

significant inverse relationship between ascaridol and alcohol solubility ($r = -0.73 \pm 0.05$).

In studies on high-test oil the correlation coefficient for ascaridol to specific gravity was 0.85 ± 0.07 . Because of insufficient data further correlation coefficients were not determined.

Calculations of the correlation coefficients and partial correlation coefficients have been greatly simplified by the use of approximation formulas and tables developed in the course of this type of statistical research (1, 2, 3, 4, 5, 6, 7, 8).

CONCLUSIONS.

- (a) Ascaridol shows a significant direct relationship to specific gravity ($r = 0.89 \pm 0.02$) and inverse relationship to alcohol solubility ($r = -0.73 \pm 0.05$).
- (b) These relationships are confirmed by partial correlation coefficients.
- (c) The other variables show no significant relationship.

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HYDROLYSIS OF ACETYLSALICYLIC ACID IN ETHANOL, GLYCEROL AND ETHANOL-GLYCEROL SOLUTIONS.*

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INTRODUCTION.

Conversion of the acetic acid ester of salicylic acid into its components in aqueous solution by the hydrolytic action of the solvent occurs with comparative rapidity. In the effort to prevent this disintegration when it is desired to dispense the analgesic in solution form it has been suggested (1) that the compound be dissolved in a menstruum consisting of portions of ethyl alcohol and glycerol. It is evident, however, since the U. S. P. grade of the latter rarely contains more than 95 per cent of the tri-hydric alcohol, while ethanol of the same quality contains a similar proportion of water—that hydrolysis cannot be entirely suppressed by the employment of these vehicles. It seemed desirable to learn to what extent the phenomenon would be induced by varying the water content of ethanol and glycerol

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and mixtures of the two liquids to which definite quantities of water were added, and which were maintained at room temperatures.

ACTION OF MEDICINAL.

While the present work deals primarily with the hydrolytic action and subsequent effect of varying concentrations of water on solutions of acetylsalicylic acid in compounds of alcoholic structure, it may not be amiss to summarize some of the more important therapeutic properties of the ester, most of which undergo partial or complete change when disintegration of the type under consideration obtains, and acetylsalicylic acid, as such, no longer exists in its entirety.

The substance is known to exert a more powerful central depression than sodium salicylate because of the presence of the acetyl group. For this reason it is extensively prescribed by the physician and employed by the laity as an analgesic, for the relief of the various types of headache and neuralgia, and as an hypnotic. The action of this drug is similar to that produced by the administration of small doses of ethyl alcohol, or of the barbitals or bromides. In definitely effective, but not paralytic, doses the effects are characterized by removal of central nervous inhibition, thus causing abolition of pain and distress with general excitation and increased heart rate, and related symptoms; in short, the typical effect of a narcotic drug.

PURIFICATION OF MATERIALS.

The ethyl alcohol used was the so-called "absolute" grade, 200 proof. Investigation disclosed the fact that this product contained 99.80 per cent C_2H_5OH , with traces of aldehydes but no electrolytes. Further purification and dehydration was deemed essential; the former was accomplished by the method of Paul (2) for the removal of this series of compounds—decreasing the proportion of the lower aldehydes to approximately 0.001 per cent—while dehydration of the requisite character was obtained by the employment of calcium oxide and activated aluminium (3). A product possessing the density value 0.78508 was produced in this manner; the reading was made at $25^\circ C$. The alcohol so treated was kept in brown glass bottles tightly stoppered and sealed with collodion so as to exclude air and eliminate moisture absorption. As a further precaution, the containers were stored in a dark room until needed; this procedure inhibiting the re-formation of aldehyde in the solvent.

A grade of glycerol suitable for the experimental portion of the work was produced by resorting to fractional vacuum distillation, using as raw material glycerol of U. S. P. quality. For this purpose a forty-eight-inch Vigreux column, covered with asbestos paper and connected to a Bruehl receiver, was employed. Distillation was carried out under a pressure of 6 to 7 mm. Hg, and the first 30–35 per cent of the product, containing all of the water and other impurities of lower boiling point than glycerol, discarded. The middle portion, up to about 70 per cent of the sample taken consisted of anhydrous glycerol, free from water and trimethylene glycol, and contained but a negligible trace of polyglycerols, chiefly diglycerol ether. The purified compound, possessing a density of 1.261 at $20^\circ C$., and the boiling point $289.8^\circ C$. (corrected), corresponding to 100 per cent $(CH_2OH)_2CHOH$, was immediately stored in a desiccator over phosphorous pentoxide; suction was then

applied to the container, and the air partially exhausted. The desiccator and its contents were taken to the dark room and kept there until required for use.

The acetylsalicylic acid employed was of U. S. P. grade, and contained but a faint trace of free acid. This product melted sharply at 133.8° C.

METHOD EMPLOYED.

A method based on colorimetric procedure (4) involving the formation of the familiar purplish tint which the ion of trivalent iron produces in the presence of salicylic acid or its salts, was used. Prior to application the method was meticulously examined for the express purpose of ascertaining if it possessed that degree of accuracy and sensitivity essential to the attainment of results concordant with work of experimental character. During the preliminary tests, solutions were prepared containing definite quantities of an extremely pure, natural salicylic acid derived from *Gaultheria procumbens*. It was found that results of a most gratifying character were realized when inspection of the comparatively dilute solutions was made; further investigation, however, evinced the fact that results equally as satisfactory for determining the free salicylic acid in the more concentrated solution—*i. e.*, those in which hydrolysis was most pronounced—were obtainable only when the volume taken for the determination was decreased accordingly, and the addition of ethyl alcohol made. Of course, standards utilized were accorded the same treatment.

Numerous confirmatory tests furnished convincing evidence of the applicability of this method, so modified, to the successful attainment of the work contemplated. Finally, the employment of the Duboscq colorimeter in comparing the intensity of the colorations produced in the experimental samples with those of the color standards greatly facilitated the analytical determinations made.

PROCEDURE.

Test samples of 5 per cent and 10 per cent solutions of the synthetic in aqueous ethanol, glycerol and ethanol-glycerol were prepared. These were immediately placed in special brown glass bottles, sealed and protected from light until examination was made. Special precautions to preserve the solutions in appropriate containers *at once* following preparation were taken and, it is believed, absorption of moisture from atmospheric air that might have occurred during this brief interval was so minute as to be without significance.

After the allotted time had elapsed, the samples were examined and tested for their free salicylic acid content. Great care, too, was exercised during these periods to work with sufficient rapidity to insure the prevention of the introduction of errors due to moisture change and possible contamination by volatile impurities existing in the air of the laboratory.

The following tables furnish data ascertained as a result of many examinations made at varying intervals of time:

Attention is directed to the fact that it had been the intention of the author to consider mixtures of ethanol and glycerol in the proportions: 50% : 50% and 25% : 75%, plus water, as solvents for acetylsalicylic acid. The former mixture was prepared, and is given due consideration here; a few experimental samples of the second series were made and examined, but results were so nearly identical with those first encountered that further examination seemed superfluous.

TABLE I.—ETHANOL SOLUTIONS OF ACETYSALICYLIC ACID.

Percentage of Compound Undergoing Hydrolysis at 20° to 22° Centigrade.

Composition of solvent. (By volume.)	5% Solution. Age in hours.				10% Solution. Age in hours.			
	24.	72.	120.	240.	24.	72.	120.	240.
Anhydrous ethanol	None	None	None	Trace	None	None	None	None
Ethanol 99.75 H ₂ O 0.25	0.8	1.4	3.7	8.3	0.5	0.9	2.2	5.8
Ethanol 99.50 H ₂ O 0.50	1.1	1.5	4.3	10.6	0.8	1.2	3.7	8.8
Ethanol 99.00 H ₂ O 1.00	1.5	1.9	4.4	11.1	1.0	1.6	4.1	9.7
Ethanol 98.00 H ₂ O 2.00	1.9	2.7	5.3	12.9	1.4	2.1	4.6	10.5
Ethanol 96.00 H ₂ O 4.00	3.9	5.1	8.8	16.7	3.2	4.8	8.1	14.9
Ethanol 95.00 H ₂ O 5.00	5.5	8.0	11.6	19.9	5.4	7.6	10.9	17.9
Ethanol 94.00 H ₂ O 6.00	5.8	8.7	12.7	20.4	5.5	8.1	11.3	18.0
Ethanol 93.00 H ₂ O 7.00	6.3	8.6	14.1	22.1	6.1	8.7	13.2	20.8
Ethanol 90.00 H ₂ O 10.00	10.8	14.8	21.9	39.9	9.6	12.9	19.2	37.4

TABLE II.—GLYCEROL SOLUTIONS OF ACETYSALICYLIC ACID.

Percentage of Compound Undergoing Hydrolysis at 20° to 22° Centigrade.

Composition of solvent. (By volume.)	5% Solution. Age in hours.				10% Solution. Age in hours.			
	24.	72.	120.	240.	24.	72.	120.	240.
Anhydrous glycerol	None	None	None	None	None	None	None	None
Glycerol 99.75 H ₂ O 0.25	0.5	0.9	2.6	5.3	0.4	0.7	2.3	5.1
Glycerol 99.50 H ₂ O 0.50	1.1	1.8	3.5	7.3	0.8	1.0	3.2	8.1
Glycerol 99.00 H ₂ O 1.00	1.2	1.8	3.9	9.6	1.0	1.4	3.9	8.9
Glycerol 98.00 H ₂ O 2.00	1.7	2.4	4.9	11.4	1.4	2.0	4.3	9.8
Glycerol 96.00 H ₂ O 4.00	3.5	4.7	7.5	14.9	3.1	4.4	7.5	12.9
Glycerol 95.00 H ₂ O 5.00	5.1	7.3	9.0	17.7	4.8	7.3	9.0	16.1
Glycerol 94.00 H ₂ O 6.00	5.4	7.9	11.9	19.1	5.1	7.4	11.1	18.3
Glycerol 93.00 H ₂ O 7.00	6.2	8.6	13.9	21.7	6.1	8.4	12.8	20.3
Glycerol 90.00 H ₂ O 10.00	9.7	13.9	19.8	34.6	8.3	12.7	19.6	32.4

TABLE III.—ETHANOL-GLYCEROL SOLUTIONS OF ACETYSALICYLIC ACID.

Percentage of Compound Undergoing Hydrolysis at 20° to 22° Centigrade.

Composition of solvent. (By volume.)	5% Solution. Age in hours.				10% Solution. Age in hours.			
	24.	72.	120.	240.	24.	72.	120.	240.
Anhydrous mixture								
C ₂ H ₅ OH 50 C ₃ H ₅ (OH) ₃ 50	None	None	None	None	None	None	None	None
Mixture 99.75 H ₂ O 0.25	0.3	0.5	0.9	2.2	None	Trace	0.7	1.9
Mixture 99.50 H ₂ O 0.50	0.5	0.9	2.1	3.7	Trace	0.5	1.5	2.8
Mixture 99.00 H ₂ O 1.00	0.8	1.3	3.2	5.2	0.4	0.7	2.8	4.8
Mixture 98.00 H ₂ O 2.00	1.1	1.8	4.1	8.0	0.7	1.3	3.5	5.4
Mixture 96.00 H ₂ O 4.00	2.8	3.9	6.7	10.9	2.2	3.4	6.0	9.7
Mixture 95.00 H ₂ O 5.00	3.9	5.4	6.9	13.3	3.1	4.9	7.1	12.3
Mixture 94.00 H ₂ O 6.00	4.1	6.9	8.7	15.1	3.8	6.6	7.9	14.8
Mixture 93.00 H ₂ O 7.00	5.5	7.2	10.1	17.2	4.9	5.9	9.8	16.1
Mixture 90.00 H ₂ O 10.00	7.8	10.1	15.2	28.7	6.7	10.0	14.6	24.3

CONCLUSIONS.

It will be observed that, with few exceptions, the results presented in the tables are in strict accord with the accepted fact that dilution favors hydrolysis. It is believed, too, that acceleration of the phenomenon in ethyl alcohol in excess of that observed in glycerol might be at least partially ascribed to a progressive alcoholysis induced by and occurring in the presence of the free hydrogen ions of dissociated acetic acid. A comparison of the constitutions of the two alcohols,

and the differences existing in their degree of physico-chemical activity would seem to warrant this assumption. This explanation, however, fails to account for the retardation of hydrolytic action in solutions of the ester in a mixture of equal parts of ethanol and glycerol. Apparently, the tri-hydric alcohol is capable of exerting, in the presence of ethanol, an inhibitory effect on the rate at which disintegration of the type considered, occurs. It is not improbable that this is induced by certain physical changes in the system, acetylsalicylic acid-ethanol-glycerol, which evidently suppress, to some extent, the tendency of water to dissociate and react with the components of the solute. Assuming that this conclusion is correct, a diminution in hydrolysis might be anticipated.

SUMMARY.

(1) The rate of hydrolysis of acetylsalicylic acid in ethanol, glycerol and mixtures of these compounds of alcoholic structure—to which varying proportions of water were added—has been studied.

(2) While hydrolysis is favored by dilution the addition of water and increasing age of the solution, this phenomenon is accentuated with respect to aqueous solutions of the ester in the primary alcohol.

(3) A mixture of equal parts (by volume) of ethanol and glycerol to which water has been added, does not hydrolyze acetylsalicylic acid to the same extent that either, alone, is capable of doing under similar conditions of concentration and temperature.

(4) A possible explanation of this difference in behavior has been suggested.

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MENTHOL CRYSTAL AND PEPPER-MINT OIL MARKET AT KOBE, JAPAN.

The combined quantity of menthol crystals and peppermint oil carried over from 1929 was about 80 tons. Total production of both commodities was about 520 tons in Hokkaido and 114 tons in the other islands, giving a total supply of about 714 tons. Of the latter amount, 260 tons of crystals and 256 tons of oil were exported, while loss in weight and domestic consumption accounted for about 100 tons. About 98 tons remained to carry over to 1930.

RESORCINOL IMPORTS DECLINE.

United States imports of resorcinol entered for consumption during the first four months of 1931 amounted to 11,200 pounds, a decline of 43 per cent compared with the quantity (19,800 pounds) entered during the corresponding period of 1930. The entire 1931 shipments originated in France, which also supplied the major portion of the 72,418 pounds and 47,760 pounds of resorcinol imported during 1930 and 1929, respectively.