amount of water. A "soft" pilular extract seldom contains more than 25 per cent of water; a "thin" extract contains a variable amount of water depending upon its "thinness." This extract should be evaporated to such a volume that enough alcohol can be added to it to bring the solution of it to the same alcohol content as that of the reserve percolate and yet keep it within the permitted volume.

(6) There is good evidence to believe that a considerable proportion of the decrease in C_2H_5OH content of extractive preparations as compared with the C_2H_5OH content of the menstruum from which they were prepared is due to loss of alcohol by evaporation during the manufacturing process. By the exercise of care to prevent the loss of alcohol by evaporation, it was possible to increase the C_2H_5OH content of fluidextracts by 5 to 6 percentage points. While variations in extractive from different lots of the same drug may be responsible for some of the variations in C_2H_5OH content of the extractive preparations of that drug, yet probably a principal reason for these variations is the loss of alcohol by evaporation during the manufacturing process.

THE SYNTHESIS AND PHARMACOLOGICAL ACTION OF SOME 2,2,2-TRIALKYL ETHANOLS.*, **

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In a study of some hydroxybenzyl alcohols Dunning, Dunning and Reid (1) found that 5-bromo-2-hydroxy and 5-ethyl-2-hydroxy benzyl alcohol possess a local anesthetic efficiency of the same relative order and it was thought possible that such a relationship might be found between other series of halogen and alkyl substituted derivatives of the same parent substance. In order to investigate this possibility four trialkyl ethanols, namely, 2,2,2-trimethyl ethanol; 2,2-dimethyl-2-ethyl ethanol; 2,2-diethyl-2-methyl ethanol and 2,2,2-triethyl ethanol were prepared and their anesthetic properties compared to those of 2,2,2-tribromoethanol which has found some use as a general anesthetic.

The method of preparation used in all cases was a modification of the one employed by Conant, Webb and Mendum (2) for preparing alcohols of the general type $R_3C\text{-}CH_2OH$. It involves three steps, namely, (*a*) preparation of the proper tertiary chloride from the corresponding alcohol by treatment with concentrated hydrochloric acid, (*b*) formation of the Grignard reagent of the tertiary chloride and (*c*) treatment of the Grignard reagent with gaseous formaldehyde followed by hydrolysis.

EXPERIMENTAL.

A description of the method employed for obtaining 2,2,2-trimethyl ethanol and an examination of Tables I and II adequately describes the preparation of all four of these compounds.

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Tertiary butyl chloride was obtained in 77–83 per cent yields by the method of Norris and Olmsted (3). Two hundred cubic centimeters of tertiary butyl alcohol (Eastman practical) and 500 cc. of concentrated hydrochloric acid were placed in a one-liter separatory funnel and shaken continuously for fifteen minutes. The layers were allowed to separate and the upper portion drawn off and washed with a saturated solution of sodium bicarbonate until it was no longer acid to litmus paper. The chloride was then dried over 20 Gm. of calcium chloride and distilled through a 20-cm. glass bead column over a water-bath. The fraction distilling at 51–52° C. was collected and kept over anhydrous sodium carbonate until ready for use.

The procedure of Puntambeker and Zoellner (4) was followed to obtain tertiary butyl magnesium chloride. Sixty-one grams (2.5 moles) of magnesium turnings were placed in a three-liter, three-necked flask fitted with a mechanical stirrer and mercury seal, a 300-cc. separatory funnel and reflux condenser. The magnesium was covered with 200 cc. of anhydrous ether followed by 5 cc. of ethyl bromide and a crystal of iodine to initiate the reaction. Stirring was started and a solution of 227 Gm. (2.45 moles) of tertiary butyl chloride in 1100 cc. of anhydrous ether was dropped slowly on the magnesium during a period of six hours. The rate of addition was regulated so that slow refluxing continued throughout the reaction. After complete addition of the halide solution, the mixture was stirred for fifteen minutes to complete the reaction.

The yield of Grignard reagent was calculated after titrating an aliquot portion of the ether solution according to the method of Gilman (5) and treated with a ten per cent excess of formaldehyde gas by heating the proper quantity of paraformaldehyde (dried over concentrated sulfuric acid for ten days) in a large test-tube connected to the reaction flask by a large-bore delivery tube. During the reaction stirring was continued and the rate of addition of formaldehyde so adjusted that gentle refluxing continued throughout the procedure. Refluxing was maintained for two hours after all the formaldehyde had been added by warming the flask on a water-bath.

TABLE I.—PREPARATION OF THE GRIGNARD REAGENTS.

Grignard Reagent.	Moles Mg. Used.	Cc. Ether Added to Mg.	Moles Chloride Used.	Cc. Ether Added to Chloride.	Time of Addition.	Yield.
I	2.5	200	2.45	1100	6 hrs.	85%
II	2.5	200	2.45	1100	8 hrs.	75%
III	2.5	200	2.5	1000	8 hrs.	65%
IV	2.23	500	2.20	800	8 hrs.	40%

I. Tert. butyl magnesium chloride.
II. Tert. amyl magnesium chloride.
III. Diethyl-methyl-carbinyl magnesium chloride.
IV. Triethyl-carbinyl magnesium chloride.

In preparing Compounds II, III and IV the reaction was carried out under an atmosphere of nitrogen to protect the Grignard reagent from the action of the air.

TABLE II.—PREPARATION OF THE SUBSTITUTED ETHANOLS.

Alcohol Prepared.	Chloride Used and % Yield.	Yield of Alcohol from Grig. Reag.	Overall Yield.	B. P.	n_D^{20} Degrees.
A	$(CH_3)_3C—Cl$ 80%	35%	30%	111–113 C.	Solid
B	$(CH_3)_2(C_2H_5)C—Cl$ 80%	33%	25%	134–135 C.	1.4203
C	$CH_3(C_2H_5)_2C—Cl$ 77%	40%	26%	150–151 C.	1.4261
D	$(C_2H_5)_3C—Cl$ 85%	10%	4%	76–77 C. at 11 mm.	1.4400

A. 2,2,2-trimethyl ethanol.
B. 2,2-dimethyl-2-ethyl ethanol.
C. 2,2-diethyl-2-methyl ethanol.
D. 2,2,2-triethyl ethanol.

Hydrolysis of the product was accomplished by pouring it onto a mixture of 1500 Gm. of cracked ice, 300 cc. of water and 300 Gm. of ammonium chloride with frequent stirring. After separating the ether layer, the aqueous portion was extracted with three 100-cc. portions of ether

and the combined ether solutions were distilled on a water-bath until most of the ether was removed. The residue was dried for several hours over anhydrous sodium sulfate. Subsequent fractionation yielded 88–95 Gm. of product, b. p. 111–113° C., m. p. 49° C.

PHARMACOLOGICAL RESULTS.

In comparing the four alchols prepared to the action of 2,2,2-tribromoethanol two different media were employed: (*a*) a ten per cent or a one per cent solution in olive oil and (*b*) a ten per cent or a one per cent solution in 95 per cent ethyl alcohol. Pharmacological studies were carried out upon mice, rats, guinea pigs and cats.

When 1–2-cc. doses of the one per cent alcohol solution were administered by rectum to rats and guinea pigs, 2,2,2-tribromoethanol was the only one found to produce complete narcosis. 2,2-diethyl-butanol-1 in doses of 3 cc. of the alcohol solution produced only a partial narcosis in guinea pigs while 4-cc. doses of 2,2-dimethyl-propanol-1 solution caused only a mild depression.

One per cent solutions of the compounds in olive oil were injected intraperitoneally in mice and the relative dosage required to produce narcosis or depression was determined. It was found that administration of 0.75 cc. of the one per cent solution of 2,2,2-tribromethanol to mice weighing 20 Gm. would produce complete narcosis which lasted about ten hours and sometimes resulted in death. One cubic centimeter of 2,2-diethyl-butanol-1, 1.2 cc. of 2-ethyl-2-methyl-butanol-1, 1.5 cc. of 2,2-dimethyl-butanol-1 and 2.1 cc. of 2,2-dimethyl-propanol-1 produced unconsciousness but of a shorter duration than the halogenated ethanol. A dose of about 8 cc. of 95 per cent ethyl alcohol was necessary to produce the same result.

Cats anesthetized with ether were injected through the fermoral vein with the respective solutions and the blood pressure taken from the carotid artery. A ten per cent solution of the compound to be tested in 95 per cent alcohol was injected slowly in doses of 0.5 cc. diluted to 10 cc. with normal saline solution. In this dose 2,2,2-tribromoethanol produced a partial paralysis of the respiration and depression of the circulation, followed by slow recovery. 2,2-diethyl-butanol-1; 2-ethyl-2-methyl-butanol-1 and 2,2-dimethyl-propanol-1 produced a similar result but in a progressively lesser degree. Most peculiarly 2,2-dimethyl-butanol-1 in the same dose was very toxic causing complete paralysis of the respiration and stoppage of the heart. Control solutions of 5 per cent ethyl alcohol had very little effect upon the circulation and produced only a slight depression of the respiration.

It was found that these alcohols will also produce their effects by absorption through the skin. When one cc. of a ten per cent solution of 2,2,2-tribromoethanol was placed on the intact skin of mice, it was rapidly absorbed to produce anesthesia lasting over twleve hours and followed by recovery. 2,2-diethyl-butanol-1; 2-ethyl-2-methyl-butanol-1; 2,2-dimethyl-butanol-1 and 2,2-dimethyl-propanol-1 were all absorbed but as found in other experiments, their effects became increasingly less as more methyl groups replaced the ethyl groups of the substituted ethanol. Ninety-five per cent ethyl alcohol (the dilution medium used above) produced no effect other than slight discomfort due to the cooling of the skin as the alcohol evaporated.

SUMMARY.

Four closely related 2,2-trialkyl ethanols have been prepared and a preliminary investigation of their pharmacological properties has shown that they all possess anesthetic action although to a much lesser degree than 2,2,2-tribromoethanol to which they were compared.

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