

dihydrochloride precipitated with dry ether. Recrystallized from absolute alcohol it forms sheaves and rosets of delicate, lemon-yellow needles which retain solvent equivalent to one molecule of water of crystallization when air-dry. The anhydrous salt shows  $[\alpha]_D^{24.5} = +18.4^\circ$  in water,  $c = 1.060$ , and gradually sinters and darkens when heated, melting to a dark red-brown liquid at  $180-5^\circ$ . It dissolves readily in water or methyl alcohol, less easily in absolute alcohol or dry chloroform, and is practically insoluble in dry acetone.

Air dry: Subs., 0.6382; loss, 0.0267 *in vacuo* at room temperature over  $H_2SO_4$ .

Calc. for  $C_{20}H_{22}ON_2 \cdot 2HCl \cdot H_2O$ :  $H_2O$ , 4.54. Found: 4.18.

Anhydrous: Subs., 0.1329; 8.8 cc. N ( $25.0^\circ$ , 756 mm.).

Subs., 0.1297; 13.85 cc.  $AgNO_3$  sol. (1 cc. = 0.00176 g. Cl).

Calc. for  $C_{20}H_{22}ON_2 \cdot 2HCl$ : N, 7.39; Cl, 18.69. Found: N, 7.55; Cl, 18.81.

### Summary.

The so-called "desoxy" derivatives of dihydro-quinine and dihydro-quinidine are described, together with certain of their salts, homologs, and the alkaloidal derivatives encountered in their preparation. It is proposed that the substitution of the suffix "ane" for the prefix "desoxy" would simplify the terminology of this group of substances. The series dihydro-quinine  $\longrightarrow$  chlorodihydro-quinine  $\longrightarrow$  dihydro-quinane  $\longrightarrow$  dihydro-cupreane  $\longrightarrow$  ethyl-dihydro-cupreane, resulting in the preparation of an analog of ethyl-dihydro-cupreine (optochin) was prepared and studied.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF PARKE, DAVIS AND CO.]

## DERIVATIVES OF TRIHALOGEN TERTIARY-BUTYL ALCOHOLS.

### III. THE BENZOIC ACID ESTER OF TRICHLORO-TERTIARY-BUTYL ALCOHOL OR CHLOROTONE BENZOIC ACID ESTER.

BY T. B. ALDRICH.

Received May 12, 1920.

Under the title, "Benzoyloxyisobuttersäure trichlorid," Willgerodt and Dürr<sup>1</sup> have described an oil which they obtained through the interaction of trichloro-tertiary-butyl alcohol on benzoyl chloride in molecular quantities. They state

"On heating the mixture there is a rapid evolution of hydrochloric acid gas. The liquid, boiling at  $270-290^\circ$ , obtained by fractionation is then dissolved in ether and shaken with an aqueous solution of sodium carbonate. After drying the ethereal solution, the ether is evaporated, and the yellowish oil remaining is distilled. The principal part of the ester distils between  $275-280^\circ$ , but on standing in the receptacle deposits crystals of benzoic acid which are removed by filtration. The oil thus obtained and further purified has finally a B. P. of  $282^\circ$  and is yellow in color. Chlorine determination: Theoretical 37.8%. Found 37.6%."

<sup>1</sup> Willgerodt and Dürr, *J. prakt. Chem. N. F.*, 39, 286 (1889).

Having prepared a number of esters of trichloro- and tribromo-tertiary-butyl alcohol acetyl chloretone,<sup>1</sup> acetyl brometone,<sup>2</sup> propionic and butyric esters of brometone<sup>3</sup>, and having obtained a *crystalline* benzoic ester of brometone (this work is unpublished) it occurred to me to repeat the work of Willgerodt and Dürr, especially since they reported their product as an oil, and compare it chemically, physically and pharmacologically with the other esters and especially with the corresponding benzoic acid ester of tribromo-tertiary-butyl alcohol. The product I obtained by carrying out this synthesis, differs so markedly from that obtained by the authors cited that I consider it imperative to publish the results of my investigation.

In carrying out the synthesis according to the very brief directions given at the beginning of this paper by Willgerodt and Dürr, the author finds that, during distillation under ordinary pressure, decomposition products are formed, consisting in part of benzoic acid, which may be recognized by its general appearance, solubility, odor, melting point, etc. Hydrogen chloride is also given off when the temperature is high. No doubt the product obtained by Willgerodt and Dürr is a mixture of benzoic acid, a small amount of the ester, the principal portion having been decomposed by the high temperature, and possibly some chloretone and other substances such as chlorine decomposition products. That benzoic acid is present is evidenced by the authors themselves who state "the distillate deposits crystals of benzoic acid on standing." Indeed the method employed by the authors for purification would naturally lead to a mixture of various products rather than to a single product, since no attempt was made to remove the uncombined chloretone and benzoyl chloride that presumably did not enter into the reaction.

According to the method to be given shortly, any excess of chloretone or benzoyl chloride is removed by thorough washing and heating the product with alkali, which decomposes the ester very slowly, and then with water before any attempt is made to purify the ester.

That the chlorine determinations made by Willgerodt and Dürr agree so closely with the theoretical value, suggests the presence of bodies with high chlorine content mixed with other bodies containing little or no chlorine.

Although distillation *under ordinary pressure*, as practiced by Willgerodt and Dürr, leads to decomposition of the ester, distillation *under reduced pressure* can be carried out, as shown later, with very little, if any, decomposition.

<sup>1</sup> THIS JOURNAL, 37, 2720 (1915).

<sup>2</sup> *Ibid.*, 38, 2740 (1916).

<sup>3</sup> *Ibid.*, 40, 1948 (1918).

### Experimental.

Molecular quantities of chloretone, dehydrated over calcium chloride in a desiccator, and benzoyl chloride are heated on the steam bath for several hours, or until hydrogen chloride ceases to be given off to any extent. The reaction is practically ended in about 6 hours, although the product may be heated longer without injury.

As soon as the reaction is fairly complete, water is added, and the ester thereby thrown out in the form of an oil which solidifies when cooled in ice water. As the oil solidifies, it is best to agitate the contents of the flask to prevent the ester from forming a hard cake which is difficult to remove. When the ester has solidified, the supernatant liquid is decanted as completely as possible, an excess of caustic soda solution (5-10%) is added, and the vessel is heated on the steam bath for about half an hour. By this procedure, any chloretone or benzoyl chloride which remains will be decomposed, or rendered soluble in water. At the end of this time, the flask is cooled as before, and its contents poured into a mortar and ground to a fine powder. It is then transferred to a suction filter and washed a number of times with cold water. It dissolves readily, in alcohol, from which it is obtained in the form of white monoclinic crystals. If the reaction is carried out carefully the yield is excellent.

Chlorine determinations (Carius) carried out with a product which melted between 34-35° after several recrystallizations from moderately strong alcohol, gave the following results.

Subs., 0.2242, 0.2629: AgCl, 0.3426, 0.4027.

Calc. for  $C_{11}H_{11}O_2Cl_2$ : 37.83. Found: 37.80, 37.89.

The ester is readily soluble in strong alcohol, acetone, chloroform, ether, glacial acetic acid, benzene, etc., but very sparingly soluble in water. It may be recrystallized to advantage from alcohol, from which it may be precipitated by water.

**Distillation.**—(a) *Under normal pressure.* Twenty-three g. of the purified ester was distilled under ordinary pressure. Three fractions were obtained: (1) 170-200° (few cc.) (neglected) distillate colorless; (2) 200-250° (small portion); (3) 250-270° (greater portion). The residue was dark reddish in color, decomposition having taken place, since vapors were given off during the distillation. To the third fraction a little alcohol was added, and the solution was placed in a vacuum desiccator. Crystals formed after standing, m. p. about 112°. This would point possibly to benzoic acid, m. p. 120°.

**Distillation.**—(b) *Under reduced pressure.* Thirty-five g. of the purified ester was distilled under a pressure of 148 mm. Four fractions were obtained: (1) 190-220° (few cc.) slight coloration in distillation flask, distillate clear and colorless; (2) 220-225° (about 5 cc.) color increasing in flask, fumes noted in receiver, distillate colorless; (3) 225

230° (about 5 cc.) color increasing slightly in flask, distillate colorless; (4) 230–235° (about 20 cc.) dark residue (small in amount) left in flask, distillate colorless.

All the fractions on cooling in ice water solidified to a mass of crystals, and, after recrystallization from alcohol, all gave the same m. p., 34.5 to 35°, the melting point of the original ester. There was a yield of 29 g. of purified product which shows very little decomposition. In this state the ester apparently boils under the above pressure without decomposition at from 220–235°. The volume of the several fractions was estimated.

The ester is very slowly volatile with steam, but does not decompose. It passes over as an oil which solidifies on cooling, especially when rubbed with a rod or when inoculated with a crystal of the substance.

Unlike chloretone, brometone, and the acetic esters, it is practically non-volatile in the air at ordinary temperature, as well as at incubator temperature (37°). The loss even after several days is very slight.

When boiled with water for 18 hours or with 10% sulfuric acid for several hours, very little decomposition occurred. The supernatant liquid gave a slight test for chloride, but in both instances practically all of the ester remained as an oil which solidified when cooled and melted between 34 and 35°.

However, when the ester is refluxed with 10% sodium hydroxide solution, it decomposes slowly, and chlorides may be recognized in the supernatant liquid. This resistance of the ester to the action of moderately strong alkali, as intimated previously, is utilized in its preparation to separate it from chloretone and benzoyl chloride, both of which are decomposed very quickly by this reagent, especially when heated with it. If the boiling with alkali is not continued too long, a portion of the ester remains undecomposed.

When *acetyl chloretone* is boiled with an excess of conc. nitric acid, saponification commences immediately and the presence of chloretone may be demonstrated in a few minutes if water is added; when acetyl, propionyl or butyryl brometone is treated in the same way saponification takes place also, but the brometone itself is decomposed to a certain extent as shown by the evolution of bromine vapors. When, however, the benzoic acid ester is treated similarly, the halogen complex apparently is not changed.

With water or 10% sulfuric acid in a sealed tube under pressure at a temperature of 160–170° for several hours the greater part of the ester is found undecomposed in the form of an oil, which, when cooled in ice water, solidifies, and after recrystallization, melts between 35° and 36°.

One fact stands out prominently: the benzoic ester is characterized by great relative stability, greater even than the other esters thus far studied. It also differs in toxicity, being  $\frac{1}{3}$  as toxic as the acetic ester of

brometone, and about  $1/10$  as toxic as the corresponding acetic ester of chloretone. As far as observed, the benzoic ester does not produce convulsions, which is at variance with the observations of Wolfenstein, Lowey and Bachstex relative to analogous esters.<sup>1</sup> Perhaps owing to the insolubility of the ester, the properties referred to do not develop, but this is hardly to be expected since the other esters are also practically insoluble.

The following pharmacological facts relative to the ester were furnished by my associate, Mr. L. W. Rowe.

"When melted and mixed with olive oil and injected intraperitoneally into guinea pigs, its M. L. D. was found to be about 1.5 g. per kg. body weight.

"Experiments upon dogs indicate that the compound has very slight physiological action, even when given in very large doses. One dog when given 0.5 g. per kg. in capsule per stomach showed slight muscular incoördination  $1\frac{1}{2}$  hours later. No other effect.

"Another dog given twice the above dose (one g. per kg.) in the same way exhibited slight incoördination and uneasiness. This dog was killed 4 days later and an examination of the stomach showed that no irritating action of a serious nature had taken place.

"A dog was given one g. per kg. by intraperitoneal injection. A slight sedative effect was observed in about 20 minutes. Marked diuresis and purgation resulted in about 30 minutes after injection. Slight nausea was observed about 2 hours after injection. Dog was very sick and died 20 hours after being dosed. Autopsy showed marked inflammation of the intestines and bladder, showing that the irritation caused by the material injected must have been largely responsible for the purgation and urination.

"Five g. of the melted sample was injected subcutaneously into a dog. No general effect was observed. Several days later the skin sloughed off at the site of injection showing that the material was very irritating and was not properly absorbed.

"That irritation is produced when the ester is injected intraperitoneally or subcutaneously is not necessarily indicative of irritant properties inherent in the substance itself; but is probably, in part at least, caused by its non-absorption, just as with any other similarly introduced foreign material.

"The insolubility of the compound as well as the fact that it is apparently not broken up in the body into soluble constituents renders it difficult to study its pharmacological action."

#### Summary.

The benzoyl ester of chloretone,  $C_6H_5CO.OC-C_3H_6Cl_3$ , is prepared by

<sup>1</sup> Wolfenstein, Lowey and Bachstex, *Ber.*, 48, 2035-43 (1916).

heating molecular quantities of benzoyl chloride and anhydrous chloretone on the steam bath until hydrogen chloride ceases to be given off. The ester is a solid which melted between 34-35° and not an oil as claimed by Willgerodt and Dürr, and may be distilled under reduced pressure without decomposition. It is not readily saponified, and in this respect is much more stable than the other esters previously studied. Boiling with conc. nitric acid does not decompose it as is the case with the aliphatic esters of both chloretone and brometone. Pharmacological tests would indicate that it possesses less hypnotic or anesthetic properties and is less toxic than the esters studies thus far.

DETROIT, MICH

[CONTRIBUTION FROM THE NORTH CAROLINA DEPARTMENT OF AGRICULTURE.]

**COCKLE-BUR OIL. A NEW SEED OIL.**

BY LELAND B. RHODES.

Received May 22, 1920.

The purpose of the investigation was to prepare cockle-bur oil and determine some of its physical and chemical constants, also to determine some of the properties of the kernels.

The burs for examination were gathered in the vicinity of Raleigh, N. C., during October, 1919, and until the middle of November. They were of the variety sometimes known as the clot-bur (*Xanthium Echinatum*), a coarse asteracious weed having rough leaves and prickly bur-like heads. The seed has the property that one-half germinates one year and the other half the succeeding year. The burs were cut in half by a trimming board; by a quick sharp movement the burs are not mashed and the kernels come out readily. After cutting, the burs were placed in a box and shaken vigorously. The hulls were then taken out, leaving the kernels on the bottom. The kernels as thus obtained were placed in a mortar and gently pounded and rubbed to remove the black shucks. By blowing into the mortar the shucks were removed, leaving the kernels.

In order to determine the per cent. yield of the kernels, the most luxuriant plants were harvested and the kernels separated by hand from a 500 g. sample of burs. 30.69% by weight was recovered.

TABLE I.—PROPERTIES OF THE KERNELS.

	1. %.	2. %.
Moisture (by heating).....	6.85	6.95
Moisture (by vacuum).....	7.22	7.23
Crude protein.....	40.34	40.53
Crude fiber (A. O. A. C. method).....	2.58	2.47
Oil (Soxhlet) extracted with ethyl ether.....	29.89	29.78
Oil (Soxhlet) extracted with petroleum ether.....	29.80	...
Ash.....	5.42	5.41