

served no indications of pain or stiffening around the point of injection. All three preparations contained small amounts of chloretone which might account for freedom from pain for a short time after injection.

Toxic symptoms with larger doses did not appear until about the sixth or eighth day after injection and death usually occurred from the fourteenth to the twenty-first day. Typical symptoms of bismuth poisoning consisting of emaciation and loss of appetite were noted.

The results of these experiments included in Table I indicate that the M. L. D. for the bismuth-methyl-camphorate is 350 mg. metallic bismuth per Kg. of rat. The bismuth-ethyl-camphorate has an M. L. D. of 250 mg. Bi/Kg. while the bismuth-butyl-camphorate is the most toxic with an M. L. D. of 150 mg. Bi/Kg. of rat.

TABLE I.—TOXICITY OF BISMUTH-CAMPHORATES IN RATS.

Bismuth-Methyl-Camphorate.				Bismuth-Ethyl-Camphorate.				Bismuth-Butyl-Camphorate.			
Dose Mg. Metallic Bi/Kg.	No. of Animals.	Days Sur-vival.	% Mortality.	Dose Mg. Metallic Bi/Kg.	No. of Animals.	Days Sur-vival.	% Mortality.	Dose Mg. Metallic Bi/Kg.	No. of Animals.	Days Sur-vival.	% Mortality.
100	5	..	0.0 %	75	5	..	0.0 %	100	5		0.0 %
150	10	24	20%	100	10	17	10%	150	10	18	60%
200	10	16	30%	125	5	30	20%	200	10	18	70%
250	10	18	20%	150	5	..	0.0%	300	5	17	80%
300	20	12	30%	200	10	15	30%				
350	10	12	80%	250	10	16	70%				
400	5	6	100%	300	10	15	80%				
				400	10	12	100%				

SUMMARY.

The preparation of the ortho-methyl, ethyl and *n*-butyl esters of the bismuth salt of camphoric acid has been described and their solubility in oil was investigated.

The toxicity in oil solutions was determined by intramuscular injections into albino rats.

REFERENCES.

- (1) Walker, *J. Chem. Soc.*, 61, 1088 (1892).
- (2) Walker, *Ibid.*, 63, 496 (1894).
- (3) Ross and Sommerville, *Ibid.*, 2770 (1926).
- (4) Edminson and Hilditch, *Transactions, J. Chem. Soc.*, 225 (1910).
- (5) Liebrecht, German Patent No. 461,830 (1928).

PREPARATION OF BENZOYL PERSULPHIDE.*

BY E. MONESS, W. A. LOTT AND W. G. CHRISTIANSEN.¹

Some preliminary clinical results obtained by Drs. Amberg and Brunsting of the Mayo Clinic had indicated that benzoyl persulphide might prove very useful in the treatment of certain selected types of dermatosis in which pruritis was the

* Scientific Section, A. Ph. A., Portland meeting, 1936.

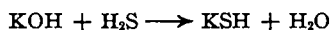
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predominating symptom. In order to provide sufficient quantities of this material for more extensive clinical trial the development of a satisfactory method for its preparation on a fairly large scale and in a state of high purity was undertaken.

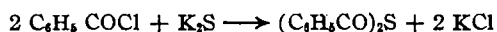
Benzoyl persulphide has been prepared in the laboratory by many investigators in the past, and many oxidizing agents have been used for its production from salts of thiobenzoic acid. Engelhardt, Latschinoff and Malischeff (1) obtained it by treating potassium thiobenzoate in aqueous solution with a solution of iodine in potassium iodide. Weigert (2) identified a substance as thiobenzoic acid by oxidizing its sodium salt with iodine. Fromme and Schmoltdt (3) precipitated benzoyl persulphide from a solution of a salt of thiobenzoic acid by means of potassium ferricyanide. Kym (4) oxidized free *p*-nitro thiobenzoic acid to the corresponding persulphide in alcoholic solution with ferric chloride. He emphasizes that only a little ferric chloride must be used; if too much is used, one obtains a gelatinous precipitate which is difficult to crystallize. For purposes of recrystallization these authors used mostly, acetone, alcohol or chloroform.

It is important that any plant process of producing benzoyl persulphide give uniform and high yields of a product which is reasonably free of impurities, and that the necessity of isolating thiobenzoic acid or its salts previous to oxidation be avoided. Furthermore, while iodine is a very suitable oxidizing agent from the chemical standpoint, it is expensive, even when a high proportion of it is subsequently recovered. It was therefore necessary to find an oxidizing agent which would be much less expensive, and which, preferably, would not involve the problem of recovery. Such an agent was found in hydrogen peroxide.

In order to explain the hydrogen peroxide process clearly it is desirable to first discuss the iodine process. An alcoholic solution of potassium hydrosulphide is prepared by saturating a solution of potassium hydroxide in absolute ethyl or methyl alcohol with hydrogen sulphide until a diluted test sample no longer gives a pink color with phenolphthalein. The reaction is:

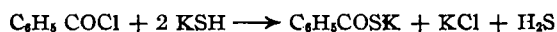


In small scale laboratory experiments the saturation is accomplished quickly, but on a large scale, unless one tests for actual saturation there is the possibility of not quite saturating the solution. If the saturation is incomplete potassium sulphide will be present and will react in the next step in the process with benzoyl chloride to form benzoyl sulphide:



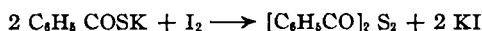
This sulphide does not yield benzoyl persulphide when treated with iodine. Therefore, the yield will be lowered in proportion to the amount of benzoyl sulphide formed from the potassium sulphide. It also serves as a source of sulphur which will contaminate the product and thereby make purification more difficult.

The alcoholic solution of potassium hydrosulphide is then treated with benzoyl chloride using one mol of the latter per two mols of the former. The chloride is added slowly with stirring and external cooling. The reaction is:



The hydrogen sulphide is evolved and the potassium chloride precipitates. It is filtered off and washed with alcohol.

This solution is now oxidized by the addition of solid iodine in small portions, using mechanical stirring and external cooling, until a slight excess of iodine is present as indicated by a slight brownish color of the reaction mixture. During the addition of the iodine, benzoyl persulphide separates out as a fine crystalline precipitate:



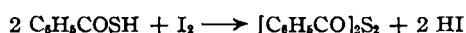
The product is collected on a filter and washed with absolute alcohol. The filter cake contains beside the benzoyl persulphide also most of the iodine in the form of potassium iodide. The latter is separated from the persulphide by washing the cake with water. The extract thus obtained is a clean, water-white solution of potassium iodide, with only a minimum of organic contaminant; from this solution iodine can be recovered either as potassium iodide or as free iodine.

In order to recrystallize the benzoyl persulphide it would be quite impracticable to use acetone or alcohol or chloroform because the benzoyl persulphide is only slightly soluble in these solvents even in the hot (6-7% in hot alcohol or acetone). Tremendous volumes of solvent would be required for recrystallization. We have found that ethylene dichloride is an excellent medium from which to recrystallize benzoyl persulphide. One part of benzoyl persulphide dissolves easily in 2.5 parts of hot ethylene dichloride, and on rapid chilling of the solution a pure white crystalline substance separates out, having a melting point of 128-128.5° C.

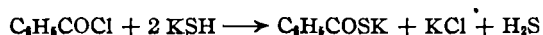
It would appear off-hand that one mol of potassium hydrosulphide per mol of benzoyl chloride should be sufficient; this would be more economical. The reaction would yield thiobenzoic acid instead of the potassium salt.



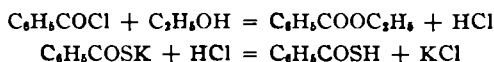
The acid should then give the desired persulphide upon oxidation.



When this was tried experimentally the correct amount of potassium chloride separated but the yield of benzoyl persulphide was only about 50% of the theory. In addition there was obtained from the filtrate an oil, which contained no sulphur and which, after purification, boiled at 208° C.; it was found to be ethyl benzoate. The amount obtained showed that it constituted a main product of the reaction and not merely an impurity. It was also noted that though the yield of benzoyl persulphide was small, the crude product was of exceptional whiteness and purity. The conception of the reactions involved, therefore, had to be revised, and the following is the explanation of what takes place when only one mol of potassium hydrosulphide is used. Since benzoyl chloride is being added to the solution of potassium hydrosulphide, the latter is present in excess and reacts as follows:



Therefore by the time half of the benzoyl chloride has been added all the potassium hydrosulphide has been used up and the second half of the benzoyl chloride reacts with the alcohol to form ethyl benzoate and hydrochloric acid. The latter reacts with the potassium thiobenzoate to produce potassium chloride and thiobenzoic acid.

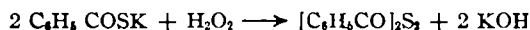


Combining the equations we have:



This equation accounts completely for the quantities of products obtained: thus the quantity of potassium chloride obtained is accounted for as well as the fact that by oxidation only 50% of the quantity of benzoyl persulphide is obtained; the rest of the benzoyl chloride forms ethyl benzoate and is not available on the further oxidation with iodine. The exceptional whiteness and purity of the crude product obtained when only one mol of potassium hydrosulphide is used is attributed to the fact that thiobenzoic acid is being oxidized, whereas when two mols are used the potassium salt is being oxidized.

Hydrogen Peroxide Process. In first trying to use hydrogen peroxide we prepared the solution of potassium thiobenzoate in the same manner as in the iodine process and expected the oxidation to proceed as indicated in the following reaction:

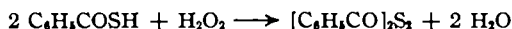


Benzoyl persulphide was indeed formed, but the yield was considerably less than when iodine was used as the oxidizing agent. With the latter the yield was 95–97% of the theory, whereas hydrogen peroxide under the same conditions never gave more than 60% of the theory. Furthermore the product was always contaminated with sulphur. This unsatisfactory result is due to the fact that potassium hydroxide is one of the reaction products, and alcoholic potassium hydroxide is known (3) to decompose benzoyl persulphide according to the equation:

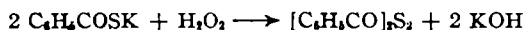


This indicated that merely changing oxidizing agents from iodine to hydrogen peroxide does not produce a satisfactory product, and that a change in the intermediate reactions is necessary.

It will be recollected that when one mol of benzoyl chloride was allowed to react with only one mol of potassium hydrosulphide, the oxidation with iodine gave only a 50% yield of benzoyl persulphide. During the work with one mol of potassium hydrosulphide, hydrogen peroxide had been tried in place of iodine and also gave a 50% yield. In other words, the yield is the same with hydrogen peroxide as with iodine, and this 50% yield was shown to be inherent in the nature of the reactions preceding the oxidation step. Moreover, the quality of the crude product obtained using hydrogen peroxide was very high and compared favorably with that obtained using iodine. The only difference between the case in which hydrogen peroxide is used on reaction mixtures prepared with one and two mols of potassium hydrosulphide is that in the former free thiobenzoic acid is being oxidized while in the latter the potassium salt of thiobenzoic acid was being oxidized. In other words, when using hydrogen peroxide, we have in one case:



while in the other we have:



In the second equation alcoholic potassium hydroxide is produced which partially decomposes the benzoyl persulphide while in the first equation only water and benzoyl persulphide result. It is therefore clear that in using hydrogen peroxide as the oxidizing agent we must deal with free thiobenzoic acid and not with its salts. Accordingly the following procedure was adopted: The solution of potassium hydrosulphide was prepared as before by reacting one mol of benzoyl chloride with two mols of the potassium hydrosulphide. At this point, however, instead of proceeding with the oxidation, the solution was acidified with an equivalent quantity of alcoholic hydro-

chloric acid, and the potassium chloride was filtered off and washed as usual with alcohol. This filtrate, which now contains free thiobenzoic acid in alcoholic solution was oxidized with hydrogen peroxide, and the yield was at once increased from the previous maximum of 60% to 70%. Moreover, the crude product was of a high degree of purity. The yield rose only to 70% because with alcoholic hydrochloric acid present, ethyl thiobenzoate is formed due to esterification (1). This can be avoided easily by using dilute aqueous hydrochloric acid instead of alcoholic hydrochloric acid, so that the reaction mixture was only 80% alcohol, instead of absolute alcohol. When this was done the yield at once rose to 91% of the theory, which was quite satisfactory.

EXPERIMENTAL.

Preparation of Benzoyl Persulphide Using Iodine as the Oxidizing Agents.—1500 Gm. of potassium hydroxide sticks (about 85% hydroxide) are dissolved in 15 liters of absolute ethyl or methyl alcohol, and saturated with hydrogen sulphide until a diluted test sample is no longer alkaline to phenolphthalein. 1650 Gm. of benzoyl chloride are added in a thin stream from a separatory funnel with good agitation, keeping the temperature of the mixture between 10–15° C. by cooling with a freezing mixture. The separated potassium chloride is filtered off and washed with about 750 cc. of alcohol.

The filtrate and washings are cooled to 10–15° C., and 1620–1740 Gm. of solid iodine are added in small portions to the stirred solution. The temperature is preferably kept at or below 15° C. The rate of the addition of iodine is such that there is only a momentary brown color as the iodine reacts with the potassium thiobenzoate. The addition of the iodine is stopped when a permanent (a few minutes' duration) brown color appears in the reaction mixture. All through the addition of the iodine crystalline benzoyl persulphide separates out. The reaction mixture appears yellow, but after filtering off the crystalline precipitate, and washing with about two liters of alcohol, the cake appears fairly white, and there is no yellow color.

The filter cake is then washed with ten liters of water, receiving the washings in a clean vessel, and the solution is later used for iodine recovery.

The filter cake is dried in air at ordinary temperature. Yield—95% of theory calculated on the basis of benzoyl chloride.

The dried crude product is dissolved with heating on the steam-bath, using 2.5 parts of ethylene dichloride per part of product. The hot solution is filtered through a hot funnel, and chilled rapidly by means of external cooling. A fine white crystalline substance is obtained, melting point 128–128.5° C. The first crop constitutes 90% of the total crude yield.

Recovery of Iodine.—The aqueous washings are slightly turbid, due to a small quantity of very finely divided benzoyl persulphide. This is filtered off, and a water-white, clear solution of potassium iodide is now at hand. The potassium iodide can be crystallized out of this solution and utilized as such or the iodine recovered by saturating the acidified solution with chlorine. The recovery of iodine is 60% of the original amount used.

Use of Hydrogen Peroxide in the Production of Benzoyl Persulphide.—The solution of potassium hydrosulphide and of potassium thiobenzoate is prepared as usual.

Without filtering off the potassium chloride and with continuous stirring, 1200 cc. of concentrated hydrochloric acid are added in a fairly rapid drip, whereupon some additional potassium chloride precipitates. This is now filtered off and washed with two liters of alcohol, adding the washings to the filtrate. This is diluted with three liters of water at room temperature. Finally 1200 cc. of a 30% solution of hydrogen peroxide is added in a fairly rapid drip with stirring and cooling externally with cold water. When the alcoholic solution of thiobenzoic acid is oxidized with hydrogen peroxide the benzoyl persulphide does not separate at once with each increment of hydrogen peroxide, as in the case when iodine is used. It may begin to separate slowly during this addition, or it may not separate at all until all the hydrogen peroxide is added, after which most of it separates during a period of one-half to one hour. This separation is accompanied by a rise in temperature, which is kept at 30° C. or below by external cooling with water. It is easy to observe the point where the reaction is complete since the yellow reaction mixture turns milky white fairly suddenly, representing a suspension of a white crystalline substance in a water-white, clear mother liquor of alcohol. It is best to permit the mixture to stand over night in the cold, before filtering, since if the suspension were to be filtered at once, only about 83% of the yield would be obtained at this stage, the rest crystallizing from the mother liquor on standing

over night. By allowing the whole reaction mixture to stand over night we obtain the total yield with one filtration. The crude product is pure enough not to need recrystallization, but may be recrystallized once from hot ethylene dichloride if desired.

REFERENCES.

- (1) *Zt. f. Chem.*, 4, 358 (1868).
- (2) *Ber.*, 36, 1010 (1903).
- (3) *Ber.*, 40, 2862 (1907).
- (4) *Ber.*, 32, 3533, footnote (1899).

EVALUATION OF LIME METHODS FOR DETERMINING MORPHINE
IN OPIUM.*

BY V. H. WALLINGFORD AND AUGUST H. HOMEYER.**

The literature on the determination of morphine in opium prior to 1920 was reviewed by Jermstad (1) who compared experimentally 16 official and 14 non-official methods. The early work was frequently unscientific and self-contradictory. Recent investigators have viewed the problem more critically and attempted to uncover the errors in the most widely used procedures. Hollman (2) investigated certain features of lime and ammonia methods. Reimers (3) made a critical review of the literature from 1920 to 1930.

Our research leads us to conclude that no method developed so far is satisfactory and that the precision obtainable varies with the type of opium tested. The behavior of pure morphine when subjected to many of the operations typical of lime methods has been studied in detail and the effects of various added substances have been quantitatively determined. Procedures have been devised for evaluating the errors of the principal methods now in use and the method proposed by the Commission of the League of Nations.

"Ammonia Methods" such as Jermstad's (1) are considered unsound in principle because, as pointed out by Reimers (3), the separation of narcotine from morphine by fractional precipitation with ammonia is not sharp. The lime method of the United States Pharmacopœia, Tenth Edition (U. S. P. X), the method of Dr. Joseph Rosin (4)¹ and "ammonia methods" use water to extract morphine from opium. In our experience and that of other workers (2), (5), (6), (7) this extraction is sometimes incomplete due to insufficient natural acidity of the opium.

In the methods of the United States Pharmacopœia X, British Pharmacopœia of 1932 (B. P.) and Rosin empirical aliquot parts are used which do not take into account variable factors of the opium which affect the solution. Our work has shown this practice to be inaccurate; in a particular case a U. S. P. X assay was

* The subject matter of this paper was submitted privately to H. J. Anslinger, United States Commissioner of Narcotics, and members of the Commission of Experts of the League of Nations engaged in standardizing opium assay methods, in two progress reports dated April 2 and June 25, 1935. Acknowledgment was made in the Quarterly Bulletin of the Health Organization of the League of Nations, Vol. IV, Extract No. 16, page 816.

** Contribution from the Organic Research Laboratory of the Mallinckrodt Chemical Works, St. Louis, Mo., submitted for publication July 24, 1935.

¹ Since this paper was prepared Dr. Rosin's method has been adopted in the U. S. P. XI and becomes official on June 1, 1936.