

A discussion is given of the patented extraction apparatus which is used in the process of diacolation as carried out by Breddin.

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ALCOHOL CONTENT OF EXTRACTIVE PREPARATIONS.*

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INTRODUCTORY.

It is required by law that the content of alcohol be stated on the label of each package of every item containing alcohol and offered for sale in interstate commerce. Manufacturers and distributors generally state this alcohol content as a single figure.

In the National Formulary the alcohol content of each preparation containing one per cent or more of alcohol is given in the monograph of such preparation with a minimum and a maximum limit. Alcohol content means the volume of C_2H_5OH present in one hundred volumes of the liquid preparation.

The official method for the determination of absolute alcohol, first introduced into U. S. P. IX, has been subject in recent years to considerable criticism, as is noted in the following papers: "Determination of Alcohol in Pharmaceutical Liquids I, Study of the U. S. P. X and U. S. P. XI Method," *Jour. A. Ph. A.*, 25, 313-316 (1936); "Determination of Alcohol in Pharmaceutical Liquids II, a New Method," *Jour. A. Ph. A.*, 25, 982-985 (1936). Both papers are by Karl Bambach and T. H. Rider.

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The alcohol content statements, especially of the extractive preparations in National Formulary VI, have been subject to considerable criticism during 1936. Data gathered from several manufacturers indicate that there may be a wide variation, sometimes as much as 15 percentage points in the alcohol content of the same preparation made by different manufacturers or even by the same manufacturer.

The conditions mentioned above led to the investigation reported in this paper. An endeavor is made to establish the reasons for the marked decrease in content of C_2H_5OH in the extractive preparation as compared with the C_2H_5OH content of the menstruum with which the preparation is made. It would be desirable to place C_2H_5OH content standards on a scientific basis and remove them from a purely empirical basis.

SHRINKAGE OF AQUEOUS-ALCOHOLIC MIXTURES.

While publications have appeared on this subject,¹ it was thought desirable to repeat the work for the purpose of confirming previous results.

For the preparation of the solution of the alcohol in water, the procedure was as follows:

(1) The content of C_2H_5OH in U. S. P. alcohol was determined by specific gravity. This was approximately 95.03 per cent by volume in all of the alcohol used.

(2) Cassia flasks were accurately calibrated to determine their exact volume at the lowest mark in the graduation on the neck of the flask.

(3) The calculated volume of alcohol was transferred into a tared cassia flask, and the weight of the alcohol was determined as a check on the measured volume.

(4) The calculated volume of water (recently boiled distilled water) was transferred into the same cassia flask and the weight of water was determined, as a check on the measured volume. The volume figures used in the table are those obtained from the weights of the alcohol and water taken.

(5) The volume of the liquid in the flask was accurately read in the graduation in the neck of the flask and compared to the total measured volume of the liquids added to the flask.

(6) All the work was done at 25° C.

The results appear on page 298.

NOTES.

(1) The U. S. P. XI states that Diluted Alcohol may be prepared by mixing 500 cc. of alcohol with 500 cc. of distilled water, that such a mixture measures about 970 cc. and that it contains not less than 48.4 per cent and not more than 49.5 per cent by volume at 15.56° C. of C_2H_5OH . Our mixture of 66.22 cc. of alcohol and 66.27 cc. of water showed a volume equal to 968.5 cc. on the basis of the U. S. P. statement and 48.96 per cent of C_2H_5OH , calculated on the actual volume of the diluted alcohol.

(2) The shrinkage in volume is most marked in the "50 and 60 per cent" alcohols (av. 3.15 cc.), next in the "40 per cent" alcohol (av. 3.0 cc.), next in the "80 per cent" alcohol (av. 2.18 cc.), and least in the "20 per cent" alcohol (av. 1.58 cc.).

(3) The largest increase in C_2H_5OH content is noted in the "60 per cent" alcohol (1.80 per cent); "80 per cent" alcohol comes next with 1.75 per cent; "50 per cent" alcohol third with 1.45 per cent; "40 per cent" alcohol with 1.14 per cent and "20 per cent" alcohol with 0.30 per cent increase.

¹ Wood, H. C., *JOUR. A. PH. A.*, 8, 730 (1919).

EXPERIMENTAL ERROR BY THE OFFICIAL METHOD FOR ALCOHOL CONTENT
DETERMINATIONS.

Three similar aqueous-alcoholic mixtures were prepared and several C_2H_5OH determinations of each one were made by the U. S. P. XI method for the purpose of determining the extent of experimental error. The results were as follows:

Theoretical C_2H_5OH Content by Volume.	Experimental C_2H_5OH Content by Volume.
78.10 per cent	77.76 per cent
	77.54 per cent
	77.88 per cent
	77.40 per cent
59.32 per cent	59.07 per cent
	58.90 per cent
	59.07 per cent
	58.74 per cent
40.70 per cent	40.00 per cent
	40.20 per cent

NOTES.

(1) Glass-stoppered volumetric flasks calibrated at $25^\circ C.$ were used for making these solutions. The solute was accurately weighed in the dry and tared flask. Solvent at $25^\circ C.$ was added from a burette to about three-quarters of the capacity and agitated with a swirling motion. If all the solute did not dissolve in this quantity, more solvent was added to a point convenient for agitation without wetting the neck above the capacity mark. In some cases it required a day or two of standing with intermittent agitation before the material was completely dissolved and in extreme cases slight heating was necessary. After complete solution, more solvent at $25^\circ C.$ was added from a burette until the meniscus was within about 0.5 cc. of the capacity mark and left to stand over night or until apparent shrinkage had ceased. The solution was then placed in a water-bath at $25^\circ C.$ for fifteen minutes after which solvent was immediately added to bring the meniscus to the capacity mark. The flask and contents were then weighed.

Solvent Added by Weight.—The difference between weight of solution and solute represented the weight of solvent added. Solvent containing no solute was made up along with the individual series of solutions by the same method used in making the solutions. From this the density, Gm. per cc., at $25^\circ C.$, of the solvent was determined. Knowing density and weight of solvent added, the volume of solvent was calculated as a double-check on solvent added; namely, by weight and by volume (burette).

A typical example is tannin, containing 6 per cent of moisture as determined by the U. S. P. XI toluene method, dissolved in diluted alcohol:

Weight of flask + tannin + moisture	81.6 Gm.
Weight of flask, 100 cc. capacity	<u>49.8 Gm.</u>
Weight of tannin + moisture	31.8 Gm.
Weight of tannin (31.8×0.94)	30.0 Gm.
Weight of moisture ($31.8 - 30$)	1.8 Gm.
Weight of flask + solution	<u>155.8 Gm.</u>
Weight of tannin + moisture + flask	81.6 Gm.
Weight of menstruum	74.2 Gm.

100 cc. of solvent weighed 92.6 Gm. at $25^\circ C.$

Density of solvent ($92.6 \div 100$) = 0.926 Gm. per cc.

Volume of solvent added by weight ($74.2 \div 0.926$) = 80.1 cc.

Volume of solvent added by volume (burette) = 79.9 cc.

Volume displaced by 30 Gm. of tannin:

(a) By volume (burette) $100 - (79.9 + 1.8)$ = 18.3 cc.

(1.8 is the volume of moisture in the tannin as used)

(b) By weight $100 - (80.1 + 1.8)$ = 18.1 cc.

Sample No.	Volume in Cc's. of			Shrinkage in Volume.		Percentage of U. S. P. Alcohol.			Percentage of C_2H_5OH at 15.56° C.		
	Alcohol Used.	Water Used.	Total Used.	In Cc.	In %.	In the Theoret. Volume.	In the Actual Volume.	Increase.	In the Theoret. Volume.	In the Actual Volume.	Increase.
	1.	2.	3.	5.	6.	7.	8.	9.	10.	11.	12.
1(a)	108.18	27.03	135.21	2.96	2.24	80.00	81.80	1.80	76.02	77.73	1.71
1(b)	105.68	26.56	132.24	2.75	2.12	79.92	81.80	1.88	75.94	77.73	1.79
2(a)	79.32	52.65	131.97	3.97	3.10	60.10	61.97	1.87	57.11	58.88	1.77
2(b)	79.12	53.09	132.21	4.11	3.21	59.85	61.76	1.91	56.87	58.69	1.82
3(a)	65.93	66.39	132.32	4.08	3.18	49.83	51.41	1.58	47.42	48.85	1.43
3(b)	66.22	66.27	132.49	4.05	3.15	49.97	51.52	1.55	47.48	48.96	1.48
4(a)	54.14	78.89	133.03	3.78	2.89	40.38	41.57	1.19	38.37	39.50	1.13
4(b)	54.23	81.36	135.59	3.99	3.03	40.00	41.21	1.21	38.01	39.16	1.15
5(a)	26.17	104.88	131.05	2.05	1.60	19.97	20.29	0.32	18.98	19.28	0.30
5(b)	26.31	105.43	131.74	2.04	1.57	19.97	20.29	0.32	18.98	19.28	0.30

1st column: Volume of U. S. P. alcohol used.

2nd column: Volume of distilled water used.

3rd column: Total volume of liquids added to the flask.

4th column: Actual volume of liquid as measured in the flask.

5th column: Shrinkage in volume in cc.

6th column: Shrinkage in volume in per cent, based on the actual volume in the flask.

7th column: Calculated percentage of U. S. P. alcohol by volume in the theoretical volume of the mixed liquids.

8th column: Calculated percentage of U. S. P. alcohol by volume in the actual volume of the mixed liquids.

9th column: Increase in percentage of U. S. P. alcohol in the actual volume as compared with that in the theoretical volume.

10th column: Calculated percentage of C_2H_5OH by volume in the theoretical volume of the mixed liquids.

11th column: Calculated percentage of C_2H_5OH by volume in the actual volume of the mixed liquids.

12th column: Increase in percentage of C_2H_5OH in the actual volume as compared with that in the theoretical volume.

EFFECT OF SOLUTES ON VOLUME INCREASE AND ALCOHOL-CONTENT DECREASE* (1).

	Solute Used.	Solvent Added.	Displacement by Solute.	C ₂ H ₅ OH Decrease (5).	
				Calculated.	Determined.
Solute: Dextrose (6) Solvent: Water (2)	5 Gm.	96.9 cc.	3.1 cc.
	10 Gm.	93.7 cc.	6.3 cc.
	15 Gm.	90.6 cc.	9.4 cc.
	20 Gm.	87.6 cc.	12.4 cc.
	25 Gm.	84.3 cc.	15.7 cc.
	50 Gm.	69.1 cc.	30.9 cc.
	5 Gm. Av.	96.9 cc.	3.1 cc.
Solute: Dextrose Solvent: Alcohol, 1 vol., Water, 1 vol. (4)	5 Gm.	96.7 cc.	3.3 cc.	1.6%
	10 Gm.	93.5 cc.	6.5 cc.	3.1%
	15 Gm.	90.4 cc.	9.6 cc.	4.6%
	20 Gm.	87.2 cc.	12.8 cc.	6.2%
	25 Gm.	83.6 cc.	16.4 cc.	8.0%
	5 Gm. Av.	96.8 cc.	3.2 cc.	1.6%
Solute: Tannin (3) Solvent: Water (2)	10 Gm.	94.4 cc.	5.6 cc.
	20 Gm.	88.7 cc.	11.3 cc.
	30 Gm.	82.1 cc.	17.9 cc.
	40 Gm.	76.2 cc.	23.8 cc.
	50 Gm.	70.9 cc.	29.1 cc.
	5 Gm. Av.	97.1 cc.	2.9 cc.
Solute: Tannin Solvent: Alcohol, 1 vol., Water, 1 vol. (4)	10 Gm.	93.9 cc.	6.1 cc.	3.2%	2.8%
	20 Gm.	87.8 cc.	12.2 cc.	6.4%	6.3%
	30 Gm.	81.7 cc.	18.3 cc.	9.7%	9.7%
	40 Gm.	75.7 cc.	24.3 cc.	12.8%	12.8%
	50 Gm.	69.5 cc.	30.5 cc.	16.1%	16.3%
	5 Gm. Av.	97.0 cc.	3.0 cc.	1.6%	1.6%
Solute: Tannin Solvent: Alcohol, 9 vol., Water, 1 vol. (4)	10 Gm.	94.4 cc.	5.6 cc.	5.3%	4.4%
	20 Gm.	88.7 cc.	11.3 cc.	10.7%	10.9%
	30 Gm.	82.9 cc.	17.1 cc.	16.2%	16.9%
	40 Gm.	76.9 cc.	23.1 cc.	21.8%	22.4%
	50 Gm.	70.8 cc.	29.2 cc.	27.6%	28.8%
	5 Gm. Av.	97.1 cc.	2.9 cc.	2.8%	2.8%
Solute: Sodium Chloride (10) Solvent: Water (2)	20 Gm.	92.7 cc.	7.3 cc.
	5 Gm. Av.	98.2 cc.	1.8 cc.
Solute: Gentian Ex. (7) Solvent: Alcohol, 1 vol., Water, 1 vol.	20.6 Gm.	85.8 cc.	14.2 cc.	6.9%	4.9%
	30.6 Gm.	78.6 cc.	21.4 cc.	10.4%	7.0%
	40.2 Gm.	72.0 cc.	28.0 cc.	13.5%	9.1%
	5.0 Gm. Av.	96.5 cc.	3.5 cc.	1.7%	1.2%
Solute: Resin of Ipomea (8) Solvent: Alcohol, 9 vol., Water, 1 vol. (4)	5.3 Gm.	95.8 cc.	4.2 cc.	3.6%	2.9%
	5.7 Gm.	95.6 cc.	4.4 cc.	3.7%	3.1%
	10.2 Gm.	92.6 cc.	7.4 cc.	6.3%	7.0%
	14.1 Gm.	87.8 cc.	12.2 cc.	10.4%	10.0%
	14.9 Gm.	87.2 cc.	12.8 cc.	10.9%	9.8%
	20.1 Gm.	83.6 cc.	16.4 cc.	13.9%	13.6%
	21.6 Gm.	81.8 cc.	18.2 cc.	15.5%	14.7%
5.0 Gm. Av.	95.9 cc.	4.1 cc.	3.5%	3.3%	

* The reference numbers refer to "Notes" that follow the tabulation.

Displacement by solute in the foregoing table is based on solvent added by volume as in (a).

(2) Distilled water was boiled fifteen minutes and used immediately after cooling. The procedure for making these solutions was the same as described in (1).

(3) Flake tannin of U. S. P. quality was used which contained 6 per cent of moisture, determined according to U. S. P. XI toluene method.

(4) The alcohol-water mixtures were prepared by mixing the required volumes of U. S. P. alcohol and recently distilled water in clean volumetric flasks, calibrated to deliver and to contain a definite volume at 25° C.

The U. S. P. alcohol used gave a sp. gr. value which corresponded to 95.34 per cent of C_2H_5OH .

On the basis of a 3 per cent shrinkage in the 50 per cent alcohol-water mixture (see page 4) the calculated content of C_2H_5OH is 49.1 per cent. Our determinations by the U. S. P. distillation method repeated on the same lot gave from 48.0 to 48.8 per cent or an average of 48.3 per cent.

The mixture of alcohol 9 volumes, water 1 volume shrinks *about* 2 per cent (see page 4) and contains about 87 per cent of C_2H_5OH by calculation. Our determinations gave an average content of 86.2 per cent before distillation and 85.6 per cent after distillation.

(5) The alcohol content was determined by the official U. S. P. XI distillation method. The calculated alcohol decrease is based on the volume of menstruum added, assuming no loss in transfer and that all alcohol in the transfer is in solution as C_2H_5OH . Theoretically, the decrease in alcohol is proportional to the volume of solute in the solution.

(6) Granulated dextrose of C.P. quality was used. The U. S. P. XI toluene method indicated 0.07 per cent of moisture. Weighings were made on the laboratory balance.

(7) Gentian extract, obtained by drying a sufficient quantity of fluidextract of gentian, made in this laboratory, in an evaporating dish on the water-bath at a maximum temperature of 70° C. to a gummy mass, was dehydrated in a vacuum desiccator over magnesium perchlorate. It was assumed to contain no moisture after an accurately weighed sample, powdered to 40 mesh, reached constant weight.

(8) Finely powdered resin of ipomea, prepared in this laboratory, was dried for two days in a vacuum desiccator over magnesium perchlorate. Since resin decomposes with continued heating it was undesirable to dry in the oven. A quantity of the resin was not available to determine moisture according to the toluene method, U. S. P. XI. Therefore, it was assumed to be completely dehydrated. Weighings of flask, solute and solution were made on the analytical balance.

(9) Density at 25° C. was determined by weighing a sample of the solute in a dry acid-tared pycnometer to one-third its volume capacity. The pycnometer was filled with xylene at 25° C., in which the test materials are insoluble, and weighed. From the density of xylene at 25° C., the volume of xylene necessary to fill the pycnometer was calculated from the weight of xylene added. This subtracted from the capacity of the pycnometer at 25° C. gave the volume occupied by the sample (solute). The weight of the sample (solute) divided by its volume gave the density, Gm. per cc. at 25° C.

The densities found are as follows:

Dextrose—1.521 at 25° C.

Tannin—1.406 at 25° C.

Gentian Extract—1.414 at 25° C.

Sodium Chloride—2.17 (from the Chemical Handbook, 1928).

(10) Powdered sodium chloride of C.P. quality dried to constant weight at 95° C. was used.

EFFECT OF MOISTURE IN THE DRUG.

These tinctures were prepared by the official method, using 200 Gm. of drug for one liter of tincture.

	C ₂ H ₅ OH Content.	Extractive (W/V).
Menstruum, 4 determinations	48.0%	
1 Gentian, commercial, No. 40 powder; moisture content, toluene method, 5.2%	46.0%	8.0 %
2 Gentian, dried at 100° C.; moisture content 0.0%	46.4%	8.3 %
3 Gentian, hydrated in desiccator 24 hours; moisture content 7.4%	46.1%	7.7 %
4 No. 1 repeated	46.0%	6.76%
5 No. 2 repeated	46.8%	7.04%
6 Gentian, 200 Gm., sprayed with 7 cc. of water and hydrated in desiccator for 12 hours; moisture content, toluene method, 9%	45.6%	6.14%
7 No. 6 ditto, except sprayed with 20 cc. of water; moisture content 13.6%	45.2%	6.12%
8 No. 6 ditto, except sprayed with 28 cc. of water; moisture content 16.25%	45.0%	5.99%
9 No. 6 ditto, except sprayed with 29 cc. of water; moisture content 17.5%	45.0%	5.84%

NOTES.

(1) The extractive present in the tinctures would increase the volume and thus decrease the alcohol content from 1.3 to 2 per cent.

(2) The effect of the water in the drug, even up to 16-17 per cent, did not reduce the alcohol content more than 1.7 per cent. If all the maximum amount of water in the drug (35 cc. in 200 Gm.) were added to 1000 cc. of the solvent, it would reduce the alcohol content of the mixture only 1.7 per cent.

The following "fluidextracts" were prepared in Oldberg glass percolators by collecting 500 cc. of "reserve" percolate from 500 Gm. of drug. The purpose is to demonstrate the effect of moisture in the "drug" on the alcohol content of the percolate. Every effort was made to prevent loss of alcohol during manipulation.

	Moisture in Drug.	Extractive. In Reserve Percolate.	Alcohol Content.		Total Decrease.	Decrease Due to Moisture in Drug (1).
			In Menstruum.	In Percolate.		
Sawdust (2)	0.4%	0.9%	48.3%	48.3%	0.0%	0.0%
Sawdust	6.8%	2.4%	94.8%	91.2%	3.6%	2.0%
Sawdust	7.6%	0.9%	49.0%	46.7%	2.3%	2.0%
Sawdust	13.7%	1.0%	48.8%	44.4%	4.4%	4.1%
Sawdust	21.2%	0.4%	48.9%	41.7%	7.2%	7.0%
Starch (3)	12.0%	0.1%	94.8%	90.6%	3.2%	3.2%
Cotton (4)	4.0%	0.2%	94.0%	93.4%	0.6%	0.6%
Gentian (5)						
Commercial	8.0%	35.6%	48.9%	36.9%	12.0%	3.5%
Dehydrated	1.9%	35.6%	48.9%	38.7%	10.2%	1.7%

NOTES.

(1) These figures are based on the following assumptions:

"95 per cent" alcohol is decreased 3.3 per cent per 5 Gm. of solute.

"50 per cent" alcohol is decreased 1.6 per cent per 5 Gm. of solute, except by gentian extract, which reduces the alcohol 1.2 per cent per 5 Gm. of the solute.

After the decrease due to solute is deducted, the remainder is considered as due to "moisture in the drug."

(2) A commercial grade of sawdust was refluxed with U. S. P. alcohol to extract some of the soluble materials, then dried in the oven at 95° C. to constant weight, then varying amounts of moisture were incorporated; except that the sawdust for the second preparation was used as received.

(3) A 500-Gm. sample of corn starch, mixed with four times its weight of dried and purified sand to prevent packing, was prepared in an Oldberg glass percolator. A reserve of 500 cc. was collected. Care was taken to prevent loss of alcohol during the process.

(4) A 250-Gm. lot of cotton batting was used and 250 cc. of reserve were collected. The process was identical to that described above.

(5) The gentian percolates were collected in liter lots from 1000-Gm. lots of the powdered drug. Dehydrated gentian was prepared by drying powdered gentian under reduced pressure at 65° C. to constant weight.

SUMMARY.

(1) Determinations of the shrinkage of aqueous-alcoholic mixtures indicate that "50 per cent" and "60 per cent" alcohols show a decrease in volume of about 3.15 per cent over theoretical, "40 per cent" alcohol decreases about 2.95 per cent, "80 per cent" alcohol about 2.20 per cent, and "20 per cent" alcohol about 1.60 per cent. The calculated increase in percentage of C_2H_5OH , due to the shrinkage in volume, averages 1.77 per cent for the "60" and "80 per cent" alcohols, 1.45 per cent for the "50 per cent" alcohol, 1.14 per cent for the "40 per cent" alcohol and 0.30 per cent for the "20 per cent" alcohol.

(2) Actual determination of the C_2H_5OH content of aqueous-alcoholic mixtures by the official distillation method gave results always lower than the theoretical, the average of many results being 0.70 of a percentage point. With solutions of vegetable extractive matter containing no volatile matter except alcohol and water, the average of many determinations was 0.76 of a percentage point lower than the theoretical value. This loss may be due in part to loss of C_2H_5OH during manipulation.

(3) The average displacement in 100 cc. of solution produced by 5 Gm. of tannin in water is 2.9 cc., in "50 per cent" alcohol is 3.0 cc., and in "90 per cent" alcohol the displacement is 2.9 cc. The reduction in C_2H_5OH content averages 1.6 per cent in "50 per cent" alcohol for each 5 Gm. of solute and in "90 per cent" alcohol 2.8 per cent for each 5 Gm. of solute.

Dextrose in water gave an average displacement of 3.1 cc. per 5 Gm. of solute; in "50 per cent" alcohol it displaced 3.2 cc. with a decrease of 1.6 per cent in C_2H_5OH content per 5 Gm. of solute.

Gentian extract dissolved in "50 per cent" alcohol displaced 3.5 cc. and decreased the C_2H_5OH content, by actual determination, to 1.2 per cent per 5 Gm. of the solute.

Resin of *Ipomea* dissolved in "90 per cent" alcohol caused an average displacement of 4.1 cc. with a consequent reduction in alcohol of 3.3 per cent per 5 Gm. of solute.

Sodium chloride, which ionizes in water solution, gave an average displacement of 1.8 cc. per 5 Gm. of solute.

(4) Evidence indicates that the effect of "tissue" moisture in crude drug has only a slight influence on the alcohol content of a tincture or fluidextract. The amount of "free or absorbed" water in the crude drug proportionally decreases the alcohol content of a fluidextract. There was found to be an average of 0.4% decrease in alcohol content for each per cent of "free" moisture in the crude drug.

(5) Moisture in the pilular extract obtained from the "weak" percolate has an influence on the alcohol content of the fluidextract equivalent to the same

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.* **

BY ROBB V. RICE,¹ GLENN L. JENKINS² AND WILTON C. HARDEN.

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-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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