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SOME CONSIDERATIONS OF SILVER PICRATE.*

BY JOHN C. BIRD AND ALFRED BAROL.

This presentation is intended to cover some of the outstanding points evolved during recent work with silver picrate, certain particular merits of which would seem to have hitherto been overlooked. It is hoped that some of the promising results reported here will act as a stimulus to further clinical investigation of this product.

A survey of the literature covering the last 100 years is disappointing in the scarcity of data concerning silver picrate. The compound was first produced as a by-product by Chevreul, in 1809, during his work on indigo and later by Liebig in 1828, who named it "silver carbazotate," and noted its explosive property. To Dumas (1) however, might be ascribed the credit of first preparing silver picrate, as such, from silver nitrate and ammonium picrate, in 1841. Dumas published an analysis of the compound and evidently stimulated further work, for both Lau-

* Scientific Section, A. PH. A., Washington meeting, 1934.

rent (2) and Marchand (3) entered the field within the next three years, making silver picrate from silver carbonate and picric acid. Nothing further was done until Carey Lea (4), working in Philadelphia in 1858, prepared the chemical by interaction of silver nitrate and magnesium picrate and briefly described it and such of its properties as were then known, before the Society for the Advancement of Science.

There appears to be no further reference to silver picrate until 1905, when it is referred to in the literature of the time as being a new medicament of use in certain conditions of urethritis, vaginitis, etc., while Yale (5) claimed good results in the treatment of diphtheria. It was supplied for some time to the medical profession and exhibited in a gelatin or petrolatum base in the form of suppositories and ointments. It is due to numerous reports of its peculiar efficacy in these and allied conditions that our recent work has been stimulated.

The preparation of silver picrate according to the old and standard methods, such as the action of picric acid upon silver oxide or carbonate in aqueous suspension, has several disadvantages, mainly because of the low solubility of silver picrate in water, about one per cent at ordinary temperature. This necessitates the use of large volumes of liquid with consequent lengthy filtrations, evaporations, etc., in capacious tanks of special construction, if a satisfactory product is to be obtained. The solubility is somewhat higher (about 5%) in hot water, but application of heat is not desirable.

In a search for a solvent for silver picrate which would facilitate its preparation, most of the usual, and many unusual solvents were tried with but little encouragement, the maximum solubility being in most cases below one per cent. It is remarkable, therefore, to find that certain of the glycol ethers (particularly diethylene glycol monoethyl ether) possess remarkable solvent powers for this otherwise comparatively insoluble silver salt. We have by its means been able to prepare non-viscous solutions of silver picrate containing up to 40% of the solid which, while serving as a means of manipulation, may also be used directly as medicaments. In our new method of preparation use is made of this property of abnormal solubility, by carrying out the reaction in the glycol ether. Silver oxide is freshly precipitated in the usual way, washed, drained and pressed free from excessive moisture. It is then mixed thoroughly in a glass or enameled vessel with a sufficient quantity of the glycol ether to form a smooth paste. Picric acid is added in the stoichiometric proportion, when reaction takes place almost immediately and silver picrate is formed. On final warming to about 80° C. the liquid becomes practically clear, and is filtered when neutral to litmus. The bright golden liquid thus forms a concentrated solution of silver picrate, usually precalculated to give a concentration of about $33^1/_3\%$ of the solid. It may be used directly for the preparation of medicinal and pharmaceutical products or to prepare the solid in crystalline form. This operation consists in merely adding water to the concentrate and is the reverse of that usually employed in the preparation of crystalline substances, whereby water is gradually removed by evaporation. In this case by pouring the warmed glycol solution into about twice its volume of water, large and beautiful golden-yellow needles of silver picrate separate rapidly. These are drained, washed with ice water and air-dried with minimum exposure to light.

CHEMICAL AND PHYSICAL PROPERTIES.

Silver picrate thus obtained forms fine golden-yellow needles of intense coloring power, odorless, but possessing a penetrating bitter taste; the dust is somewhat irritating to nasal membrane. The bitterness and staining power are, however, much modified in solutions of the strength used in medications. The crystals usually separate with one molecule of water of crystallization but may, on occasion, be anhydrous. The substance contains about 30% of silver and is soluble, 1 part in 113 of water at room temperature; solubility at temperatures around 90° C. rises to about 5%. Boiling water or prolonged exposure of aqueous solutions to light result in gradual decomposition with separation of silver oxide, as is the case with many silver salts. The yellow color of the solutions, however, is some aid toward stability to light; colloidal silver chloride, for example, remains suspended in a solution of silver picrate without discoloration for many days, even in bright light. The solid detonates mildly on rapid heating, but it is not as violent; for example, as the sodium, potassium, ammonium or calcium salts. Silver picrate forms a well-defined compound with ammonia, first noted by Carey Lea (6) in 1861. By gradually adding ammonia solution to the glycol ether concentrate, no precipitation of silver oxide is formed, as might be expected. The solution turns deep orange and eventually precipitates long, thick, dark yellow needles of a compound which on analysis is shown to contain $2NH_3$ per molecule of silver salt. This substance possesses interesting properties which are still under investigation. It is not as stable as silver picrate, nor is it as soluble in water and other solvents. The solutions rapidly darken with separation of silver oxide or silver and the slightest application of heat causes the deposition of a shining silver mirror on containing vessels. If increase in bactericidal efficiency and therapeutic activity can be associated with this tendency to decomposition under ordinary circumstances, silver ammonio picrate should possess some interesting possibilities in therapeutic application.

The high solubility of silver picrate in the glycol ethers renders possible, in a simple and rapid manner, the formation of numerous ethers of picric acid. The required alkyl or aryl halide, such as ethyl iodide, phenyl chloride, etc., is merely dissolved in the same glycol solvent and added to the silver picrate solution. Silver halide is at once precipitated in the cold, practically quantitatively, leaving the required picric ether in solution. After filtering, water may be added to the liquid as previously described to produce fine crystals of the picric acid derivative. In this way methyl, ethyl, phenyl and benzyl picric ethers have been prepared with rapidity and ease. The method is not limited to organic derivatives, for metallic compounds may also be similarly produced. Mercuric chloride, for example, being soluble in the glycol ether, may be used to prepare mercuric compounds. It is hoped that this method may be extended to cover the preparation of other promising derivatives which are not readily obtained by the usual procedures.

PHARMACOLOGY AND BACTERIOLOGY.

From the pharmacologic and therapeutic standpoints silver picrate combines the effects of silver and of picric acid. It may be said to occupy an intermediate position having silver nitrate, with its caustic and irritating, but strongly germicidal properties on the one hand, and the non-irritating, mild, perhaps doubtfully germici-

dal, so-called colloidal silver preparations on the other. Silver picrate retains the medicinal qualities of the silver ion but possesses in addition, the well-known analgesic, healing and antiseptic properties of picric acid. Much of the bactericidal power is due to the silver which, although ionized in solution to a less extent than silver nitrate, makes silver picrate more efficient bactericidally than the colloidal silver or protein-masked products. The therapeutic properties of picric acid are well known, it having been used with success for many years in various skin lesions, including eczema, intertrigo, body ringworm, etc., Wilson (7) stating that in these particular complaints picric acid treatment gave results far superior to any other materials he had used. Kolmer (8) found that the use of picric acid as an application to the skin after vaccination proved four times more efficient than phenol in lessening the degree of local inflammatory action.

As an astringent, picric acid has been found superior to zinc sulphate or alum, while its penetrating powers are considerable, as shown by the fact that the hands are stained by the solution even through rubber gloves. Its use in burns and ulcers is well known, Muncy (9) stating that he had "failed to find an ulceration which did not respond to picric acid," while its "marked anodyne properties (when applied to wounds) made the use of aspirin or morphine rare."

In ophthalmic work, picric acid has met with approval, having been found "far superior in antiseptic action, in the strengths used, to other antiseptics usually administered in ophthalmology." Ehrenfried's (10) summation of the desirable therapeutic qualities of picric acid states the case particularly well:

> "Over any clean denuded surface it forms a protective aseptic scab by coagulation of secreted serum, which seals up ruptured lymph spaces, protects exposed nerve endings and splints the wound in such a manner that epithelial proliferation may proceed rapidly beneath, stimulating nature's method. This artificial scab protects against infection from external sources and promotes rapid and painless epidermatization."

If any corroboration of the above is required, Broon (11) reporting on results of picric acid in war surgery states:

> "One per cent picric acid is recommended for dressing superficial wounds, syringing sinuses, fractures and corroded tissues. It kills bacteria without corrosive effect and prevents suppuration, stimulates granulation of tissue, has marked anodyne properties and is less irritating and more efficacious than iodine. It may be used for sterilization of the skin in surgical cases and shortens the convalescent period."

In February of this year Stewart (12) reported his investigations into the maggot treatment of osteomyelitis, showing that a mixture of calcium carbonate and picric acid, or calcium picrate had practically the same effect as the maggots in stimulating phagocytosis and healing the wound. In the light of these and many other gratifying reports on the desirability and efficacy of picric acid, it would seem that silver picrate should be worthy of even greater consideration under similar circumstances. The additive effects of silver and picric acid would seem to be particularly desirable, as the action of the two constituents is apparently synergistic. The liberation of picric acid or picrates by interaction with tissue fluids should be preferable to the corrosive or caustic results of silver nitrate, particularly as the picrate radical would appear to exert such beneficial side effects. The irritating effects of silver picrate solutions in the concentrations normally used are insignifi-

cant, for in the course of this work silver picrate solutions of strength 1:1000 have been instilled into the eyes of dogs, cats and guinea pigs thrice daily for ten days and more without sign of irritation or deleterious effect. The solutions are less injurious than silver nitrate and definitely of greater efficacy and more rapid action than colloidal silver products. Baum (13) in testing a series of silver preparations including argyrol, protargol and silver picrate in several cases of gonorrhea, found that $^1/_4$ to $1^1/_2\%$ solutions of the picrate were as effective as 2 to 10% of some of the colloidal silver preparations in stopping the discharges present. By agar plate tests using typhosus, aureus, diphtheriæ and gonococcus organisms silver picrate was found to be the equal of similar strengths of silver nitrate in all cases but one (*C. diphtheriæ*). *Trichomonas Vaginalis*—the organism frequently found in cases of leucorrhea—is killed instantly by 1% silver picrate solutions, and pus cells are immediately coagulated. In short, silver picrate would appear to possess germicidal properties both physical and chemical in nature, picric acid apparently acting by precipitation of albuminous matter, and in some way denaturing the cell constituents. These effects, together with its powerfully penetrative properties, probably render the field more suitable for the subsequent action of the silver ion.

CLINICAL APPLICATIONS.

Silver picrate should be capable of application over a considerable therapeutic field, although with the exception of the recent work of Vanstane (14) who applied it successfully in *otitis media*, vaginitis, cervicitis, and diseases of the bladder, rectum and colon, its existence and usefulness appear to have been overlooked. The reason for this may possibly be accounted for by the number of reported fatalities among factory workers during the war period, resulting in the undeservedly restricted use of picric acid compounds.

The thought is therefore presented that, in the light of the above findings in which the combination of silver and picric acid has proved equal or superior to the usual silver medicaments without some of their disadvantages, this chemical should be worthy of recognition in medical and pharmaceutical armamentaria.

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