grown in pots, with a presumably uniform soil and kept under controlled and constant greenhouse conditions, two lots of 6 plants each, both under "Sunlit" glass, show as much as 36% U. S. P. variation. The averages obtained in the experiments here reported do not permit any assumption that the influence of the extreme ultraviolet region of sunlight, either during the seedling stage or throughout the life of the plant, affects the yield of active glucosides.

SUMMARY.

No significant differences in glucoside yield could be observed between digitalis plants grown under a glass having a higher ultraviolet transmission and those grown under ordinary window glass, whether the plants were kept until sampled in the air-conditioned greenhouses or were set out after some months of such treatment into the open field.

Digitalis plants were found to require a cold dormant period in order to induce flower stalk formation. Miller (4) and Thompson (5) have reported a similar cold period requirement for the flowering of two other biennials, celery and cabbage.

Dried powdered leaf from young plants 4 to 6 months old has nearly double the glucoside content of that from older plants (9–17 months old) whether a flower stalk is formed on the older plants or not.

The authors desire to thank Dr. S. H. Culter and Mr. R. W. Henderson for preparing the U. S. P. tinctures, and Dr. Merl E. Fisk and Dr. Marvin R. Thompson for the assay results herein reported.

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STUDY OF GERMICIDAL AND ANTISEPTIC ACTIVITIES OF SOME DERIVATIVES OF 8-HYDROXY QUINOLINE.*

BY E. MONESS AND W. G. CHRISTIANSEN.

8-Hydroxy quinoline has bacteriostatic properties and is generally used in the form of its sulphate, which is water soluble. Matzumura (1) prepared 5-8-dihydroxy quinoline, and the presence of the additional hydroxyl suggested the possibility that such a compound may be soluble in an aqueous medium without resorting to salt formation.

This compound was prepared, as well as two chlorinated derivatives of it, and all were found to be soluble in a vehicle containing 30 parts of alcohol, 40 parts of

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glycerin and 30 parts of water. Such a solution was found to be miscible with water in all proportions. In the germicidal and bacteriostatic tests 0.25% solutions of these compounds in alcohol-glycerin-water were used and diluted with suitable amounts of water at the time of test.

Chlorination of 5-8-dihydroxy quinoline always yielded a mixture of the mono-chlor and di-chlor compounds. Recrystallization from alcohol separated the mixture into two fractions: one was largely 7-chlor, 5-8-dihydroxy quinoline admixed with some non-chlorinated 5-8-dihydroxy quinoline, while the other was largely 6-7-dichlor, 5-8-dihydroxy quinoline, admixed with some of the mono-chlor derivative.

The germicidal and bacteriostatic activity of these compounds was found to be only moderate as seen from the following table:

Solution.	Dilution at Which Compound Kills. Typhoid. 5 Min.	Typhoid. 10 Min.	Staphylococcus. 5 Min.	Staphylococcus. 10 Min.	Dilution at Which Compound Is Bacteriostatic. Typhoid. 24 Hours.	Staphylococcus. 24 Hours.
5-8-dihydroxy quinoline	< 1–400	1–400	< 1–400	< 1–400	1–10,000	1–10,000
84.2% mono-chlor compound + 15.8% non-chlorinated dihydroxy quinoline	1–400	1–400	1–400	1–400	1–10,000	1–20,000
72.6% dichlor compound + 27.4% mono-chlor derivative	1–400	1–400	1–400	1–400	1–10,000	1–20,000

All the solutions are unstable due to the fact that the compounds oxidize easily; this is characteristic of compounds in which two hydroxyl groups are para- or ortho- to each other. Due to this oxidation the solutions darken with time from an original yellow-brown color to a dark red, and deposit a slight dark sediment.

According to Klarmann (2) the mono-ethers of hydroquinone exhibit germicidal power far greater than that of the original substance. It was thought that by preparing mono-ethers of 5-8-dihydroxy quinoline a similar increase in germicidal activity could be obtained, coupled with the additional advantage that such compounds would not be subject to oxidation and would give stable solutions. With this object in view, two compounds were prepared—the mono-ethyl and butyl ethers of 5-8-dihydroxy quinoline.

At first an attempt was made to fix the position of the alkoxy group by starting with 8-ethoxy quinoline, which was nitrated to 5-nitro-8-ethoxy quinoline and reduced to the amino derivative. This compound could be diazotized without any difficulty, but the attempt to replace the diazonium group by hydroxyl was unsuccessful; the yield was insignificant, and the reaction yielded complicated tarry and resinous compounds. Consequently the method of Klarmann was used, and the mono-ethers were prepared by the direct alkylation of 5-8-dihydroxy quinoline; the mono-ethers were separated from the di-alkylated derivatives by treatment

with alkali. When this method is used the exact position of the alkoxy group cannot be stated—it may be either in the 5- or 8-position.

When solutions of these compounds were made up in a vehicle consisting of a mixture of 30 parts of alcohol, 40 parts of glycerin and 30 parts of water, it was found that unlike the solutions of 5-8-dihydroxy quinoline, they were not miscible with water in all proportions. Thus a 1–400 solution of the mono-ethyl ether would become turbid on the addition of one volume of water, and would deposit crystalline material when two more volumes of water were added. A 1–400 solution of the mono-butyl ether deposited some crystalline material on being diluted with only one volume of water. However, both compounds formed water-soluble salts with great ease: the addition of one equivalent of tartaric acid to the alcohol-water-glycerin solutions to the ethoxy and butoxy compounds made it possible to dilute these solutions with water without having precipitation occur. The ethoxy compounds dissolve in aqueous tartaric acid; sufficient material was not available to enable us to make a similar test with the butoxy compound.

The germicidal and bacteriostatic activities were greatly enhanced, especially the germicidal activity of the butoxy compound.

Solution.	Dilution at Which Compound Kills. Typhoid. 5 Min.	Typhoid. 10 Min.	Staphylococcus. 5 Min.	Staphylococcus. 10 Min.	Dilution at Which Compound Is Bacteriostatic. Typhoid. 24 Hours.	Staphylococcus. 24 hours.
Mono-ethoxy compound of 5-8-dihydroxy quinoline	1–400	1–400	1–800	1–800	1–200,000	1–400,000
Mono-butoxy compound of 5-8-dihydroxy quinoline	1–2000	1–2000	1–800	1–800	None	1–200,000

It is not quite clear why the bacteriostatic test for the butoxy compound was negative for typhoid bacilli, and this will be checked in the course of work now in progress on derivatives of hydroxy quinoline.

EXPERIMENTAL.

5-8-Dihydroxy Quinoline.—Ten Gm. of 5-nitroso-8-hydroxy quinoline was dissolved in a solution of 75 cc. of concentrated hydrochloric acid in 2700 cc. of water. The solution was kept at 95° C. and 16 Gm. of iron filings was added to it with constant stirring in small portions over a period of one hour. The solution was then stirred for one more hour at 95° C. It was filtered and evaporated to a volume of 150 cc. On cooling a crystalline mud separated out, which was filtered off. The dark brown crystalline substance was resuspended in 150 cc. of a mixture of equal parts of concentrated hydrochloric acid and water, brought to a boil and cooled. In this way 8 Gm. of light brown crystals of the hydrochloride of 5-8-dihydroxy quinoline was obtained. A sample dissolved in water and precipitated with sodium carbonate gives a grayish brown substance, melting point 180° C. The melting point for the purified substance as given in the literature is 181–183° C.

Chlorination of 5-8-Dihydroxy Quinoline.

5-8-Dihydroxyquinoline	4 Gm
Glacial acetic acid	80 cc.
Sulphuryl chloride	6 cc.

The compound was dissolved in the acid and to the solution was added slowly and with mechanical stirring a solution of the sulphuryl chloride in a little glacial acetic acid. A large excess of SO_2Cl_2 was used, since it was found that with a small excess the chlorination proceeded only partially.

An orange precipitate was obtained and was filtered off, dissolved in water and neutralized with sodium bicarbonate.

The filtrate was evaporated to a small volume and a second crop of orange crystals was obtained.

Yield—3.8 g. of a gray crystalline substance, m. p.—150° C.

Analysis.

Chlorine:	Found	21.22%
	Calculated for $C_9H_6O_2NCl$	18.30%
	Calculated for $C_9H_5O_2NCl_2$	30.88%

Evidently some of the di-chlor compound was also formed. By a fractional crystallization from alcohol we obtained two fractions, one analyzing as a mixture of 72.6% di-chlor and 27.4% mono-chlor compound, with a melting point of 163° C. and the other as a mixture of 84.2% mono-chlor compound and 15.8% non-chlorinated 5-8-dihydroxy quinoline, with a melting point of 128° C.

Both substances are easily soluble in alcohol and a solution in alcohol and glycerin is miscible with water in all proportions.

Preparation of the Mono-ethyl Ether of 5-8-Dihydroxy Quinoline.—4.03 Gm. of 5-8-dihydroxy quinoline and 3.9 Gm. ethyl iodide were dissolved in 4 cc. of alcohol. The solution was refluxed and a solution of 1.5 Gm. KOH in 4.2 cc. water was added dropwise during one hour; the refluxing was continued for 3 hours. A solution of 2 Gm. of KOH in a little water was then added, and on cooling the reaction mixture was extracted with ether. The ether extract was washed several times with a 10% solution of KOH; these alkaline extracts were combined with the alkaline reaction mixture and precipitated with acetic acid. A somewhat tarry precipitate was obtained which was purified by extracting with ether. This ether extract was washed with water, purified with charcoal, dried over anhydrous sodium sulphate and the ether was evaporated off; 0.8 Gm. of a yellowish crystalline substance was obtained, m. p. 96–98° C.

Analysis: Found—C, 69.7%; H, 5.37%; calculated for $C_{11}H_{11}O_2N$—C, 69.7%; H, 5.82%.

Preparation of the Mono-butyl Ether of 5-8-Dihydroxy Quinoline.—2.65 Gm. of 5-8-dihydroxy quinoline and 2.22 Gm. butyl bromide were dissolved in 2.65 cc. of alcohol. This solution was refluxed and a solution of 1 Gm. of potassium hydroxide in 3 cc. of water was added dropwise during an hour. The refluxing was continued for another 3 hours. The reaction mixture was worked up in the same manner as the ethoxy compound.

Yield—0.7 Gm. of yellowish white crystalline substance, slightly contaminated with a trace of an oily admixture; m. p. 92° C.

Analysis: Found—C, 70.60%; H, 6.50%; calculated for $C_{13}H_{15}O_2N$—C, 71.80%; 6.90%.

Both the ethoxy and the butoxy derivatives of 5-8-dihydroxy quinoline form orange, water-soluble salts, such as the hydrochloride and the tartrate.

The biological tests on compounds reported herein were made in the Biological Research Laboratories of E. R. Squibb and Sons and we gratefully acknowledge their assistance.

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RESEARCH DEPARTMENT OF THE CHEMICAL AND PHARMACEUTICAL LABORATORIES,
E. R. SQUIBB AND SONS, BROOKLYN, N. Y.

A STUDY OF VEHICLES FOR MEDICINES.*

BY BERNARD FANTUS, H. A. DYNIEWICZ AND J. M. DYNIEWICZ.

V. COMPOUND ELIXIR OF CHLORAL AND BROMIDE.

As an "horrible example" of an undesirable N. F. preparation, must be mentioned the "Compound Mixture of Chloral and Potassium Bromide," which in addition to 20% each of chloral and bromide has 0.2% each of extracts of cannabis and of hyoscyamus added to it. The extracts are triturated with pumice and then the hot solution of the chloral and bromide is added, the mixture is set aside for twenty-four hours with occasional agitation, whereupon all but a trace of the extracts of cannabis and hyoscyamus is unceremoniously filtered out. Any statement as to the quantity of cannabis and hyoscyamus extracts contained in the finished preparation is a mere guess and worse. The quantity present is certainly not as given in the official dose statement; but a great deal less. In view of the unsatisfactory formula, it is not to be wondered at that it has a usage of only 0.25 per 10,000 prescriptions, according to the Gathercoal survey.

We must, therefore, either delete these insoluble ingredients or so modify the formula that they will remain in solution. With this in view we have experimented a great deal and would like to propose deleting the "Compound Mixture of Chloral and Potassium Bromide," which would be entirely justified by its limited use; and to introduce the following preparation to supersede the one deleted.

ELIXIR CHLORALIS ET BROMIDI COMPOSITUM.

Compound Elixir of Chloral and Bromide.

Synonym—Compound Mixture of Chloral and Potassium Bromide.

Chloral Hydrate	**62.5 Gm.**
Sodium Bromide	**125.0 Gm.**
Soluble Gluside	**0.5 Gm.**
Fluidextract of Cannabis	**12.5 cc.**
Fluidextract of Hyoscyamus	**25.0 cc.**
Alkaline Elixir of Eriodictyon (1), to make 1000.0 cc.	

Mix the solid ingredients by trituration in a mortar and dissolve them in 900 cc. of alkaline elixir of eriodictyon. Add the fluidextracts of cannabis and of hyoscyamus and enough of the aromatic elixir of eriodictyon to make 1000 cc. Average dose: 4 cc. (1 teaspoonful).

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* From the Laboratory of Pharmacology of the College of Medicine of the University of Illinois.