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## DERIVATIVES OF TRIHALOGEN TERTIARY-BUTYL ALCOHOLS

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## IV. The Benzoyl Ester of Tribromo-tertiary-butyl Alcohol or Brometone Benzoyl Ester

In a recent paper<sup>1</sup> it was shown that the benzoyl ester of trichloro-*tert.*-butyl alcohol (chloretone) is not an oil at ordinary temperatures as claimed by Willgerodt and Durr<sup>2</sup> but a solid, crystallizing in the monoclinic system and having a melting point of 34–35°. Brief reference was also made in the above mentioned paper<sup>1</sup> to a crystalline benzoyl ester of tribromo-*tert.*-butyl alcohol (brometone).

The preparation of this ester is similar to that of the corresponding ester of chloretone. Equimolecular weights of brometone, dehydrated by placing it over calcium chloride in a desiccator, and of benzoyl chloride are heated together on the steam-bath for about 6 hours, or until hydrogen chloride ceases to be given off, although the mixture may be heated longer with very little injury to the ester. Any excess of brometone or benzoyl chloride is removed by heating the oil-like mixture with a 5% solution of caustic soda on the steam-bath. This treatment decomposes or changes any residual brometone or benzoyl chloride to products that may subsequently be removed by thoroughly washing the material with warm water.

The ester is an oil when hot, but solidifies as it cools. While it is still warm it is advisable to pour it from the flask into a mortar and stir it at the same time to prevent it from caking. Obtained in this way, it is crystalline and, after a thorough washing, it may be recrystallized to advantage from 80% alcohol from which it is obtained in the form of monoclinic crystals similar to those of the corresponding ester of chloretone. The yield is excellent. The pure compound melts at 90°.

Subs., 0.4133, 0.2133; CO<sub>2</sub>, 0.4774, 0.2517; H<sub>2</sub>O, 0.1008, 0.0616. Subs., 0.2060, 0.2120; AgBr (Carius), 0.2788, 0.2845. Calc. for C<sub>11</sub>H<sub>11</sub>O<sub>2</sub>Br<sub>3</sub>; C, 31.8; H, 2.5; Br, 57.83. Found: C, 31.50, 32.2; H, 2.71, 3.2; Br, 57.62, 57.12.

The ester is readily soluble in strong alcohol, acetone, chloroform, ether, glacial acetic acid, benzene, etc., but is insoluble in water. Unlike brometone and chloretone, it is non-volatile at room or incubator temperature. It is very slowly volatile with steam.

Chloretone and brometone, heated with an aqueous solution of caustic soda, are decomposed readily, and at the same time the halogen is quite completely removed, whereas the benzoyl esters are not affected by this treatment except, possibly, to a very slight extent.

<sup>1</sup> THIS JOURNAL, 42, 1502 (1920).

<sup>2</sup> Willgerodt and Durr, *J. prakt. Chem.*, N. F., 39, 286 (1889).

Refluxing with water for several days has very little effect on the aromatic esters, even heating them under pressure at 170° does not decompose them materially.

Our associate, Mr. L. W. Rowe, has kindly furnished us with the following pharmacological data relative to the benzoyl ester of brometone.

"Experiments upon dogs indicate that this compound is inert pharmacologically when administered by the oral route and that it is very stable, not being hydrolyzed to any appreciable extent by the digestive enzymes.

"The above conclusions were reached by the following experiments with the compound itself as well as from certain experiments with brometone alone.

"A dog weighing 10.2 kg. was given 1.0 g. per kg. (total dose 10.2 g.) of the benzoyl ester in capsules per stomach and showed absolutely no sedative or other appreciable symptoms during a period of observation lasting 8 days.

"A second dog weighing 12.1 kg. was given 1.0 g. per kg. of the ester, orally, and was also given 250 cc. of water immediately following this to aid absorption, if possible. No symptoms were observed during a period of one week, and the dog was apparently perfectly normal at the end of that time.

"Brometone, on the other hand, when tested similarly in doses of 1.0 g. and 0.5 g. per kg. respectively on 2 dogs caused gradual but complete narcosis in each case, resulting in the death of both animals in about 48 hours.

"It is thus evident that the benzoyl ester does not possess pharmacologic action similar to brometone and that it is less active than the benzoyl ester of chloretone, which was reported to have slight action."

The benzoyl esters of chloretone and brometone have the following points in common: both are white, monoclinic crystals, insoluble in water, soluble in the organic solvents, very slightly volatile in the air or with steam, not decomposed by boiling with strong nitric acid, and have very little physiological action.

## V. Mononitro Derivatives of the Benzoyl Esters of the Trihalogen-tertiary-butyl Alcohols

It has been emphasized by one of us in former papers<sup>3</sup> that the aliphatic esters of trihalogen *tert.*-butyl alcohols without exception, when heated a short time with conc. nitric acid, split up into the respective halogen alcohols and the acids. For example, when the acetyl ester of chloretone is heated for a few minutes with an excess of conc. nitric acid it is broken up into chloretone and acetic acid. What is true of the acetyl ester is also true of all other aliphatic acid esters studied so far, and it was to be presumed that the benzoyl esters of both chloretone and brometone would conduct themselves similarly. However, in trying to decompose the aromatic ester of chloretone with nitric acid, it was found that it conducted itself differently toward this acid, forming nitro compounds as evidenced by the presence of nitrogen in the product. After purification and analysis of the derivative, it was shown that a mononitro compound was formed

<sup>3</sup> Aldrich, *THIS JOURNAL*, **37**, 2720 (1915); **38**, 2740 (1916); **40**, 1948 (1918); **42**, 1502 (1920).

almost exclusively and, later, this compound was found to be identical in every respect with the *m*-nitrobenzoyl ester of chloretone, prepared by using *m*-nitrobenzoyl chloride. This was to be expected, since when a benzene molecule which contains a carboxyl group, or carboxyl residue is nitrated the nitro group enters the *meta* position.

When suitable precautions are taken, the benzoyl ester of brometone conducts itself toward nitric acid similarly, and a *meta*-nitro compound is produced.

Although we have not attempted to prepare the mononitro esters from the respective mononitrobenzoic acids and the trihalogen tertiary butyl alcohols by the use of a dehydrating agent, it is to be presumed that this procedure would lead to similar nitro derivatives.

We have then the following two customary methods of preparing the mononitrobenzoyl esters of the trihalogen *tert.*-butyl alcohols: (I) by nitration; (II) by the use of the mononitrobenzoyl chlorides.

Method I has been used in the preparation of the *meta* compounds of the benzoyl esters of chloretone and of brometone, while Method II has been employed in the preparation of the *o*-, *m*- and *p*-nitrobenzoyl esters of chloretone and brometone.

In the preparation of the *meta*-nitro compound from the benzoyl ester of chloretone according to Method I it is necessary only to use an excess of strong nitric acid, and to add the powdered ester to it while the temperature is kept under 50°. In the case of the brometone ester, it seems to be desirable to keep the mixture much colder. After the reaction is completed, water is added while the solution is being cooled. This precipitates the nitro compound as an oil which may solidify. The compound is washed repeatedly with water, then recrystallized from alcohol. Since any excess of the benzoyl ester is freely soluble in alcohol it remains in the solution as it cools, while the nitro compounds crystallize in the form of needles or plates.

In the case of Method II molecular quantities of the acyl chloride and chloretone or brometone are placed in a suitable flask attached to a reflux condenser and warmed gently over an asbestos mat, until hydrogen chloride commences to be given off. The heat is then moderated so that the reaction continues slowly. After several hours, the mixture has assumed a dark color. It is then removed to a steam-bath and the heat is applied until very little gas is evolved. The product usually solidifies as it cools. Water is added, the content of the flask heated, then cooled and the wash water decanted. The residue is washed until the wash water is neutral. The product is purified by crystallizing it from alcohol.

The nitro compounds are beautifully crystalline substances, practically insoluble in water but soluble in the organic solvents. All are stable and non-volatile in the air or with steam.

Herewith are given some of the properties of the 6 mononitro compounds, together with analytical data, etc.

	M. p. ° C.	Cryst. form	Sol. cold alcohol	Sol. glac. acet. acid	Subs. taken	Silver		Halogen	
						halide	Found	Found	Calc.
<i>o</i> -Nitrobenzoyl ester of chloretone	91°	Monoclinic plates	Slightly	Very sol.	G.	0.2782	0.3613	32.1	32.6
					G.	0.2520	0.3270	32.1	
						0.3490	0.4523	32.06	
						0.3159	0.4123	32.29	
<i>o</i> -Nitrobenzoyl ester of brometone	97°	Monoclinic plates	Sparingly	Sol.		0.2666	0.3208	51.20	52.17
						0.3107	0.3759	51.48	
						0.2591	0.3111	51.10	
<i>m</i> -Nitrobenzoyl ester of chloretone	87°	Monoclinic plates	Slightly	Sol.		0.3164	0.4145	32.4	32.6
<i>m</i> -Nitrobenzoyl ester of brometone	121°	Flat needles	Sparingly	Very sol.		0.2732	0.3590	32.5	
						0.2807	0.3430	52.01	52.17
<i>p</i> -Nitrobenzoyl ester of chloretone	145°	Flat needles	Sparingly	Sol.		0.3605	0.4420	52.14	
						0.2414	0.3176	32.55	32.6
						0.2293	0.3075	33.17	
						0.2605	0.3400	32.29	
<i>p</i> -Nitrobenzoyl ester of brometone	148°	Needles	Sparingly	Very sol.		0.3395	0.4472	32.68	
						0.3001	0.3662	51.92	52.17
						0.2961	0.3630	52.18	

Although it is more convenient to prepare the nitro esters by using the respective nitrobenzoyl chlorides, it must not be lost sight of that they may be prepared by using the respective nitrobenzoic acids with a suitable dehydrating agent.

These esters are being studied further.

### Summary

The benzoyl ester of brometone ( $C_6H_5-CO-O-C_4H_8Br_3$ ) is prepared in a manner similar to that employed for the corresponding chloretone derivative. It is a white solid crystallizing in the monoclinic system and has a melting point of 90°. It is not readily saponified. Its insolubility probably accounts for its lack of physiological action.

Through the interaction of nitrobenzoyl chloride and the trihalogen *tert*-butyl alcohols 6 derivatives have been prepared.

By nitrating the benzoyl esters of trichloro- and tribromo-*tert*-butyl alcohols, nitro esters were also obtained which corresponded in every respect with the *meta*- compounds made by using *m*-nitrobenzoyl chloride.

These nitro derivatives crystallize from alcohol in the form of colorless plates or needles. They are insoluble in water but are readily soluble in the organic solvents, not readily saponified, practically odorless and tasteless, and may be reduced to amino compounds. They are not as active physiologically as the alcohols from which they are prepared, due possibly to their insolubility in water.