Contrary to previous reputation, they were found not poisonous to rats or rabbits, even when given in enormous doses.

No evidence could be found for the presence of arbutin which had been claimed as a constituent of *L. grœnlandicum*. The glucoside ericolin may be in the leaves of both species, as attested by hydrolysis to an oil probably containing ledum camphor. However, since no one has ever isolated this glucoside in the pure state from any vegetable source, we have doubts as to the uniformity of its composition.

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SEATTLE, WASH.,
June 20, 1933.

DETERMINATION OF CERTAIN MEDICAMENTS UNDER THE INFLUENCE OF LIGHT.*

BY H. V. ARNY, A. TAUB AND R. H. BLYTHE.

I.—INTRODUCTION.

This report covers the third and fourth years of research on the deterioration of chemicals and pharmaceuticals when stored in colored glass containers. A complete report of the work of the years 1929–1931 conducted by Dr. Abraham Steinberg under the personal direction of Professor Abraham Taub and the senior author was presented by Dr. Steinberg as an "Arbeit" submitted in partial fulfilment of the requirements set for the degree of Doctor of Pharmacy of Columbia University, while the material in condensed form was published as a paper by Arny, Taub and Steinberg in the JOURNAL OF THE AMERICAN PHARMACEUTICAL ASSOCIATION, 20 (1931), 1014 and 1153.

During 1931–1932, a second fund of $2000 was raised to continue the work where it was discontinued by Dr. Steinberg. The second fund of $2000 was obtained through the generosity of the following firms and organizations:

Subscriptions of $100 each from Burroughs Wellcome & Co., London and New York; Dow Chemical Co., Midland, Michigan; Hynson, Westcott and Dunning, Baltimore, Md.; Lehn & Fink, Bloomfield, N. J., and New York City; Merck & Co., Rahway, N. J., and New York City; Charles Pfizer & Co., Brooklyn and New York City; Smith, Kline & French Laboratories, Philadelphia, Pa.; E. R. Squibb & Sons, Brooklyn and New York City; the Upjohn Co., Kalamazoo, Mich.; and the Proprietary Association.

A subscription of $200 from William R. Warner & Co., Inc., New York.

A grant of $300 from the Breitenbach Fund of the College of Pharmacy of the City of New York. A grant of $500 from the Board of Trustees of the U. S. Pharmacopœial Convention.

As research fellow for 1932–1934, the senior author selected Rudolph H. Blythe, B.S., who gave the subject his devoted attention during two years as a stu-

* Joint Session, Scientific Section and Section on Practical Pharmacy and Dispensing, Washington meeting, 1934.

dent of the graduate course of the College of Pharmacy of Columbia University. His efforts won the degree of Doctor of Pharmacy of Columbia in June 1934, and in fulfilling the requirements set for the degree, Dr. Blythe submitted an inaugural dissertation of 168 typewritten pages. The present paper represents a condensation of the Blythe "Arbeit."

In connection with the research, the following firms donated bottles, chemicals and pharmaceuticals:

Charles Cooper & Co., Corning Glass Works, Dodge & Olcott Co., Fritzsche Bros., Inc., Heine & Co., Eli Lilly & Co., Mallinckrodt Chemical Works, Maryland Glass Corporation, Merck & Co., Monsanto Chemical Works, New York Quinine and Chemical Works, Owens-Illinois Glass Co., Charles Pfizer & Co., Schieffelin & Co., Sharp & Dohme, Smith, Kline & French Laboratories, E. R. Squibb & Sons and W. R. Warner & Co.

To these firms we are very grateful.

II.—PHYSICAL MEASUREMENTS.

(A. Taub and R. H. Blythe.)

As in the case of the Steinberg research of 1929–1931 each type of bottle used was submitted to spectrophotometric readings by means of the Bausch and Lomb apparatus of the physics laboratory of the College of Pharmacy. This instrument gave measurements from 400–800 mμ. For transmission values in the ultraviolet region, we employed a Hilger quartz spectrograph, kindly placed at our disposal by the Department of Physics of Columbia University. Our readings gave practically the same values as reported on the graphs shown in the Steinberg paper of 1931. This is not surprising since the bottles employed were furnished by the same firms who contributed their glassware for the 1929–1931 investigation. While there has been during the past two years considerable talk about new types of glass bottles, numerous requests on our part failed to bring us practical samples of new types. The six types of bottles used by us represent the average run of the bottle market of to-day, as applied to the drug trade.

III.—DETERIORATION OF CHEMICALS AND PHARMACEUTICALS.

(H. V. Arny and R. H. Blythe.)

The procedure in the 1932–1934 investigation was identical with that described in the Steinberg paper of 1931. All chemicals studied were subjected to a complete physical and chemical examination as prescribed by the U. S. P. or the N. F. and all pharmaceuticals were either prepared by Mr. Blythe or were tested by him as per standards set by the Pharmacopœia or the Formulary. In all but a few special cases, the observed substance was placed in a pyrex tube which in turn was placed in a colored container that was being studied. The medicaments were then observed under the following conditions:

(1) 15 liquids and 13 solids (all of U. S. P. or N. F. strength and quality when prepared or received) were stored in pyrex test-tubes (or ampuls) and these tubes placed into commercial glass containers (2 flint, 2 amber, 1 blue and 1 green). Five sets of these specimen chemicals (1300 samples in all) were exposed to light on the roof of our College building, in cases protected by a single sheet of window glass.

(2) One set of specimens (225 samples in all) was exposed in diffused light in cases in the office of the senior author.
(3) One set (170 samples in all) was kept in a closet in our dark room.
(4) Of the five sets on the roof, one was brought in after one month's exposure and studied. The second set was examined after two months' exposure. The third, fourth and fifth sets were examined after exposures representing 4, 6 and 12 months, respectively.

As to our results, we submit three tables of comparison; two based upon exposure to light during one year. Results obtained after exposure for 1, 2, 4 and 6 months will be found in the original Blythe "Arbeit." As to these tables, the first discusses, in general terms, the effect of direct light, diffused light and darkness upon the chemicals examined. The second table gives degree of deterioration when the chemicals were exposed in diffused (day) light for one year; while the third table shows time limit of stability when exposed to direct (sun) light. The first 10 chemicals in Table II were assayable, hence the change can be expressed mathematically. The others on the list were judged by the degree of color change or by special types of qualitative tests.

TABLE I.—GENERAL FINDINGS AS TO DETERIORATION.

Exposure for 1 Year.

Stable in All Types of Glass Containers under All Conditions.	Stable in All Conditions of Diffused Light.	Unstable in Light; Stable in Dark.
*Ferrous carbonate, saccharated	Acetyltannic acid	Aloin
Solution of picric acid (1%)	Chloramine	*Quinidine sulphate
	Dichloramine	*Quinine
Unstable in All Conditions of Light and Darkness.	Gallic acid	*Quinine sulphate
	Liquid petrolatum	
*Elixir of glycerophosphates, compound	*Solution of ferric chloride	
*Elixir of iron, quinine and strychnine	*Solution of formaldehyde	
*Nitric acid	Strontium salicylate	
*Compound solution of iodine	Tannic acid	
*Oil of bitter almond		
*Syrup U. S. P.		
Compound syrup of hypophosphites		

* See special notes following tables.

TABLE II.—DEGREE OF DETERIORATION IN GLASS CONTAINERS AFTER ONE YEAR OF EXPOSURE IN DIFFUSED LIGHT.

Group A.

Percentage of Deterioration Shown by Actual Assay.

	Amber A.	Amber B.	Blue.	Green.	Flint A.	Flint B.
Chloramine	0%	0%	0.7%	0.7%	0.7%	0.7%
Dichloramine	1.2%	0%	3.7%	0.8%	2.1%	2.8%
Ferrous carbonate saccharated	9.1%	8.4%	8.4%	8.4%	0.6%	0.7%
*Nitric acid	21.5%	17.2%	16.9%	14.2%	11.5%	16.9%
Oil of bitter almond	11.0%	11.4%	12.8%	10.8%	10.1%	....
*Solution of ferric chloride	1.4%	1.5%	1.5%	1.6%	1.9%	0.6%
*Solution of formaldehyde	0.3%	G	G	0.4%	0%	0.4%
Solution of iodine, compound	50%	46%	46%	63%	60%	....

Solution of picric acid (1%)	0%	0%	0%	0%	0%	0%
*Syrup U. S. P.	15%	13%	6%	7%	22%	....

* See special notes following tables.

Group B.

Deterioration Shown by Color Change or by Special Tests.

Abbreviations.

C.D.—considerable darkening. S.D.—slight darkening. V.S.D.—very slight darkening. N.C.—no change.

	Amber A.	Amber B.	Blue.	Green.	Flint A.	Flint B.
Acetyltannic acid	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.
Aloin	N.C.	N.C.	V.S.D.	V.S.D.	V.S.D.	V.S.D.
Elixir of glycerophosphates, compound	S.D.	V.S.D.	V.S.D.	S.D.	S.D.	S.D.
Elixir of iron, quinine and strychnine	S.D.	S.D.	C.D.	C.D.	C.D.	C.D.
*Ferrous carbonate saccharated	V.S.D.	V.S.D.	V.S.D.	V.S.D.	V.S.D.	V.S.D.
Gallic acid	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.
Oil of bitter almond	S.D.	V.S.D.	V.S.D.	V.S.D.	V.S.D.	....
Quinidine sulphate	N.C.	N.C.	V.S.D.	V.S.D.	V.S.D.	V.S.D.
Quinine	N.C.	N.C.	V.S.D.	V.S.D.	V.S.D.	V.S.D.
Quinine sulphate	N.C.	N.C.	V.S.D.	V.S.D.	V.S.D.	V.S.D.
Strontium salicylate	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.
Syrup of hypophosphites, compound	S.D.	S.D.	S.D.	S.D.	S.D.	S.D.
Tannic acid	V.S.D.	V.S.D.	V.S.D.	V.S.D.	V.S.D.	V.S.D.

* See special notes following tables.

TABLE III.—SPEED OF DETERIORATION IN GLASS CONTAINERS EXPOSED IN DIRECT (SUN) LIGHT.

(Expressed in Months.)

Abbreviation: "−1" means less than 1 month.

	Amber A.	Amber B.	Blue.	Green.	Flint A.	Flint B.
Acetyltannic acid	4	4	4	4	4	4
Aloin	−1	−1	−1	−1	−1	−1
Chloramine	2	2	−1	1	1	1
Dichloramine	2	2	−1	−1	−1	−1
*Elixir of glycerophosphates, compound	1	1	−1	−1	−1	−1
Elixir of iron, quinine and strychnine	1	1	−1	−1	−1	−1
Ferrous carbonate, saccharated	12	12	12	12	12	12
Gallic acid	12	12	1	1	1	1
Liquid petrolatum	6	6	2	2	2	2
Nitric acid	2	2	1	1	1	1
*Oil of bitter almond	12	12	−1	−1	−1	−1
*Quinidine sulphate	2	2	−1	−1	−1	−1
Quinine	2	2	−1	−1	−1	−1
Quinine sulphate	2	2	−1	−1	−1	−1
*Solution of ferric chloride	2	2	1	1	1	1
*Solution of formaldehyde	6	12	6	6	12	12
*Solution of iodine, compound	−1	−1	−1	−1	−1	−1
Solution of picric acid (1%)	12	12	12	12	12	12
Strontium salicylate	6	6	2	2	2	2
*Syrup U. S. P.	4	4	2	2	2	2
Syrup of hypophosphites, compound	1	1	1	1	1	1
Tannic acid	2	2	1	1	1	1

* See special notes following tables.

IV.—PECULIARITIES OF CERTAIN CHEMICALS.

Elixir of Glycerophosphates, Compound.—This preparation darkens in diffused light and deposits a precipitate in sunlight. It even darkens when kept in a dark place. Amber glass is the best protective.

Elixir of Iron, Quinine and Strychnine is another pharmaceutical that readily deteriorates. This deterioration appears to be essentially a photochemical change, the preparation being especially susceptible to rays below 4800 Å. The ferric salt appears to act as a sensitizer and is itself affected by the light rays. As reported by Fry and Gerwe some years ago, the citric acid of the citrate is partially broken down to carbon dioxide and acetone, while some of the ferric ions are reduced to the ferrous form. This preparation should be submitted to long and intensive study.

Ferrous Carbonate, Saccharated.—This preparation is one which sunlight improves. Our ferrous assays indicate the greatest deterioration after storing in the dark and the least in the sunlight. In diffused light, flint glass is a better protective than amber glass. When stored in loosely stoppered bottles, the reducing action of light seems counteracted by the oxidizing action of the air.

Fluidextract of Ergot.—In the original plan the deterioration studies of this fluidextract and also tinctures of aconite and digitalis were started. Lacking facilities for pharmacologic assaying and failing to find what were to us, satisfactory colorimetric tests, work on these three pharmaceuticals was postponed.

Nitric Acid.—The erratic results obtained in the study of this chemical were largely due to evaporation. In all cases of exposure to light, the acid suffered serious loss in strength. Color of glass container had apparently little influence except that amber was the best protective. Sample stored in the dark in its original glass-stoppered container for one year lost only 1 per cent of HNO_3.

Oil of Bitter Almond was studied from its change in color, from its loss of benzaldehyde and from its deposition of benzoic acid crystals. Decrease in benzaldehyde occurred even in the dark; being about 9 per cent loss within 1 year. Direct sunlight produces as much as 50 per cent deterioration except when the oil is stored in amber bottles.

Quinidine Sulphate, Quinine and *Quinine Sulphate* are uniformly stable when stored in the dark. In the light, amber glass affords the best protection.

Solution of Ferric Chloride keeps fairly well in diffused light; almost as well as when stored in the dark. In sunlight, ferrous iron begins to appear within one or two months.

Solution of Formaldehyde.—In diffused light, this solution suffers little or no loss in strength. In fact, as shown in Table II, Group A, two samples (those indicated by the letter "G") actually gained a fraction of 1 per cent in strength; due undoubtedly to evaporation of the solvent.

Solution of Iodine, Compound.—When stored in containers provided with cork or rubber stoppers, deterioration proceeded rapidly whether stored in light or dark. On the other hand, a sample stored in the dark in a glass-stoppered bottle during one year showed only little or no deterioration. Likewise a sample sealed in an ampul and exposed to sunlight for 4 months suffered no loss in strength.

Syrup U. S. P.—Our experiments were based upon degree of inversion. Those

samples exposed to sunlight showed inversion within 4 months. Samples stored in the dark for one year, indicated over 10 per cent inversion. The sample exposed to diffused light for one year in the second type of flint bottle gave such a discrepant figure that it is omitted from the table.

Syrup of Hypophosphites, Compound.—The color of this preparation darkens even when stored in the dark. The darkening is greater in sunlight than in diffused light. The deterioration is evidently an oxidation phenomenon. In sunlight, precipitation occurs, while in diffused light and in the dark, the darkening of the color is the only indication of change. Color of glass container has evidently little or no influence.

Tincture of Aconite and *Tincture of Digitalis.*—See Fluidextract of Ergot.

Lard, Expressed Oil of Almond and *Ointment of Rose Water, U. S. P.* were studied from the standpoint of rancidity. While no authoritative statements may be made by us concerning this annoying phenomenon we venture to express the following opinions:

(*a*) Rancidity progresses in the dark as well as in the light.
(*b*) In actual practice, the color of the glass container seems of little importance.
(*c*) Oxygen (of the air) and moisture are essential factors in producing rancidity. Light acts as an accelerator but is not an essential factor in the reaction.

V.—BIBLIOGRAPHY.

Dr. Blythe's dissertation includes a bibliography of 162 titles. Limitations of space prevent its inclusion in this paper.

VI.—CONCLUSIONS.

(1) Amber glass affords the most protection of any glass now commercially available.

(2) Red and green Corning filters, used as described in our paper of 1931, offer the greatest protection of any glass tried. These are not, however, available as commercial glass containers.

(3) The ordinary easily available green glass containers are not, however, as good protectives for medicaments as is amber glass.

(4) The following tables summarize the Steinberg and the Blythe studies of the deterioration of 50 medicaments classified as to causes of deterioration: (*a*) light, (*b*) simple volatilization, (*c*) chemical changes produced by factors other than light. In the first table "A" indicates that amber glass was the best protective; while "G" means that green glass also acted as protective.

(A) Deterioration Due to Light.

Acetyltannic acid	A	Hydriodic acid syrup	
Adrenalin hydrochloride	A	Hydrobromic acid	
Aloin	A	Liquid petrolatum	A
Benzoic acid	A	Mercuric oxide, red	
Betanaphthol	A & G	Mercuric oxide, yellow	
Chloroform	A & G	Mercurous chloride	A & G

Chloramine	A
Dichloramine	A
Ephedrine hydrochloride	
Ether	A & G
Ferric chloride solution	
Ferric citrate	
Ferric phosphate soluble	A
Ferric pyrophosphate soluble	A & G
Formaldehyde solution	
Gallic acid	A
Hydriodic acid	
Mercurous iodide	
Pyrogallol	A & G
Quinidine sulphate	A
Quinine	A
Quinine sulphate	A
Resorcinol	A & G
Santonin	A & G
Strontium salicylate	A & G
Tannic acid	A
Thymol iodide	A & G

(B) To Volatilization.

Hydrocyanic acid diluted
Nitric acid
Solution of chlorinated soda
Solution of chlorine, compound
Solution of iodine, compound
Spirit of ethyl nitrite

(C) To Chemical Changes Produced by Factors Other Than Light.

Apomorphine hydrochloride
Elixir of glycerophosphates, compound
Elixir of iron, quinine and strychnine
Oil of bitter almond
Physostigmine salicylate
Silver nitrate
Solution of arsenous and mercuric iodide
Solution of hydrogen dioxide
Sulphurated potassa
Syrup U. S. P.
Syrup of hypophosphites, compound

(D) Stable to Light.

Ferrous carbonate saccharated[1]
Ferrous iodide, syrup[1]
Mercuric iodide, red
Liquefied phenol
Picric acid solution (1%)[2]
Silver proteins (mild and strong)

VII.—UNSOLVED PROBLEMS.

A research of the character just described usually brings in its trail a series of questions more puzzling than the original investigation. We have studied the 50 medicaments as summarized above and we find that among these 33 cases of deterioration due to light, 6 due to volatilization and 11 due to chemical changes produced by factors other than light. These bare facts immediately inspire such questions as (*a*) How does the light react upon the chemical? (*b*) Why does syrup hydrolyze in the light and to a lesser extent in the dark? (*c*) Why does lard turn rancid in the dark as well as in the light?

These queries coming within our ken, set us to work on certain experiments which we hoped would explain some of the phenomena observed, but up to the present time, the results of this phase of our work have been far from satisfactory. Hesitatingly we raise the following questions:

(1) Of the many possible causes of deterioration the four outstanding are heat, light, air and moisture. Is it possible that air and moisture play a more important rôle in the deterioration phenomena than does light?

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[1] Actually improved by action of light rays.

[2] When preserving catalyst is present.

(2) In the case of the average light-sensitive chemical, does light act directly or merely as an accelerator of oxidation or reduction?

(3) In certain cases, notably the halide salts of such metals as silver, mercurous mercury and iron, the reducing action of light is clearly discernible. Thus photographic studies have cleared up the situation as far as the silver halides are concerned. Will further investigations of other metallic compounds indicate definitely which deteriorations due to light are reducing and which are oxidizing phenomena?

(4) In rancidity, is not the deterioration due to presence of air and moisture rather than to light?

We hope in the near future to make further efforts toward answering these interesting questions.

COLLEGE OF PHARMACY,
COLUMBIA UNIVERSITY,
July 10, 1934.

THE STABILIZATION OF SYRUP OF FERROUS IODIDE, U. S. P. X.*[1]

BY WILLIAM J. HUSA[2] AND LYELL J. KLOTZ.[3]

INTRODUCTION.

Ferrous iodide was discovered by Courtois (1) who reported its preparation in 1811. It was introduced into medicine in 1824 by Dr. Pierquin (2) who used the chemical as prepared by Caillot (3), a French pharmacist. In 1831, Pierquin (4) published formulas for the administration of ferrous iodide in the form of a water, chocolate, pastille, salve, tincture and wine and added that 2 oz. of the salt in sufficient water might be used for bathing. The voluminous literature concerning Syrup of Ferrous Iodide has been adequately reviewed (5). The purpose of the present investigation was to evaluate previous work, determine the mechanism and rate of decomposition and effect a satisfactory method of stabilization.

EXPERIMENTAL.

Chemicals and Reagents.—Two kinds of iron wire were employed, *i. e.*, card teeth and Merck's Reagent Iron. The former assayed 99.6% iron and contained 0.07% of sulphur as well as some carbon and silicon; the latter showed 99.9% iron and contained 0.05% sulphur as well as traces of silicon. Sulphur was determined by the cadmium acetate absorption method (6).

Mallinckrodt's U. S. P. and Merck's C.P. and Reagent Iodine were used. Mallinckrodt's U. S. P. Hypophosphorous Acid assaying 31.04% H_3PO_2 was employed. Colgate's C.P. glycerin; Merck's C.P. dextrose and U. S. P. Honey were used. The sucrose satisfied all U. S. P. requirements; its specific rotation at 22° C. was 66.15 determined according to the U. S. P. method. Distilled water having a p_H of 5.7 was used throughout.

General Methods.—All volumetric and gravimetric work was carried out using calibrated weights and apparatus. The progress of decomposition was followed in most cases by titration of free iodine using approximately 0.01N solution of sodium thiosulphate and freshly prepared starch T.S.

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* Scientific Section, A. PH. A., Washington, D. C., 1934.

[1] This paper is based on a dissertation submitted by Lyell J. Klotz to the Graduate Council of the University of Florida in partial fulfilment of the requirements for the degree of Doctor of Philosophy, June 1934.

[2] Head Professor of Pharmacy, University of Florida.

[3] Graduate Scholar, University of Florida, 1932–1934.