia, 1914, 229) by dissolving 250 g. of lead acetate in 750 millilitres * of distilled water, adding 175 g. of powdered lead oxide, setting the mixture aside for 48 hours and shaking it occasionally; the solution is filtered and sufficient distilled water is passed through the filter to produce 1000 millilitres. The following are the stated characteristics of the solution: "A clear colourless liquid, with a sweet astringent taste; alkaline to litmus. Becomes turbid by exposure to the air. Forms an opaque, white jelly with mucilage of gum acacia. Yields the reactions characteristic of lead and of acetates. Specific gravity 1·275. When 1 gramme is diluted with 20 millilitres of water and mixed with excess of *N*-solution of oxalic acid, the precipitate collected,

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* 1 Millilitre (ml.) = vol. at 4° of 1 g. of water. The term "millilitre" (without definition) was given in the 1867 edition of the British Pharmacopœia in the metrical system of measures of capacity. In the present work, the unit of volume employed is the c.c., = 0·001 litre at 15°.

washed, transferred to a flask, and decomposed with excess of diluted sulphuric acid, the mixture thus obtained, heated to 60°, decolorises not less than 17 millilitres of *N*/10-solution of potassium permanganate."

The solution made by shaking mechanically for 8 hours lead acetate (250 g.), lead oxide (175 g.), and water (750 c.c.), filtering the liquid from the very considerable quantity of white precipitate, and making the filtrate up to 1 litre had a specific gravity of 1·283 at 13°, and 1 g. of the solution, treated as described above, decolorised 20·5 c.c. of 0·1*N*-potassium permanganate. The solution is conveniently preserved and delivered from an apparatus similar to that employed for an aqueous solution of barium hydroxide. Under these conditions it keeps almost indefinitely and there is little difficulty in obtaining a clear liquid. For most of the present work, the solution prepared from the above quantities was made up to 2 litres with distilled water.

When the solution was evaporated under reduced pressure at the ordinary temperature, a solid product was obtained of which the analytical figures approximated to the formula $Pb(OH)_2,Pb(O_2C{\cdot}CH_3)_2$ or $Pb(OH)(O_2C{\cdot}CH_3)$, but, from its appearance, there was considerable doubt as to its purity. The solution can be titrated against nitric acid or acetic acid and a fairly good end-point obtained, bromcresol-purple being used as indicator, and from this a method of standardisation of the solution can be developed. By using standard acetic acid and carrying out the titration in Nessler tubes, the end-point being determined colorimetrically, the following results were obtained with 5·0 c.c. of the solution : Pb present as $Pb(OH)_2$, by titration, 0·3070 g. Total Pb present, determined as $PbSO_4$, 0·5870 g. Hence Pb present as $Pb(O_2C{\cdot}CH_3)_2$, 0·2800 g. Therefore the molecular proportion of lead hydroxide and lead acetate is 1·0 : 0·91.

This result is obviously subject to error due to hydrolysis of the lead acetate in solution, which was partly corrected as follows. By titrating the solution against a known volume of standard acetic acid, the total amount of lead hydroxide in the solution can be calculated and, by using the above result, the total weight of lead acetate in the neutralised solution can be estimated approximately. This weight of lead acetate was then dissolved in a known volume of standard acetic acid and titrated back to neutrality with a standard aqueous solution of sodium hydroxide. (Any error due to hydrolysis of sodium acetate will be small compared with that of lead acetate.) From the results so obtained, it is possible to calculate the amount of acetic acid necessary to suppress the hydrolysis of the lead acetate; and on applying this correction the molecular proportion of lead hydroxide to lead acetate in the solution becomes 1 : 1·01.

Additional confirmation of this result was obtained by the following method. A standard solution of hydrochloric acid (50 c.c.) was boiled and 6·0 c.c. of the basic lead acetate solution were added, followed by an excess of an aqueous solution of sodium sulphate. To the cooled solution, neutral ethyl alcohol (20 c.c.) was added, and the resulting mixture titrated with standard sodium hydroxide solution. The following results were obtained: Pb as $Pb(OH)_2$, 0·3583 g. Total Pb, determined as $PbSO_4$, 0·7042 g. (mean of 0·7026, 0·7020, and 0·7080). Hence Pb as $Pb(O_2C{\cdot}CH_3)_2$, 0·3459 g., and the molecular proportion of lead hydroxide to lead acetate is 1·0 : 0·97. Allowing for experimental error, these results strongly indicate the nature of the solute as $Pb(OH)_2,Pb(O_2C{\cdot}CH_3)_2$.

The relative quantities of lead oxide and lead acetate used in making the Goulard's extract are in approximately molecular proportion. The residue from which the solution is filtered is an apparently homogeneous, white solid, which must contain lead hydroxide and lead acetate in approximately molecular proportion, probably as the solid basic acetate of lead of the above composition. A solution was made up as described above, lead oxide (52 g.) and lead acetate (25 g.), *i.e.*, 3 mols. of the former to 1 mol. of the latter substance, being used, and the following analytical figures were obtained when 5 c.c. of the solution were analysed by the second method described above: Pb as $Pb(OH)_2$, 0·3004 g. Total Pb, determined as $PbSO_4$, 0·4508 g. Hence Pb as $Pb(O_2C{\cdot}CH_3)_2$, 0·1504 g., and the molecular proportion of lead hydroxide to lead acetate in the solution is 1·998 : 1·000. This indicates the nature of the solute in this solution as being $2Pb(OH)_2,Pb(O_2C{\cdot}CH_3)_2$. The insoluble residue from which the solution was filtered in this case was certainly not homogeneous, unchanged lead oxide obviously being present.

Products of the Reaction between " Goulard's Extract " and Phenols.—In the first experiments, the precipitate produced on mixing the extract with an aqueous solution of phenol was immediately extracted with benzene or chloroform, and the extract was washed with water and dried with anhydrous sodium sulphate. The solvent was evaporated, but the substance did not separate until it was precipitated with ligroin. After drying in a vacuum desiccator over sulphuric acid or phosphorus pentoxide, the substance was found to be insoluble in the original solvent at the ordinary temperature, and although it was appreciably soluble in the warm solvent some decomposition always took place under these conditions. Products were obtained in this way from phenol, the naphthols and nitrophenols, but duplicate analyses carried out on several preparations of these showed considerable variation in composition.

An apparatus was specially designed in which the reaction could be carried out, and the product filtered off and washed, in an atmosphere free from carbon dioxide. By its means, the action of " Goulard's Extract " on numerous phenols and their derivatives, *e.g.*, methyl salicylate and 3-nitro-4-hydroxyphenylarsinic acid (U.S. Pat. 1607299), has been examined and found to be of general application. The following may be regarded as typical :

Phenol compound. Phenol (6 g.), dissolved in water (150 c.c.) at 20°, was allowed to react with the solution (40 c.c.). The white precipitate was washed with water (200 c.c.) at 20°. (Hot water used for washing caused shrinkage and decomposition of the compound.) The compound is a white micro-crystalline powder which begins to melt at about 80° (decomp.) and then chars, leaving a deposit of lead and some lead oxide (PbO) (Found : C, 25·4, 25·4, 24·9; H, 2·0, 1·95, 2·0; Pb, 61·1, 61·8.* $C_{14}H_{14}O_5Pb_2$ requires C, 24·85; H, 2·1; Pb, 61·25%). It is suggested that the composition of the compound is best represented by the formula $Pb(O{\cdot}C_6H_5)_2,Pb(OH)(O_2C{\cdot}CH_3)$.

The compound dissolves with decomposition in warm aqueous sodium hydroxide and is not precipitated when this solution is acidified with nitric acid. It is soluble in dilute acetic acid, and this solution gives an immediate yellow precipitate with potassium chromate. It is sparingly soluble in chloroform and pure olive oil. It is also sparingly soluble in benzene, but decomposition of the compound takes place when the solution is heated.

o-*Nitrophenol compound.* A solution of *o*-nitrophenol (4 g.) in hot water was cooled to 40° and mixed with the Goulard's extract (45 c.c.), and the yellow precipitate was filtered off, washed with water (200 c.c.) at 40°, and dried in a vacuum desiccator, being obtained as a yellow, crystalline powder. When the dilute aqueous solution was allowed to stand, the substance was obtained in thin needles, which, however, were not quite pure (Found : C, 22·3, 21·5; H, 2·4, 2·0; N, 3·7; Pb, 54·6, 54·3. $C_{14}H_{12}O_9N_2Pb_2$ requires

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* The lead in these compounds was conveniently determined as lead sulphate. 0·2—0·3 G. was treated with 15 c.c. of concentrated nitric acid and 10 c.c. of concentrated sulphuric acid, and the mixture evaporated almost to dryness in a beaker. The cooled residue was diluted with 20 c.c. of water and 20 c.c. of ethyl alcohol and allowed to stand for 12 hours. The lead sulphate was weighed in the usual manner. The method was checked by using pure lead acetate.

C, 21·9; H, 1·4; N, 3·7; Pb, 54·05%). It is suggested that the compound should be represented by the formula

$$Pb(O{\cdot}C_6H_4{\cdot}NO_2)_2,Pb(OH)(O_2C{\cdot}CH_3).$$

The compound explodes on heating, leaving a deposit of lead. If warmed gently, it changes in colour from yellow to red at 120—130°. As in the similar case of mercuric iodide, the reverse colour change can be brought about by rubbing. The compound dissolves in warm sodium hydroxide solution with decomposition, and nitric acid does not give any precipitate with this solution. Potassium chromate gives an immediate yellow precipitate with the solution in dilute acetic acid. The substance is slightly soluble in water, chloroform, and benzene.

o-Bromophenol compound. This was prepared by mixing a solution of *o*-bromophenol (4 g.) in water (600 c.c.) at 35° with Goulard's extract (40 c.c.). The white precipitate was washed with distilled water (200 c.c.) at 35° and dried in a vacuum desiccator over sulphuric acid (Found: C, 20·65, 20·3; H, 1·35, 1·3; Br, 21·9, 22·1, 21·7, 21·7;* Pb, 49·65, 49·6. $C_{14}H_{12}O_5Br_2Pb_2$ requires C, 20·1; H, 1·4; Br, 19·2; Pb, 49·6%). It is suggested that the compound is best represented by the formula

$$Pb(O{\cdot}C_6H_4Br)_2,Pb(OH)(O_2C{\cdot}CH_3).$$

On being heated, the substance begins to melt at 255° and later chars. It is soluble in warm sodium hydroxide solution and decomposes, nitric acid producing no precipitate and sulphuric acid giving a precipitate of lead sulphate. The substance is readily soluble in dilute acetic acid at the ordinary temperature, and addition of potassium chromate to this solution produces an immediate yellow precipitate. The substance is slightly soluble in chloroform, ethyl alcohol, and pure olive oil. It dissolves slightly in benzene, but with obvious decomposition.

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* In view of the constancy of the results of these bromine determinations by Carius's method made on different specimens, it is difficult to explain why they are so much higher than the suggested theoretical value, since it is highly probable that all the lead compounds described are of the same type. It is, however, significant that the redistilled *o*-bromophenol had a bromine content of 45·7%, but when it was mixed with pure lead acetate the apparent bromine content was 47·4%, both determinations being done simultaneously and by Carius's method (theory requires Br, 46·2%).

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