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A STUDY OF ANTISEPTIC COMPOUNDS FOR THE TREATMENT OF BURNS.*,[1]

BY D. T. MEREDITH[2] AND C. O. LEE.[3]

INTRODUCTION.

The anesthetic properties of cocaine were noted in 1884, twenty-four years after the discovery of the alkaloid was announced (1). As a local anesthetic it has never been entirely acceptable because it often produces untoward effects. Since the determination of its structure many synthetic substitutes have been prepared and introduced into Medicine and Pharmacy.

The idea of reacting a local anesthetic with an antiseptic to form a new compound having both anesthetic and antiseptic action was first reported by Thayer (2) who prepared such a compound from butesin (normal-butyl-para aminobenzoate) and picric acid. His preparation represented a combination of one mole of picric acid and two moles of butesin and had the antiseptic and anesthetic properties of these respective compounds. Butesin picrate in the form of an ointment has been widely used in the treatment of burns.

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[1] An abstract of a thesis submitted to the faculty of Purdue University in partial fulfilment of the requirements for the degree of Master of Science, by Donald T. Meredith, August 1938.

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This study has been directed toward the preparation of a compound of the same type using benzocaine as the anesthetic. Such a product will be described later.

HISTORICAL.

Picric acid has long been known to have an antiseptic action and its phenol coefficient has been reported as 4 to 7. Its ability to form salts was the basis for Thayer's butesin picrate (2). Marshal (3) has given an interesting history of picric acid.

The value of picric acid as a treatment for burns was accidentally discovered by a French medical student about 1896 (4). Since then it has been used in the form of a saturated aqueous solution for this purpose.

There has been much conjecture as to the chemical nature and structure of complexes formed between polynitro-aromatic compounds, such as picric acid, and aromatic hydrocarbons and bases. Sudborough (5), (6) proposed several formulas to explain such reactions, concluding that they were additive and made possible by the latent valency in the trivalent nitrogen of the amines. He worked with α-naphthylamine and trinitrobenzene.

In discussing the probable structure of these complexes, Taylor and Baker (7) indicate that the point of attachment is the nitro group. Coghill and Sturtevant (8) suggest that such compounds do not represent a chemical union in the ordinary sense as the picric acid is joined to the second component by the so-called secondary valency forces such as are represented in the compound $CuSO_4.5H_2O$. Desha (9) suggests that double salts, such as the alums, furnished the best analogy to these complexes. From these and other authorities it is clear that there are many opinions and theories regarding the chemical nature of these complexes. Taylor and Baker concluded their discussion of the subject by saying that, "There is, however, insufficient evidence for any definite conclusion to be reached."

Benzocaine was introduced by Einhorne and Henry between 1897 and 1899, as a synthetic local anesthetic, to take the place of cocaine. It was named "anesthesine" in 1902 by Ritsert (11) and its anesthetic properties were described. The name "anesthesine" was changed to "benzocaine" in 1920 by the Council on Pharmacy and Chemistry of the American Medical Association (12). It was official in the United States Pharmacopœia X and has been retained in the present revision.

EXPERIMENTAL.

In undertaking the study it was our idea to try to prepare several anesthetic antiseptics but the work has been limited chiefly to the picrate of benzocaine.

Thayer (2) in 1925 indicated that the reaction of two moles of the local anesthetic with one mole of the picric acid yielded a compound in the combining ratio of 2:1. A year later (13) he directed that three moles of local anesthetic and one of picric acid would give a compound in the combining ratio of 3:1. He had previously reported an analysis (1) which indicated a compound of the 2:1 ratio. In his patent Thayer described benzocaine picrate as a solid with a melting point of 120° to 121°. Our results are not in agreement with his.

A picrate of benzocaine was first prepared following the procedure suggested for the preparation of butesin picrate, namely the reaction of one mole of picric acid, dissolved in water, with two moles of benzocaine, dissolved in alcohol. A yellow, amorphous precipitate resulted but it gave no definite melting point. In an effort to prepare a compound with a definite melting point, other solvents were used including those which had been suggested in the preparation of butesin picrate. The solvents used, melting points and descriptions of the compounds are given in Table I.

TABLE I.

	Solvents for Benzocaine.	Solvents for Picric Acid.	Product.	Melting Point (Uncorrected).
1	Alcohol	Water	Yellow, amorphous solid	Indefinite
2	Acidified water	Water	Yellow, crystalline solid	160–162°
3	Alcohol	Alcohol	Yellow, crystalline solid	160–162°
4	Ether	Ether	Yellow, crystalline solid	160–162°
5	Chloroform	Chloroform	Yellow, crystalline solid	160–160°
6	Benzol	Benzol	Yellow, crystalline solid	160–162°

Discussion.—Each of the six products in Table I was prepared in the same way, two moles of the benzocaine and one mole of the picric acid being dissolved separately in the respective solvents and the solutions mixed. The picric acid was dried over sulfuric acid before being used in the reaction.

In an effort to determine the difference between the first compound in Table I and the remaining five it was decided to analyze them for picric acid. This was done by titrating the picrate with tenth normal sodium hydroxide as suggested by Thayer (1). The results of the analyses of the compounds given in Table I are shown in Table II. The percentages of picric acid are averages of several titrations.

TABLE II.

	Solvents for Benzocaine.	Solvents for Picric Acid.	Melting Point (Uncorr.).	Per Cent Picric Acid.
1	Alcohol	Water	Indefinite	37.5%*
2	Acidified water	Water	160–162°	58.4%
3	Alcohol	Alcohol	160–162°	57.7%
4	Ether	Ether	160–162°	58.4%
5	Chloroform	Chloroform	160–162°	58.2%
6	Benzol	Benzol	160–162°	58.0%

* The percentages shown are the averages of two determinations.

Discussion.—From the results as shown in Table II, it is evident that compounds 2 to 6 are different from number 1, and they (2 to 6) are probably all alike. The calculated amounts for picric acid in picrates representing different combining ratios are as follows:

Benzocaine.	Picric Acid.	Ratio.	Calculated Per Cent Picric Acid.
3 moles	1 mole	3:1	31.62
2 moles	1 mole	2:1	40.96
1 mole	1 mole	1:1	58.11

A comparison of the calculated percentages of picric acid and the results obtained by analysis would suggest that benzocaine picrate is formed by one mole of benzocaine reacting with one mole of picric acid.

Several of the picrate compounds were assayed for benzocaine by making the solutions basic and extracting the latter by means of benzol, evaporating the solvent and weighing the benzocaine. Thayer (1) used ether as the solvent but it appeared to extract some of the picric acid. Since benzol did not extract any of the picric acid we preferred to use it as the solvent.

The calculated amount of benzocaine, in benzocaine picrate, is 41.90%. The yield of benzocaine by the assay just described was 41.30% in those compounds of the 1:1 ratio.

We were unable to prepare benzocaine picrate in the 3:1 or 2:1 ratios as suggested by Thayer. By purifying the compounds by means of recrystallization it was possible to get a product which would analyze as a compound of a 1:1 ratio. Furthermore, we were able to show that there was free benzocaine in compound 1, Tables I and II, while compounds 2 to 6 showed it to be absent.

THE PREPARATION OF BENZOCAINE PICRATE.

The following procedure for the preparation of benzocaine picrate is recommended:

Dissolve one mole of benzocaine in alcohol and one mole of picric acid in water. The latter may be warmed to facilitate solution. Mix the two solutions and allow to stand six to twelve hours. Filter off the precipitate, wash it with distilled water and dry it in the air.

The benzocaine picrate obtained by this procedure need not be recrystallized. It is a yellow, crystalline solid melting at 161–162° (uncorrected). The yield is 88% of the theoretical. The averages of several assays are as follows:

	Picric Acid.	Benzocaine.
Amounts calculated	58.10%	41.90%
Amounts obtained by assay	58.20%	41.30%

Following the method of Thayer butesin picrate was prepared which conformed to his descriptions for the product. We have no explanation for the difference in behavior exhibited by butesin and benzocaine in the formation of picrates.

BACTERIOLOGY AND PHARMACOLOGY.

Bacteriological and pharmacological tests were made on the various compounds which had been prepared. Two per cent ointments, in a special cold cream base, were prepared from benzocaine picrate 1:1; benzocaine picrate mixture, compound 1, Table I; and butesin picrate. None of these were antiseptic to Staphylococcus aureus when tested by the agar plate method. No further tests were made.

To test the anesthetic action of these various compounds the so-called "rabbit's eye" test was used, the procedure being similar to that employed by Rider (14). The results showed that all of the compounds studied have anesthetic action of like duration.

SUMMARY.

1. A picrate of benzocaine has been prepared which represents a compound of benzocaine and picric acid in the ratio of one mole of benzocaine to one mole of picric acid. This compound is a yellow, crystalline solid melting at 161–162° (uncorrected). Solvents and methods of preparation for this picrate are given, together with methods of determination of the amounts of benzocaine and picric acid.

2. This picrate differs from that one prepared by Thayer and covered by U. S. Patent 1,596,259, in the combining ratio of the benzocaine and picric acid. By analysis it is shown that the compound prepared in this investigation represents a compound in the ratio of one mole of benzocaine to one of picric acid. The compound has a melting point of 161–162°. The one described by Thayer in the patent mentioned above represents a combination in the ratio of three moles of benzocaine to one of picric acid and has a melting point of 120–121°.

3. All of the compounds studied; benzocaine picrate, the impure mixture of benzocaine picrate and benzocaine, and butesin picrate have an anesthetic action as indicated by the "rabbit's eye" test.

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FIELD TRIPS AUGMENT INTEREST IN PHARMACOGNOSY.*

BY VICTOR LEWITUS.[1]

(ABSTRACT.)

In order to increase interest in the course in Pharmacognosy, the writer thought it opportune to exhibit as many plants in their natural habitats as possible. He inaugurated a series of outdoor field trips, two during the fall of the year and two during the spring months.

Surprisingly enough, it was found worthwhile to use this method regularly as a part of the course since students introduced to this procedure were much more appreciative of the work in Pharmacognosy after a few introductory ramblings among the growing plants used in official medicine.

Remembering that a field trip is not a picnic (as the youthful student is apt to consider it), but a regular lesson for a serious, though enjoyable, portion of the day's study, careful plans must be laid by the instructor beforehand. Chronologically scheduled, the outdoor trips may be arranged so that two will come in the fall, when rhizomes, roots, barks and woods are usually treated of in the standardized courses; and two will occur in the spring, when flowers, leaves, etc., are taken up. The fall trip should come not earlier than the third or fourth lesson in the subject, since it will take that long to cover the introductory phases of the subject. Once acquainted with the purpose and procedure, the student is then ready to profit by his or her experiences.

The following rules should be a guide to those wishing to augment studies in Pharmacognosy by field trips:

I. The purpose of the trip should be clearly outlined a week or so beforehand.

II. Depending on the proximity of the area to be visited, the time devoted to such a trip should be arranged on an "exchange" basis with some other department (*e. g.*, exchange of hours).

III. Students should equip themselves with a special notebook; taking notes and making sketches as they go along.

IV. Notes should bring out the following details regarding each living drug: (*a*) Habitat (kind of soil, moisture, elevation); (*b*) Name of plant and synonyms;

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