PHILADELPHIA.

The May meeting of the Philadelphia Branch, AMERICAN PHARMACEUTICAL ASSOCIATION was held May 21, 1935, at the Philadelphia College of Pharmacy and Science, President E. H. MacLaughlin in the chair.

The speaker of the evening, Dr. Robert P. Fischelis, president of the AMERICAN PHARMACEUTICAL ASSOCIATION, spoke on "The AMERICAN PHARMACEUTICAL ASSOCIATION and the Future of American Pharmacy." Dr. Fischelis's speech was one of the most interesting heard during the past year. He emphasized the pitfalls of American pharmacy and the need of wholehearted coöperation on the part of pharmacists throughout the United States, if they hoped to survive the great wave of influence which is tending to degrade pharmacy and to eliminate the individual pharmacist.

He stressed the importance of the organization of pharmacists into one powerful cohesive group, pointing out that the AMERICAN PHARMACEUTICAL ASSOCIATION, with its present set-up, was able to cope with any major Pharmaceutical problem. He emphasized the need of a new type A. PH. A. JOURNAL—one that would hold interest and be helpful for the pharmacist as well as the scientist.

A rising vote of thanks was given Dr. Fischelis in appreciation of his most valuable talk.

Respectfully submitted,

GEORGE E. BYERS, *Secretary.*

(*Concluded on page 521.*)

A PHARMACEUTICAL STUDY OF p_H.

BY FREDERICK F. JOHNSON.

(*Concluded from page 412, May Journal, A. Ph. A.*)

p_H AND STABILITY OF GALENICAL PREPARATIONS.

Digitalis Preparations.—The question of p_H and digitalis stability has been a matter of controversy for many years and is far from settled at the present time. Hintzelmann and Joachimoglu (89) stated that the tincture was most stable in an acid medium. Emig (238) reported that tinctures prepared from menstruums of p_H 4.5–5.2 showed the least loss in potency although the initial potency was less than for normal tinctures. Rowe and Scoville (248) stated that adjustment of the tinctures to p_H 4.0 with hydrochloric acid increased the stability and later stated (289) that tinctures of p_H 3.0 were more stable than those of p_H 6.0 or 7.0.

In contrast to these results, Haag and Hatcher (127) reported that HCl decomposed constituents of digitalis, Wokes (187) reported that acidifying did not increase stability, Haag and Jarrett (206) reported that no definite relation existed between the activity of the tinctures and p_H, and Foster and Van Dyke (264) stated that the most stable tinctures were those of highest p_H.

Hintzelmann and Joachimoglu (83), (42) reported that alkalinizing the tinctures with $NaHCO_3$ greatly increased deterioration, while Wokes (187) reported that the addition of Na_2CO_3 caused very little deterioration. Joachimoglu and Bose (65) reported that the addition of tartaric acid increased the stability. Rowe and Scoville (248) reported that the addition of hypophosphorous acid as a reducing agent was detrimental. It seems to be definite that the addition of anhydrous sodium acetate or anhydrous sodium sulphate as antihydrolytic agents does result in increased stability (248), (289), (301).

Several investigators have reported that stability is increased by destroying the ferments of the crude drug or preparations by heat (95), (248), (289). Rowe and Scoville (289) reported that tinctures prepared from a 77% alcoholic menstruum were more stable than those prepared from an 87% menstruum, but Stasiak (329) claimed that absolute alcohol tinctures were more stable than 70% alcohol tinctures. Macht and his co-workers (88), (98), (99) stated that ultraviolet light and polarized light hastened destruction of the tinctures, but Bond and Gray (108) claimed that no destruction was produced by exposure to either light.

There is plenty of evidence that the crude drug, tincture and infusion tend to become more acid during storage (92), (162), (214). Krantz (163), (274) has determined the buffer capacity of the tincture as 0.009 between p_H 5.75–2.50, and as 0.012 between p_H 5.75–9.50, 5.75 being the p_H of a U. S. P. tincture. He further stated (243) that the acids of the leaf are probably combined

with potassium and are extracted by the alcohol-water mixture yielding a system having a high buffer capacity, consisting of a strong base combined with a weak acid, and also some slightly dissociated acid.

Carr and Krantz (308), while investigating for the Revision Committee of the U. S. P. XI, arrived at the following conclusions concerning the tincture of digitalis: The official tincture has a p_H of 5.50–6.00. Considering the manner of dosage, it is a stable product. There is no distinct evidence that its stability can be increased by buffering or by adding acid to the product.

Concerning infusions of digitalis, the consensus seems to be that preservative agents increase stability, that the infusions become more acid with age, and that a neutral infusion is most stable (77), (92), (214). The infusion is less acid than the tincture.

Ergot Preparations.—In 1926, an article in the *Public Health Reports* (79) stated:

> "In order to insure the stability of the liquid extract, the hydrogen-ion concentration should be adjusted within the limits represented by p_H 4.0 and p_H 5.0. The extract should be sterilized and sealed in ampules of non-alkaline resistant glass."

The p_H of the U. S. P. Fluidextract of Ergot is approximately 4.5. In the last few years there has been a great variety of opinions concerning the efficacy of further reductions of the p_H. The confusion in the literature is augmented by the undependable results of the various assay methods.

Six investigators have concluded that adjusting the p_H to about 3.0 favors stability of the fluidextract and the alkaloid solutions (138), (188), (229), (247), (288), (306). These workers disagreed, however, concerning which acid was most effective. Powell and his co-workers (247) favored tartaric acid, Rowe and Scoville (288) favored reducing acids and Bernerowna (306) claimed that phosphoric acid was best. Swanson (250) stated that a p_H of 3.0 appeared to favor stability of the fluidextract, hypodermic solutions of ergot, and alcoholic solutions of ergotamine tartrate, but that the results were very questionable and no conclusions could be drawn. Three investigators (227), (269), (294) reported that lowering the p_H either did not increase stability or resulted in even more decomposition.

Smith and Stohlman (227) reported that the addition of 2.5% sodium thiosulphate or 2.5% sodium hyposulphite or 1% cysteine hydrochloride as reducing agents to the fluidextract or alkaloid solutions favored stability if above p_H 5.0. Bartsch (191) claimed that ergotamine tartrate was most stable at p_H 2.04. Bernerowna (306) stated that of the various salts of the ergot alkaloids, the organic salts were most stable, and the sulphuric acid salts were more stable than the hydrochloric acid salts. Wokes and Elphick (188) claimed that for proper extraction of ergot, the p_H of the menstruum must be not less than 5.4.

Aconite Preparations.—The attempts to stabilize aconite preparations by adjusting the hydrogen-ion concentration have been quite successful. Swanson (64), (69), (105) performed the original work and recommended that the p_H values of the tinctures and fluidextracts be adjusted between p_H 2.5–3.00. Without addition of acid, the p_H of the U. S. P. tincture lies between 5.1–5.6. By lowering the p_H, Swanson was able to decrease the deterioration from 90% to 5%. He pointed to the discrepancies in the assay methods as deterioration increases. The chemical assay at no time showed any loss of potency; the guinea pig and white mice methods were concordant for standard preparations but the difference between the two increased as deterioration progressed.

Haag and Hawkins (155) thoroughly verified the results of Swanson. Baker (304) also agreed with Swanson and established the optimum p_H range for all aconite preparations as p_H 2.3–3.0. He recommended the use of hydrochloric acid rather than a reducing acid like hypophosphorous acid. He also reported that all of the tinctures became decidedly less acid during storage. The only disagreement to the established optimum p_H range was put forward by Munch and Pratt (282) who claimed that adjusting the p_H to 2.5–3.10 did not increase the stability of the tincture or fluidextract.

Carr and Krantz (308) recommended to the Revision Committee of the U. S. P. XI the adoption of the p_H range 2.5–3.0 for Tincture of Aconite. It was reported that if the tincture is acid to methyl orange and shows an orange color with thymol blue, it will be within the stable p_H range. Carr and Krantz reported the buffer capacity of Tincture of Aconite as 0.0086 in the acid range. This is very close to the buffer capacity of Tincture of Digitalis, which is 0.0090.

Miscellaneous Vegetable Preparations.—Krantz and Slama (97) reported that the precipitation in the Compound Tincture of Gentian could be minimized by adjusting the reaction to p_H

7.0. The official tincture has a p_H of 5.2. The precipitate was composed of starch, gentian sugars and albuminous material. Beguin (120) found that by exposing the crude gentian to hot alcohol vapors, the hydrolysis and inversion of gentian sugars and glucosides were considerably reduced.

Swanson and Hargreaves (118), (182) have studied the effect of the hydrogen-ion concentration upon veratrum, gelsemium and nux vomica preparations. The optimum p_H for both the fluidextract and the tincture of veratrum was between p_H 4.3–4.8. The p_H of the U. S. P. IX fluidextract is 5.0 and of the U. S. P. X tincture, 5.4. The N. F. Fluidextract of Gelsemium of p_H 3.45 was stable and remained so when the p_H was reduced to 1.0. The N. F. Fluidextract of Nux Vomica of p_H 5.30 was stable and remained that way when the p_H was reduced to 0.75.

Lichtin (215) reported that acidifying the menstruum or percolate of Tincture of Cinchona did not increase stability. Caines and Evers (260) have reported concerning the loss of color in mixtures containing the B. P. Compound Tincture of Cardamon. From p_H 7.0–9.5 the mixtures were stable in the dark but fading occurred in the dark at higher p_H values. Calcium salts caused precipitation of calcium carminate at p_H 4.0 and above.

Scoville (103) has studied the effect of acid upon the precipitation in many of the less important tinctures. The acid increased precipitation of red cinchona, aloe, frangula, juglans, rhubarb, senna, rhus glabra, quercus, wild cherry and stillingia. It retarded precipitation of cinchona calisaya, castanea, geranium and rose. Sodium acetate retarded precipitation of aloe, frangula, senna, chionanthus, glycyrrhiza, salix nigra and senega. It seemed that the tannin-containing drugs were especially prone to precipitation by hydrolytic action. Krantz (162) reported that Fluidextract of Cascara becomes slightly more acid upon standing and that Elixir of Iron, Quinine and Strychnine becomes much less acid upon standing, irrespective of the type of light to which they are exposed.

Turner (230) stated that the syrup and mucilage of acacia rapidly decompose because of the development of acidity. Attempts to produce acid-free preparations by heat sterilization and the use of preservatives were unsuccessful. Eschenbrenner (199) has reported that infusions of ipecac can be stabilized if prepared with dilute hydrochloric acid and 15% alcohol. This corresponds to the U. S. P. acid fluidextract. The p_H of Eschenbrenner's infusion was 4.5. Madsen (216) claimed that such an infusion was unstable and proposed a formula which produces an alcoholic infusion of p_H 3.6. This was claimed to be stable for three years.

Conduche and Gregoire (148) have reported that in aromatic waters, both filtered and unfiltered, there was a diminution of acidity on keeping. The p_H usually changed from about 3.8–7.0. The reduction of acidity was almost proportional to the amount of volatile oils which separated and was evidently a result of the removal of the volatile oils. The reaction could best be stabilized by preventing the growth of microörganisms. Krantz and Carr (164) have investigated the effects of different filtering mediums upon the reaction of Aromatic Elixir. Using talc, as in the U. S. P. preparation, the p_H values were between 7.00–7.35. Elixirs prepared with magnesium carbonate had p_H values from 9.10–9.80, with magnesite or normal magnesium carbonate the p_H was 6.8, and with precipitated calcium phosphate the p_H was between 5.95–6.30.

Miscellaneous Chemical Preparations.—Husa and Klotz (314), (315) have studied the mode of decomposition of Syrup of Ferrous Iodide. During storage the p_H always dropped from 4.1 or above to 3.2. The hydrolysis predominated according to the equation:

$$FeI_2 + H_2O \rightleftarrows Fe(OH)I + HI.$$

Two equilibria existed in the hydrolysis: one at p_H 4.1, and the other at p_H 3.2. Precipitation occurred at p_H 3.2. Alkaline glass of the container retarded the hydrolysis. It was shown by solubility product data that precipitation of $Fe(OH)_3$ cannot occur in the syrup. Ewe (200) reported that Syrup of Hydriodic Acid caramelized, due to excessive acidity. Attempts to lower the acidity by reducing the proportion of hypophosphorous acid resulted in the appearance of free iodine in the syrup. When the acidity was reduced by diluting the syrup with water until the sugar content was 35%, the syrup remained colorless for a year. Husa and Magid (271) also reported that the decomposition of the Syrup of Hydriodic Acid increased with increasing hydrogen-ion concentration. Mercuric iodide, barium iodide, aluminum sulphate and calcium chloride caused a marked retardation of the decomposition of the syrup.

Guyote (74) reported that a solution of arsenous iodide hydrolyzes to hydriodic acid which becomes oxidized to free iodine. This was overcome by neutralizing the solution with sodium

hydroxide, thus converting the arsenous iodide to an arsenite. The arsenite solution appeared to be stable. Knight (112) criticized the U. S. P. Fowler's Solution, claiming that 2% of potassium bicarbonate causes an unnecessary increase in alkalinity. He stated that 1% of potassium bicarbonate would be sufficient. Smelt (293) recommended that the B. P. Fowler's Solution be adjusted to a p_H less than 4.0. The growth of molds was favored between p_H 5.0–7.8, and precipitation occurred between p_H 4–9. The acid solution was favored because of greater compatibility.

Donovan's Solution can be sufficiently stabilized by adjusting the p_H to neutrality. The U. S. P. preparation is very acid, due to the hydrolysis of the arsenous iodide. Cocking (122) and Husa (160) both showed that the hydrolysis of dilute arsenous iodide is complete, the p_H of tenth normal solutions of arsenous iodide and hydriodic acid being the same, 1.1. Duncan (14) first showed that the liberation of iodine from Donovan's Solution could be checked by neutralizing the free hydriodic acid. Husa (158), (241), (270) found that the p_H of Donovan's Solution was 1.2. There was no liberation of iodine when the p_H was adjusted to 6.0–8.0. He recommended the use of a carbonate as the neutralizing agent as it prevented oxidation by replacing the air with carbon dioxide.

Husa (272) stated that the stability of Solution of Iron and Ammonium Acetate was slightly increased when the acetic acid was omitted and the solution buffered with hydrochloric acid, ammonium chloride and sodium chloride. Jones and Glass (161) reported that properly prepared Iron and Ammonium Citrate is a neutral substance of p_H of about 7.5. Its incompatibility with magnesium sulphate could not be correlated with any increase of p_H. Morton (168) stated that the commercial bismuth and ammonium citrate and the B. P. Solution of Bismuth and Ammonium Citrate are unsatisfactory preparations. The complex was stable only in the presence of an excess of alkali citrate. Kleinschmidt (212) claimed that the Solution of Magnesium Citrate would not precipitate if the citric acid content were reduced. Oakley and Krantz (246), however, decided that the precipitation was due to the conversion of a large amount of the magnesium acid citrate to the neutral salt, $Mg_3(C_6H_5O_7)_2$, and that the presence of an excess of citric acid would shift the equilibrium to the acid salt and favor stability.

Éwe (200) reported that the fungous growths in the Acid Solution of Phosphates could be prevented by the addition of about 1% of concentrated hydrochloric acid and 0.4% formic acid. Éwe further stated that the Compound Elixir of Glycerophosphates develops a precipitate within a few months. The precipitation was reduced by increasing the lactic acid content, and was completely corrected by substituting phosphoric acid instead.

Dekay and Lee (262) found that samples of the official Elixir of Ferric Pyrophosphate, Quinine and Strychnine underwent a color change which was roughly proportional to a simultaneous increase in p_H. Those samples which were carefully neutralized in their preparation were most constant in p_H but the neutralization did not affect their stability.

Thompson and his co-workers (296) reported that the p_H values of Spirit of Ethyl Nitrite changed greatly during deterioration. The following are the p_H values of different samples corresponding to the ethyl nitrite content during 23 months' storage:

4.25% (fresh)	2.95%	1.54%	0.00%	0.00%
p_H 0.82	p_H 0.46	p_H 1.00	p_H 5.95	p_H 4.34

Davis (197), (198) reported the p_H of various hypochlorite preparations as follows: Dakin's Solution, p_H 9.71; Eusol, p_H 7.21; Daufresne's Solution, p_H 10.23; 1% Chloramine, p_H 10.05. Eusol decomposed more rapidly than the more alkaline Dakin's Solution. When Davis prepared mixtures of chlorinated lime, sodium carbonate and boric acid, p_H 9.53 was the lowest p_H value which could be obtained with stable preparations.

Noyes and Wilson (52) obtained evidence that hypochlorous acid ionizes in an amphoteric fashion, forming both positive and negative chlorine ions. They assumed the presence of two compounds, H^+ Cl O^- and Cl^+ OH^-. Lynch and Nodder (245) have published the most extensive data concerning the ionic condition of hypochlorite solutions. They included a method for calculating the displacement of the p_H of buffer solutions, due to the presence of sodium hypochlorite. The development of the glass electrode enabled Davidson (261) to accurately determine the dissociation constant of hypochlorous acid as 3.7×10^{-8} at 20° C. He reported that bleaching powder decomposed, forming oxalic and carbonic acids with an accompanying reduction of p_H. The more alkaline solutions decomposed the least, and decomposition was much less when the acids were removed as they were formed.

p_H AND STABILITY OF ALKALOIDS.

It has been shown that p_H is an important factor in the stability of alkaloids during sterilization. It is obvious, also, that the p_H of these solutions for injection must be stabilized to a value comparable to the p_H of the blood. Trendelenburg (70), Schon (225), Regnier (285), (328), Schou (291), and Woelm (299) have pointed out the importance of buffering to the physiological p_H solutions of morphine, cocaine, tutocaine and larocaine solutions which are intended for injection. This buffering is necessary not only to counteract the alkaline tendency of the glass containers but to prevent a spontaneous change in hydrogen-ion concentration as a result of the decomposition of a small amount of the alkaloid.

Dietzel and Huss (111) studied the decomposition of morphine at high temperatures and at different p_H values. The decomposition was detected by changes in the absorption spectrum. At p_H values of less than 5.5, the morphine was stable for 60 minutes at 100° C. Neutral and alkaline solutions were very unstable. The free morphine was not any less stable than the morphine hydrochloride, the decomposition being due to oxidation by hydroxyl-ion catalysis. It was found that alkaline glass caused decomposition at room temperature. Dietzel (311) verified his results in 1934 and again attributed the stability at reduced p_H to catalytic neutrality. The p_H of morphine hydrochloride and morphine sulphate solutions is about 4.0.

Cocaine also requires an acid medium for stability and undergoes a decrease in p_H during storage and sterilization. Regnier and his co-workers (285), (286) demonstrated the change to acidity during storage and pointed out the dangers of the pharmacological use of such acid solutions. Macht and Anderson (98) and Macht and Krantz (99) reported that exposure to polarized light increased the hydrogen-ion concentration of cocaine solutions. Ditezel and Steeger (263) reported that the hydrolysis of cocaine by heat was a minimum between p_H 2–5. The type of glass container had a negligible effect. Schon and Helm (225) reported that the hydrolysis of benzoylecgonine was a minimum between p_H 2–7. When they attempted to buffer cocaine solutions to the physiological p_H, hydrolysis was accelerated unless the p_H was as low as 3.4. A pure solution of cocaine hydrochloride changed in 2 months from p_H 5.17 to 4.2 without any perceptible decomposition. One buffered to p_H 6.05 showed 31% hydrolysis in the same time. Regnier and David (287) found that solutions buffered to neutrality by being saturated with calcium carbonate and magnesium carbonate retained their potency during sterilization but rapidly deteriorated afterward. Their anesthetic power was inferior to that of pure solutions of cocaine. Regnier and David (327), (328) later reported that solutions of cocaine buffered by NaH_2PO_4 almost completely deteriorated during sterilization, but those buffered by acetic acid and sodium citrate retained their activity. Dietzel (311) reported that of the various cocaine salts, cocaine sulphate was most stable during the first 25 hours of heating. The p_H of cocaine sulphate solutions is about 5.2.

Dietzel and Steeger (263) determined the dissociation constants for cocaine and its hydrolysis products. The results were as follows:

Cocaine	2.4×10^{-6}	
Methylecgonine	3.0×10^{-6}	
Benzoylecgonine	$\frac{(\text{benzoylecgonine})(OH^-)}{(\text{benzoylecgonine})}$	1.9×10^{-12}
	$\frac{(\text{benzoylecgonine})(H^+)}{(\text{benzoylecgonine})}$	1.8×10^{-18}
Ecgonine	$\frac{(\text{ecgonine})(OH^-)}{(\text{ecgonine})}$	6.0×10^{-12}
	$\frac{(\text{ecgonine})(H^+)}{(\text{ecgonine})}$	7.6×10^{-12}

The authors pointed out that in the choice of an acid to be combined with cocaine, its dissociation constant must not be smaller than that of methylecgonine or cocaine, that is, not smaller than 10^{-6}. Otherwise the dissociation forms hydroxyl ions which promote hydrolysis by hydroxyl-ion catalysis.

Abildgaard (190) reported that solutions of procaine hydrochloride in hydrochloric acid showed no appreciable decomposition when heated. Under the same conditions and in a pure water solution, 5% of the procaine hydrochloride was hydrolyzed, and, when buffered to a p_H of 6.5, 19–35% was hydrolyzed. Wiedhopf (231) claimed that pantokain is very stable and can withstand several hours' boiling near the neutral point. An aqueous solution has a p_H of 7.0 and a 1% solution in physiological salt solution has a p_H of 6.7. Procaine was more easily hydrolyzed. Schou and Staggemeier (291) reported that tutocaine, when heated to 120° C. for 20 minutes, decomposed 24% at p_H 7.0 and 12.2% at p_H 6.5. Under the same conditions larocaine decomposed 20.9% at p_H 7.0 and 11.4% at p_H 6.5. The solutions were adjusted with phosphate buffers. Dietzel and Kuhl (310) reported that during storage of eucaine hydrochloride the p_H dropped from 6.98 to 5.26 in 1 year with 39.7% decomposition. Heat sterilization or exposure to oxygen did not hasten the decomposition.

Schou and Bjerregaard (249) have studied the decomposition of atropine and homatropine solutions. Pure 0.4% aqueous atropine sulphate was sterilized for 20 minutes at 120° C. with only 3.4% hydrolysis. Buffering to higher p_H values caused greater loss. Pure 0.4% aqueous homatropine hydrobromide was less stable and decomposed 8.2% under the same conditions. Complete hydrolysis occurred at p_H 7.3 and above.

Biddle and Watson (28) noted that changes in the hydrogen-ion concentration caused a change in the ionic condition of the cinchona alkaloids. Dietzel and Sollner (149) have elaborated on this work. They stated that in the water-soluble salts of quinine, quinidine and cinchonidine, the nitrogen of the quinuclidine ring is ionized while the nitrogen of the quinoline ring is not. In the presence of an excess of acid, the latter nitrogen ionizes and forms salts. With decreasing p_H there was in each case an increase of optical rotation which paralleled the ionization of the quinoline nitrogen. Macht and Anderson (99) reported that quinine and cinchonidine salts decreased in toxicity upon exposure to polarized light.

Dietzel (311) reported that hydrastine decomposed very rapidly at 100° C. but that hydrastinine showed very little change. Decomposition of berberine was very slight and evidently was not altered by an increase in hydrogen-ion concentration.

Gifford and Smith (265) reported that physostigmine and pilocarpine decomposed more rapidly in an alkaline buffer solution of p_H 7.6 than in an acid buffer solution of p_H 5.5.

p_H AND STABILITY OF MISCELLANEOUS ORGANIC COMPOUNDS.

Nielson (284) reported that the decomposition of sodium luminal increased with increasing p_H. A 10% solution has a p_H of about 8.9. A 10% solution decomposed 1.0% in 3 weeks at room temperature and 22% in 1 month at 39° C. Madsen (319) reported that the decomposition of sodium barbital also increased with increasing p_H. A 10% solution has a p_H of 8.9; the decomposition was accompanied by a decrease in p_H. Sixty minutes at 100° C. caused 2.5% decomposition of the sodium barbital with the formation of diethylacetylurea.

Kolthoff (128) claimed that the decomposition of a thiosulphate with acid was due to the formation of the undissociated thiosulphuric acid which is unstable. Schou and Bennekou (290) stated that sodium thiosulphate solutions could be sterilized without decomposition only when the p_H was 7.0. The solutions were adjusted by phosphate buffers.

Macht and Shohl (37) have published data concerning the decomposition of benzyl alcohol solutions. Solutions stored in insoluble glass were stable over long periods of time but showed a slight increase in hydrogen-ion concentration. Solutions stored in soft or alkaline glass quickly became alkaline and rapidly deteriorated. The deterioration was evidently an oxidation process. The authors claimed that the oxidation was hastened by neutralizing the benzoic acid which was formed. It was recommended that solutions of benzyl alcohol be sealed in hard glass containers with the addition of a buffer to keep the p_H between 6.8–7.0.

Nijhoff and Van Oort (171) found that urotropin solutions could not be sterilized by boiling because of decomposition into ammonia and formic acid. The type of glass did not influence the decomposition. The authors recommended that urotropin be sterilized by tyndallization after the addition of 2% of sodium bicarbonate.

Levy and Cullen (36) found that the autoclaving of strophanthin solutions changed the reaction from p_H 6.0 to p_H 9.0. This increase in p_H greatly reduced the biological action of strophanthin. Autoclaving at p_H 5.0 caused only 2% deterioration. Haag and Hatcher (127) have

also demonstrated the alkaline instability of strophanthin. They reported that ouabain solutions slowly decomposed in ampuls of hard glass.

Dubrisay and Emschwiller (237) have completed a thorough study of the decomposition of iodoform. Iodoform in solution was oxidized by light with the formation of iodine and hydriodic acid, which, in turn, accelerated further oxidation. Other mineral acids promoted oxidation, whether in the light or dark. Oxidation was the slowest with ether, carbon disulphide or toluene as the solvent. Very small amounts of phenol or hydroquinone retarded the oxidation.

Lindholm (276) reported that hydrogen peroxide solutions were stabilized by the addition of any one of the following: acetanilid, quinine hydrochloride, urea, methyl parahydroxybenzoate, acetphenetidin, oxalic acid and iodine. A 3% peroxide solution was stabilized by 0.04% iodine for 5 years.

Pertaining to the stabilization of phenol, Vergez (252) stated that a solution containing 20 Gm. of phenol, 8 Gm. of crystalline boric acid and 1000 cc. of water remained unchanged for 18 months.

In 1929, Smith and his co-workers (136) reported the finding of large discrepancies in the p_H values of commercial neoarsphenamine. The values ranged from p_H 5.80–8.74. Upon dilution, some samples increased in p_H and others decreased.

GENERAL PRINCIPLES CONCERNING p_H AND STABILITY.

Much work has been performed which, at the present time, has little practical application in the stabilizing of drugs. However, the results of these investigations have established certain fundamental principles which can broaden our conception concerning the mechanism of the ionic condition.

For instance, Kolthoff (128) has shown conclusively that ions which are in an adsorbed state possess reaction qualities different from those of free ions. If the ions of the reacting substance are adsorbed upon some stratum, the reaction is greatly retarded and, if the ions of a product of a reaction are adsorbed, the reaction is greatly accelerated. In his experiments the ions were adsorbed upon charcoal.

Kiehl and Hansen (84) have investigated the ionization during the hydration of pyrophosphates. By the use of reference curves obtained by making hydrogen-ion concentration measurements on synthetic solutions and plotting the molar concentrations of hydrogen ions against the molar concentrations of disodium orthophosphate, each hydration was followed to completion by hydrogen-ion concentration measurements. The hydrogen-ion concentration decreased progressively with time, reaching a final fixed value as complete conversion to the orthophosphate occurred. This fact indicates that pyrophosphoric acid produces more hydrogen ions than does orthophosphoric acid and, consequently, that the withdrawal of hydrogen ions will displace the reaction toward the pyro acid.

Buchanan and Barsky (144) reported that the rate of polymerization of cyanamide is a function of the hydrogen-ion concentration, the velocity of the reaction being greatest at p_H 9.6 and decreasing rapidly above and below this point. Between p_H 6–10 the polymer alone (param or cyanguanidine) was formed. Between p_H 10–12 both the polymer and urea were formed. Above p_H 12 no polymerization occurred and only urea was formed. Zappi and Williams (255) noted also that there was an optimum p_H in the region of 9.5 for the polymerization of aldehydes. Zappi's article was also of interest concerning the effect of p_H upon the concentrations of the tautomeric forms of aldehydes.

Volfkovich (253) and Bryan (258), (259) have demonstrated the presence of a transition point at p_H 4.3 between the two types of oxidation, addition of oxygen and hydrogen evolution. The hydrogen evolution occurred below p_H 4.3. This was applied experimentally to iron salts and to sulphites.

Bolin (107) has determined a number of p_H values for the maximum stability against hydrolysis of esters. The reactions occurred at 25° C. unless stated otherwise. His results indicate that esters are hydrolyzed by hydrogen- and hydroxyl-ion catalysis. He drew the following conclusions: For esters of fatty acids, the optimum p_H for a weak acid is lower than for a strong acid. For methyl esters, the optimum p_H is lower than for the corresponding ethyl esters. Introduction of a phenyl group lowers the optimum p_H and increases the ve-

locity of decomposition. Bolin claimed that derivatives of secondary amines and similar compounds which are not prone to hydrolysis are most stable at p_H 7.0.

	p_H.		p_H.
Ethyl butyrate	5.65	Ethyl phenylacetate	4.9
Methyl benzoate	4.0 (80° C.)	Ethyl acetoacetate	4.4
Ethyl benzoate	4.15 (80° C.)	Ethyl alphachloropropionate	4.0
Phenyl acetate	4.1	Ethyl hippurate	4.4
Benzyl acetate	4.3	Methyl acetanilide	6.0

Olivier (134) claimed that the influence of the hydrogen-ion concentration upon hydrolysis is conditioned by the nature of the organic compound. Such an influence is absent in alkyl halides and acid chlorides, as well as in other compounds in which the water molecule, as such, may be expected to add directly. Olivier further stated that the concordant and regular influence of the substituents upon the hydrogen ion catalyzed hydrolysis of esters are best explained by the theories of induced alternating polarities of Lapworth, Kermak and Robinson. For further information concerning the reaction of different molecular structures to hydrogen-ion catalysis the reader is referred to Olivier (321), (322), (323).

BIBLIOGRAPHY.

(1) Helmholtz, H. V. 1881. *J. Chem. Soc.*, 39, 292.
(2) Arrhenius, Svante. 1887. *Z. physik. Chem.*, 1, 631.
(3) Nernst, W. 1889. *Ibid.*, 4, 129.
(4) Arrhenius, Svante. 1890. *Ibid.*, 5, 1.
(5) Ostwald, W. 1893. *Ibid.*, 11, 521.
(6) Wijs, J. J. A. 1893. *Ibid.*, 12, 514.
(7) Nernst, W. 1894. *Ibid.*, 14, 155.
(8) Kohlrausch, F., and Heydweiller, A. 1895. *Ann. physik. Chem.*, 53, 209.
(9) Bugarszky, S., and Liebermann, L. 1898. *Arch. ges. Physiol.*, 72, 51.
(10) Peters, R. 1898. *Z. physik. Chem.*, 26, 193.
(11) Arrhenius, Svante. 1899. *Ibid.*, 31, 197.
(12) Crotogino, F. 1900. *Z. anorg. allgem. Chem.*, 24, 225.
(13) Euler, Hans. 1900. *Z. physik. Chem.*, 32, 348.
(14) Duncan, William. 1903. *Pharm. J.*, (1903), 586. Through PROC. A. PH. A., 51, 631.
(15) Salessky, W. 1904. *Z. Elektrochem.*, 10, 204.
(16) Salm, E. 1906. *Z. physik. Chem.*, 57, 471.
(17) Fitzgerald, E., and Lapworth, A. 1908. *J. Lond. Chem. Soc.*, 93, 2163.
(18) Lapworth, A. 1908. *Ibid.*, 93, 2187.
(19) Haber, F., and Klemensiewicz. 1909. *Z. physik. Chem.*, 67, 385.
(20) Lewis, G. N., and Sargent, L. W. 1909. *J. Am. Chem. Soc.*, 31, 362.
(21) Sorensen, S. P. L. 1909. *Biochem. Z.*, 21, 131.
(22) Goldschmidt, Heinrich. 1909. *Z. Elektrochem.*, 15, 4.
(23) Michaelis, L., and Davidsohn, H. 1911. *Biochem. Z.*, 35, 386.
(24) Dawson, H. M., and Powis, F. 1913. *J. Lond. Chem. Soc.*, 103, 2135.
(25) Hildebrand, J. H. 1913. *J. Am. Chem. Soc.*, 35, 847.
(26) Stieglitz, Julius, 1913. *Ibid.*, 35, 1774.
(27) Dawson, H. M., and Powis, F. 1914. *J. Lond. Chem. Soc.*, 105, 1093.
(28) Biddle, H. C., and Watson, Thomas. 1917. *J. Am. Chem. Soc.*, 39, 968.
(29) Clark, W. M., and Lubs, H. A. 1917. *J. Bact.*, 2, 1, 109, 191.
(30) Harkins. 1917. *J. Am. Chem. Soc.*, 39, 354.
(31) Lewis, G. N., Brighton, T. B., and Sebastian, R. L. 1917. *J. Am. Chem. Soc.*, 39, 2245.
(32) Dudley, H. W. 1919. *J. Pharmacol. Exp. Ther.*, 14, 295.
(33) Loeb, Jacques. 1919. *J. Gen. Physiol.*, 1, 717.
(34) Thomas, Arthur W., and Baldwin, M. E. 1919. *J. Am. Chem. Soc.*, 41, 1981.
(35) Abel, John J., and Nagayama, T. 1920. *J. Pharmacol. Exp. Ther.*, 15, 347.
(36) Levy, Robert L., and Cullen, G. E. 1920. *J. Exp. Med.*, 31, 267.
(37) Macht, David I., and Shohl, A. T. 1920. *J. Pharmacol. Exp. Ther.*, 16, 61.
(38) Northrop, John H. 1920. *J. Gen. Physiol.*, 2, 465.

1921.

(39) Biilmann, E. *Ann. chim.*, (9), 15, 109.
(40) Biilmann, E., and Lund, H. *Ibid.*, (9), 16, 321.
(41) Crane, Marian M. *J. Pharmacol. Exp. Ther.*, 18, 319.
(42) Joachimoglu, G. *Arch. exptl. Path. Pharm.*, 91, 156. Through *C. A.*, 16, 3130.
(43) Kendall, James. *Proc. Nat. Acad. Sci.*, 7, 56.
(44) Kolthoff, I. M. *Pharm. Weekbl.*, 58, 961. Through YEAR BOOK, A. PH. A., 10, 305.
(45) Northrop, John H. *J. Gen. Physiol.*, 3, 715.

1922.

(46) Bogue, Robert H. *J. Physic. Chem.*, 26, 801.
(47) Cohen, Barnett. *J. Bact.*, 7, 183.
(48) Corran, J. W., and Lewis, W. C. M. *J. Am. Chem. Soc.*, 44, 1673.
(49) Fleisch, Alfred. *Arch. exptl. Path. Pharmakol.*, 94, 22. Through *Chem. Zentralbl.*, 93, 1205.
(50) Kolthoff, I. M. *Pharm. Weekbl.*, 59, 104. Through YEAR BOOK A. PH. A., 11, 378.
(51) Northrop, John H. *J. Gen. Physiol.*, 5, 263.
(52) Noyes, William A., and Wilson, T. A. *J. Am. Chem. Soc.*, 44, 1630.
(53) Van Slyke, D. D. *J. Biol. Chem.*, 42, 525.
(54) Williams, John R., and Swett, M. *J. Am. Med. Assoc.*, 78, 1024.
(55) Williams, John R., and Swett, M. *Proc. Soc. Exptl. Biol. Med.*, 19, 266.

1923.

(56) Biilmann, E. *Trans. Faraday Soc.*, 19, 676.
(57) Joachimoglu, G. *Biochem. Z.*, 134, 489.
(58) Kolthoff, I. M. *J. Soc. Chem. Ind.*, 42, 427A.
(59) Lewis, G. N., and Randall, M. "Thermodynamics and the Free Energy of Chemical Substances.," McGraw-Hill Book Co., N. Y.
(60) Masucci, Peter, and Moffat, M. I. JOUR. A. PH. A., 12, 609.
(61) Rice, F. O. *J. Am. Chem. Soc.*, 45, 2808.
(62) Robertson, O. H., Woo, S. T., and Sia, H. P. *Proc. Soc. Exptl. Biol. Med.*, 21, 119.
(63) Smith, R. B., and Giesy, P. M. JOUR. A. PH. A., 12, 955.
(64) Swanson, E. E., and Walters, A. L. JOUR. A. PH. A., 12, 957.

1924.

(65) Joachimoglu, G., and Bose, P. *Arch. exptl. Path. Pharmakol.*, 102, 17. Through *C. A.*, 18, 2787.
(66) Kuhn, Richard, and Sobotka, H. *Z. physik. Chem.*, 109, 65.
(67) Northrop, J. H. *J. Gen. Physiol.*, I. 6, 337. II, 7, 603.
(68) Risch, C. *Biochem. Z.*, 148, 147.

(69) Swanson, E. E. JOUR. A. PH. A., 13, 1108.
(70) Trendelenburg, Paul. Oe. P., 90,276. Through *Chem. Zentralbl.*, 95, 1060.
(71) Waterman, H. I., and Kuiper, P. *Rec. trav. chim.*, 43, 323. Through *C. A.*, 18, 2582.

1925.

(72) Abt, G., and Loiseau, G. *Ann. inst. Pasteur*, 39, 114. Through *C. A.*, 19, 2511.
(73) Brownlee, John. *Biochem. J.*, 19, 377.
(74) Guyot, R. *Bull. soc. pharm. Bordeaux*, 63, 217. Through *C. A.*, 20, 965.
(75) Johnston, J. H., and Peard, G. T. *Biochem. J.*, 19, 281.
(76) Kerridge, P. M. T. *Biochem. J.*, 19, 611.
(77) Plaut Research Lab. (Lehn and Fink). *Am. J. Pharm.*, 97, 456.
(78) Roy, L. *J. Pharm. chim.*, (8) 1, 525.

1926.

(79) Anonymous. *Pub. Health Rep.*, 41, 505.
(80) Eggerth, Arnold H. *J. Gen. Physiol.*, 10, 147.
(81) Geill, Torben. *Compt. rend. soc. biol.*, 95, 1219, and 1221. Through *C. A.*, 22, 250.
(82) Ghosh, S., and Dhar, N. R. *J. Phys. Chem.*, 30, 830.
(83) Hintzelmann and Joachimoglu. *Arch. exptl. Path. Pharmakol.*, 112, 56. Through *Yahresber. Pharm.*, 61, 233 and *Quart. J. Pharm. Pharmacol.*, 3, 215.
(84) Kiehl, Samuel J., and Hansen, W. C. *J. Am. Chem. Soc.*, 48, 2802.
(85) Kraemer, Elmer O. *Colloid Symposium Monograph*, 4, 102.
(86) Krantz, John C., Jr., and Gordon, N. E. JOUR. A. PH. A., 15, 83.
(87) Lepper, E., and Martin, C. J. *Biochem. J.*, 20, 45.
(88) Macht, D. I., and Krantz, J. C., Jr. *Proc. Soc. Exptl. Biol. Med.*, 23, 340.
(89) Sherman, H. C., and Burton, G. W. *J. Biol. Chem.*, 70, 639.
(90) Stasiak, A. *J. Pharmacol. Exp. Ther.*, 28, 1.
(91) Strom, K. M. *Nyt. Mag. Naturvidenskab*, 64, 109. Through *C. A.*, 22, 2729.
(92) Tainter, M. L. JOUR. A. PH. A., 15, 255.
(93) Vahlteich, H. W. *Ibid.*, 15, 193.

1927.

(94) Hassan, A., and Drummond, J. *Biochem. J.*, 21, 653.
(95) Iselin, Ernst. *Pharm. Acta. Helv.*, 2, 80.
(96) Kofler, L., and Lazar, Z. *Arch. Pharm. u. Ber. deut. pharm. Ges.*, 265, 610.
(97) Krantz, J. C., Jr., and Slama, F. J. JOUR. A. PH. A., 16, 1156.
(98) Macht, D. I., and Anderson, W. T., Jr. *J. Am. Chem. Soc.*, 49, 2017.
(99) Macht, D. I., and Krantz, J. C., Jr. JOUR. A. PH. A., 16, 106.
(100) Marrack, J., and Hewitt, L. F. *Biochem. J.*, 21, 1129.
(101) Ringer, W. E., and Grutterink, B. W. *Z. Physiol. Chem.*, 164, 112.
(102) Sadolin, Erik. *Dansk. Tids. Farm.*, 1, 223. Through *C. A.*, 21, 1869.
(103) Scoville, Wilbur L. JOUR. A. PH. A., 16, 1136.
(104) Smorodinzew, J. A., and Danilow, V. A. *Biochem. Z.*, 181, 149.
(105) Swanson, E. E., and Hargreaves, C. C. JOUR. A. PH. A., 16, 296.

1928.

(106) Behrens, W. U. *Z. anal. Chem.*, 73, 129.
(107) Bolin, Ivan. *Z. anorg. allgem. Chem.*, 177, 227.
(108) Bond, W. R., and Gray, E. W. *Quart. J. Pharm. Pharmacol.*, 32, 351.
(109) Bronsted, J. N. *Trans. Faraday Soc.*, 24, 630.
(110) Clark, W. M. "The Determination of Hydrogen Ions," 3rd edition, page 36. Williams and Wilkins Co., Baltimore, Md.
(111) Dietzel, R., and Huss, W. *Arch. Pharm. u. Ber. deut. pharm. Ges.*, 266, 641.
(112) Knight, W. A. *Pharm. J.*, 121, 396.
(113) Krantz, J. C., Jr., and Gordon, N. E. *Colloid Symposium Monograph*, 6, 173.
(114) Krogh, A., and Hemmingsen, A. *Biochem. J.*, 22, 1231.
(115) Malquori, G. *Gass. chim. ital.*, 58, 203. Through *Chem. Zentralbl.*, 99, 217.
(116) Mayeda, Siebung. *Biochem. Z.*, 197, 410.
(117) Northrop, J. H., and Simms, H. S. *J. Gen. Physiol.*, 12, 313.
(118) Swanson, E. E., and Hargreaves, C. C. JOUR. A. PH. A., 17, 22.
(119) Tschirch, A., and Fluck, H. *Pharm. Acta. Helv.*, 3, 140.

1929.

(120) Beguin, M. C. *Pharm. Acta. Helv.*, 4, 213.
(121) Chapin, Robert M. *J. Am. Chem. Soc.*, 51, 2112.
(122) Cocking, T. Tusting. *Quart. J. Pharm. Pharmacol.*, 2, 409.
(123) Cornog, J., and Hershberger, A. *Proc. Iowa Acad. Sci.*, 36, 264. Through *C. A.*, 25, 1146.
(124) Cruess, W. V., and Richert, P. H. *J. Bact.*, 17, 363.
(125) Fluck, H. *Pharm. Acta. Helv.*, 4, 58.
(126) Guha, B., and Drummond, J. *Biochem. J.*, 23, 880.
(127) Haag, H. B., and Hatcher, R. A. *J. Am. Med. Assoc.*, 93, 26.
(128) Kolthoff, I. M. *Rec. trav. chim.*, 48, 298. Through *C. A.*, 23, 2872.
(129) Krantz, J. C., Jr. JOUR. A. PH. A., 18, 469.
(130) Krantz, J. C., Jr., and Gordon, N. E. *Ibid.*, 18, 797.
(131) Miller, Edgar G. *Biochem. J.*, 23, 876.
(132) Mulford, H. G., and Greenbaum, F. R. JOUR. A. PH. A., 18, 564.
(133) Nasset, E. S., and Greenberg, D. M. *J. Am. Chem. Soc.*, 51, 836.
(134) Olivier, S. C. J. *Chem. Weekbl.*, 26, 518. Through *C. A.*, 24, 1338.
(135) Reader, Vera. *Biochem. J.*, 23, 689.
(136) Smith, R. B., Jurist, A. E., and Christiansen, W. G. JOUR. A. PH. A., 18, 1142.
(137) Svedberg, T., and Heyroth, F. *J. Am. Chem. Soc.*, 51, 550.
(138) Swanson, E. E. JOUR. A. PH. A., 18, 1129.
(139) Temple, J. W. *J. Am. Chem. Soc.*, 51, 1754.
(140) Van Winkle, R., and Christiansen, W. G. JOUR. A. PH. A., 18, 797.
(141) Williams, Waterman, and Gurin. *J. Biol. Chem.*, 83, 321.

1930.

(142) Acree, S. F., and Fawcett, E. H. *Ind. Eng. Chem., Analyt. Ed.*, 2, 78.
(143) Benda, Louis. U. S. 1,758,425, May 13. Through *C. A.*, 24, 3326.
(144) Buchanan, G. H., and Barsky, G. *J. Am. Chem. Soc.*, 52, 195.
(145) Chick, H., and Roscoe, M. *Biochem. J.*, 24, 105.
(146) Chick, H., and Copping, A. *Ibid.*, 24, 932.
(147) Chick, H., and Copping, A. *Ibid.*, 24, 1764.
(148) Conduche, E., and Gregoire, F. *Bull. Sci. Pharmacol.*, 37, 529.
(149) Dietzel, R., and Sollner, K. *Arch. Pharm. u. Ber. deut. pharm. Ges.*, 268, 629.
(150) Eddy and Gurin. *J. Biol. Chem.*, 87, 729.
(151) Fosdick, L. S., H. L. Hansen, and Dragstedt, C. A. *Proc. Soc. Exptl. Biol. Med.*, 27, 529.
(152) Gaddum, J. H. *Biochem. J.*, 24, 939.
(153) Gerlough, T. D. *J. Am. Chem. Soc.*, 52, 824.
(154) Guerrant, N. B., and Salmon, W. D. *J. Biol. Chem.*, 89, 199.
(155) Haag, H. B., and Hawkins, L. W. JOUR. A. PH. A., 19, 1284.
(156) Hoen, E., and Chertkov, L. *Zentr. Bact. Parasitenk*, 117, 364. Through *C. A.*, 24, 5855.
(157) Hofmann, E. *Helv. Chim. Acta.*, 13, 138.
(158) Husa, W. J., and Enz, W. W. F. JOUR. A PH. A., 19, 328.
(159) Husa, W. J. *Ibid.*, 19, 825.
(160) Husa, W. J. *Ibid.*, 19, 1287.
(161) Jones, A. J., and Glass, N. *Quart. J. Pharm. Pharmacol.*, 3, 488.
(162) Krantz, J. C., Jr., and Carr, C. J. JOUR. A. PH. A., 19, 32.
(163) Krantz, J. C., Jr. *Ibid.*, 19, 366.
(164) Krantz, J. C., Jr., and Carr, C. J. *Ibid.*, 19, 1095.
(165) Krantz, J. C., Jr. *Ibid.*, 19, 1181.
(166) McGillivray, Ivor. *Biochem. J.*, 24, 891.
(167) Morris, T. N. *Dept. Sci. Ind. Research Rept. of Food Investigation Board* (1930), 119. Through *C. A.* 25, 4837.
(168) Morton, C. *Quart. J. Pharm. Pharmacol.*, 3, 561.
(169) Morton, C. *Ibid.*, 3, 438.
(170) Narayanan, B., and Drummond, J. *Biochem. J.*, 24, 19.

(171) Nijhoff, G. H., and Van Oort, H. D. *Pharm. Weekbl.*, 67, 884. Through *Yahresber. Pharm.*, 65, 302 and *Quart. J. Pharm. Pharmacol.*, 4, 127.
(172) Pace, James. *Biochem. J.*, 24, 606.
(173) Pleass, W. B. *Ibid.*, 24, 1472.
(174) Remesow, Igor. *Biochem. Z.*, 218, 86.
(175) Schmidt, S. *Kgl. Danske Videnskap, Selskap. Biol. Medd.*, 9, 1. Through *C. A.*, 25, 3383.
(176) Schmidt, S. *Dansk. Tids. Farm.*, 4, 173. Through *C. A.*, 24, 5855.
(177) Schmidt, S. *Z. Immunitäts*, 66, 506.
(178) Sjogren, B., and Svedberg, T. *J. Am. Chem. Soc.*, 52, 5187.
(179) Smith, E. L. *Quart. J. Pharm. Pharmacol.*, 3, 499.
(180) Svedberg, T. *Trans. Faraday Soc.*, 26, 740.
(181) Svedberg, T., and Sjogren, B. *J. Am. Chem. Soc.*, 52, 2855.
(182) Swanson, E. E., and Hargreaves, C. C. JOUR. A. PH. A., 19, 122.
(183) Thimann, K. V., and Page, A. B. *Biochem. J.*, 24, 1058.
(184) Thompson, M. R. JOUR. A. PH. A., 19, 705.
(185) Weeks, I. C. *Physical Review*, 35, 668.
(186) Williams, J., and Corran, J. *Biochem. J.*, 24, 37.
(187) Wokes, F. *Quart. J. Pharm. Pharmacol.*, 3, 205.
(188) Wokes, F., and Elphick, G. K. *Ibid.*, 3, 599.
(189) Wokes, F., and Elphick, G. K. *Ibid.*, 3, 59.

1931.

(190) Abildgaard, J. *Dansk. Tids. Farm.*, 5, 129. Through *Quart. J. Pharm. Pharmacol.*, 4, 644.
(191) Bartsch, O. *Dansk. Tids. Farm.*, 5, 172. Through *C. A.*, 26, 3873.
(192) Berg, E. *Pharm. Zeit.*, 76, 959. Through YEAR BOOK A. PH. A., 20, 37.
(193) Bruck. *Apoth. Zeit.*, 46, 994.
(194) Chapin, R. M. *J. Am. Chem. Soc.*, 53, 912.
(195) Cruess, W. V., Richert, P. H., and Irish, J. H. *Hilgardia*, 6, 295.
(196) Daniels, T. C., and Lyons, R. E. *J. Phys. Chem.*, 35, 2049.
(197) Davis, H. *Quart. J. Pharm. Pharmacol.*, 4, 360.
(198) Davis, H. *Pharm. J.*, 127, 81.
(199) Eschenbrenner, H. *Pharm. Zeit.*, 76, 694. Through *Yahresber. Pharm.*, 66, 236.
(200) Ewe, G. E. JOUR. A. PH. A., 20, 360.
(201) Freudenberg, K. D. W., and Eyer, H. *Z. physiol. Chem.*, 202, 128.
(202) Freudenberg, K. D. W., *Ibid.*, 202, 159.
(203) Friedman, L., and Evans, D. N. *J. Am. Chem. Soc.*, 53, 2898.
(204) Gerlough, T. D. *J. Pharmacol. Exp. Ther.*, 41, 307.
(205) Guha, B. C. *Biochem. J.*, 25, 945.
(206) Haag, H. B., and Jarrett, L. E. JOUR. A. PH. A., 20, 474.
(207) Harada, T. *Ind. Eng. Chem., Analyt. Ed.*, 3, 1.
(208) Hartley, P. *Lancet*, 221, 582.
(209) Hazel, F., and Sorum, C. H. *J. Am. Chem. Soc.*, 53, 49.
(210) Jacobs, M. H., and Parpart, A. K. *Biol. Bull.*, 60, 95.
(211) Janistyn, H. *Seifensieder Zeit.*, 58, 363. Through *Chem. Zentralbl.*, 102, II, 741.
(212) Kleinschmidt, F. JOUR. A. PH. A., 20, 47.
(213) Kordatzki, W. *Z. f. Untersuchung der Lebensmittel*, 62, 480.
(214) Krantz, J. C., Jr. *Arch. Pharm. u. Ber. deut. pharm. Ges.*, 269, 470.
(215) Lichtin, A. *Am. J. Pharm.*, 103, 279.
(216) Madsen, E. H. *Pharm. Zeit.*, 76, 901. Through YEAR BOOK A. PH. A., 20, 31.
(217) Mattheus, A. O. JOUR. A. PH. A., 20, 767.
(218) Mogilskii, A. V. *Byull. Nauch. Issledovatel Khim. Farm. Inst.* (1931), 111. Through *C. A.*, 27, 5474.
(219) Morton, C. *Quart. J. Pharm. Pharmacol.*, 4, 1.
(220) Morton, C. *Ibid.*, 4, 161.
(221) Morton, C. *Ibid.*, 4, 451.
(222) Price, T. S. *Phot. J.*, 71, 59.
(223) Rae, A. *Pharm. J.*, 127, 467.
(224) Rowe, L. W., and Scoville, W. L. JOUR. A. PH. A., 20, 1030.
(225) Schon, S. A., and Helm, E. *Dansk. Tids. Farm.*, 5, 1. Through *C. A.*, 26, 256, and YEAR BOOK A. PH. A., 20–21, 166, and *Quart. J. Pharm. Pharmacol.*, 4, 541.
(226) Sjogren, B., and Svedberg, T. *J. Am. Chem. Soc.*, 53, 2657.
(227) Smith, M. I., and Stohlman, E. F. *J. Pharmacol. Exp. Ther.*, 43, 621.
(228) Taft, R., and Malm, L. E. *J. Phys. Chem.*, 35, 874.
(229) Thompson, M. R. JOUR. A. PH. A., 20, 1027.
(230) Turner, H. A. *Pharm. J.*, 126, 160.
(231) Wiedhopf, O. *Deuts. Med. Wschr.*, 53, 13. Through *Quart. J. Pharm. Pharmacol.*, 4, 159.

1932.

(232) Aberhalden, E., and Buadze, S. *Fermentforschung*, 13, 363. Through *C. A.*, 27, 106.
(233) Back, S. *Pharm. J.*, 128, 392.
(234) Barker, J., Evers, N., and Eastland, C. *Biochem. J.*, 26, 2129.
(235) Bye, M. *Proceedings A. D. M. A.*, (1932), 298.
(236) Cruess, W. V. *J. Ind. Eng. Chem.*, 24, 648.
(237) Dubrisay, R., and Emschwiller, G. *Compt. rend.*, 195, 660. Through YEAR BOOK A. PH. A., 21, 448.
(238) Emig, H. M. JOUR. A. PH. A., 21, 1273.
(239) Enz, W. W. F., and Jordan, C. B. JOUR. A. PH. A., 21, 34.
(240) Hering, K. *Arch. Pharm. u. Ber. deut. pharm. Ges.*, 270, 402.
(241) Husa, W. J. JOUR. A. PH. A., 21, 211.
(242) Krantz, J. C., Jr., and Carr, C. J. JOUR. A. PH. A., 21, 1291.
(243) Krantz, J. C., Jr., and Munch, J. C. JOUR. A. PH. A., 21, 16.
(244) Linser, H. *Biochem. Z.*, 244, 157.
(245) Lynch, L. P., and Nodder, C. R. *J. Textile Institute*, 23, 309T.
(246) Oakley, M., and Krantz, J. C., Jr. JOUR. A. PH. A., 21, 132.
(247) Powell, C. E., Schulze, and Swanson. *Ibid.*, 21, 1003.
(248) Rowe, L. W., and Scoville, W. L. *Ibid.*, 21, 160.
(249) Schou, S. A., and Bjerregaard, P. B. *Dansk. Tids. Farm.*, 6, 185. Through YEAR BOOK A. PH. A., 21, 477.
(250) Swanson, E. E., Powell, Stevens and Stuart. JOUR. A. PH. A., 21, 320.
(251) Tanko, Bela. *Biochem. Z.*, 250, 7.
(252) Vergez, G. *Bull. soc. pharm. Bordeaux*, 2, 144. Through *C. A.*, 27, 2759.
(253) Volfkovich, S. I., and Belopolskii, A. P. *J. Applied Chem.* (U. S. S. R.), 5, 529. Through *C. A.*, 27, 35.
(254) Wilcox, L. V. *Ind. Eng. Chem., Analyt. Ed.*, 4, 38.
(255) Zappi, E. V., and Williams, A. T. *Bull. Soc. Chim.*, 51, 1258.

1933.

(256) Bedford, M. H., Keller, W. H., and Gabbard, J. L. *J. Am. Chem. Soc.*, 55, 3953.
(257) Britton, H. T. S., and Dodd, E. *Trans. Faraday Soc.*, 29, 537.
(258) Bryan, J. M. *Ibid.*, 29, 830.
(259) Bryan, J. M. *Ibid.*, 29, 1198.
(260) Caines, C. M., and Evers, N. *Quart. J. Pharm. Pharmacol.*, 6, 486.
(261) Davidson, G. F. *J. Textile Institute*, 24, 185T.
(262) Dekay, H. D., and Lee, C. O. JOUR. A. PH. A., 22, 316.
(263) Dietzel, R., and Steeger, O. *Arch. Pharm. u. Ber. deut. pharm. Ges.*, 271, 521.
(264) Foster, R. H. K., and Van Dyke, H. B. JOUR. A. PH. A., 22, 381.
(265) Gifford, S. R., and Denton, S. R. *Arch. Ophth.*, 9, 227.
(266) Goldberg, S. D. U. S. 1,924,685. Through *C. A.*, 27, 5483.
(267) Haddock, L. A. *Quart. J. Pharm. Pharmacol.*, 6, 496.
(268) Hansen, S., Schou, and Tonnesen. *Dansk. Tids. Farm.*, 7, 26. Through *C. A.*, 27, 5146, and *Pharm. Zentralh.*, 75, 443.
(269) Hersant, E. F., and Linnell, W. H. *Pharm. J.*, 131, 3.
(270) Husa, W. J. *Druggists Circular*, 77, 17.
(271) Husa, W. J., and Magid, Louis. JOUR. A. PH. A., 22, 278.
(272) Husa, W. J., and Birmingham, G. W. JOUR. A. PH. A., 22, 495.
(273) Klobusitzky, D. *Kolloid Z.*, 62, 98.
(274) Krantz, J. C., Jr. JOUR. A. PH. A., 22, 106.

(275) Kunzmann, T. *Z. Hyg. Infektionskrankh*, 114, 623. Through *C. A.*, 27, 5889.
(276) Lindholm. *Farm. Tidende* (1933), 68. Through *Pharm. Zentralh.*, 75, 381.
(277) Loughlin, W. *Biochem. J.*, 27, 1779.
(278) Marshall, P. G. *Ibid.*, 27, 621.
(279) McBain, J. W., and McClatchie, W. L. *J. Am. Chem. Soc.*, 55, 1315.
(280) Milne, G. R., and Rattray, G. *Pharm. J.*, 130, 246.
(281) Morton, C. *Quart. J. Pharm. Pharmacol.*, 6, 492.
(282) Munch, J. C., and Pratt, H. J. *Proceedings A. D. M. A.* (1933), 220.
(283) Murray, D. *Biochem. J.*, 27, 543.
(284) Nielsen, L. *Dansk. Tids. Farm.*, 7, 137. Through *Pharm. Zentralh.*, 75, 352.
(285) Regnier, J., Liot and David. *Bull. sci. pharmacol.*, 40, 271.
(286) Regnier, J., Liot and David. *Ibid.*, 40, 353.
(287) Regnier, J., and David. *Ibid.*, 40, 650.
(288) Rowe, L. W., and Scoville, W. L. JOUR. A. PH. A., 22, 938.
(289) Rowe, L. W., and Scoville, W. L. *Ibid.*, 22, 1087.
(290) Schou, S. A., and Bennekou, I. *Dansk. Tids. Farm.*, 7, 17. Through *C. A.*, 27, 5146.
(291) Schou, S. A., and Staggemeier, O. M. *Dansk. Tids. Farm.*, 7, 106. Through *C. A.*, 27, 5146 and *Pharm. Zentralh.*, 75, 417.
(292) Schrek, R. *J. Immunol.*, 25, 183.
(293) Smelt, E. M. *Quart. J. Pharm. Pharmacol.*, 6, 375.
(294) Swoap, O. F., Cartland and Hart. JOUR. A. PH. A., 22, 8.
(295) Taketomi, N., and Horikoshi, T. *J. Soc. Chem. Ind. Japan*, 36, 187. Through *C. A.*, 27, 1933.
(296) Thompson, M. R., Andrews and Ichniowski. JOUR. A. PH. A., 22, 487.
(297) Walbum. *Dansk. Tids. Farm.*, 7, 37. Through *Pharm. Zentralh.*, 75, 433.
(298) Wintersteiner, O. *J. Biol. Chem.*, 102, 473.
(299) Woelm, Max. U. S. 1,916,089. Through *C. A.*, 27, 4630.
(300) Woodward, W. A., and Cowlan, A. N. *Pharm. J.*, 131, 132 and *Quart. J. Pharm. Pharmacol.*, 6, 363.

1934.

(301) Anonymous. *Pharm. J.*, 132, 111.
(302) Anonymous. *Drug and Cosmetic Ind.*, 34, 399.
(303) Baborovsky, J. *Collection Czechoslov. Chem. Communications*, 6, 283. Through *C. A.*, 28, 6362.
(304) Baker, W. B. JOUR. A. PH. A., 23, 974.
(305) Bartole, A. *Scienza farm.*, 1, 255. Through *C. A.*, 28, 5299.
(306) Bernerowna, M. *Wiadomosci Farm.*, 61, 169 and 207. Through *C. A.*, 28, 4839.
(307) Boutaric, A., and Morizot, F. *Bull. soc. chim.*, (5) 1, 153.
(308) Carr, C. J., and J. C. Krantz, Jr. JOUR. A. PH. A., 23, 50.
(309) Cocking, T. T. *Pharm. J.*, 132, 110.
(310) Dietzel, R., and Kuhl, G. W. *Arch. Pharm. u. Ber. deut., pharm. Ges.*, 272, 369.
(311) Dietzel, R. *Pharm. Zentral.*, 75, 469.
(312) Howland, R. B., and Bernstein, A. *Biol. Bull.*, 66, 276.
(313) Hurd, C. B., Lawrence, and Miller. *J. Phys. Chem.*, 38, 663.
(314) Husa, W. J., and Klotz, L. J. JOUR. A. PH. A., 23, 679.
(315) Husa, W. J., and Klotz, L. J. *Ibid.*, 23, 774.
(316) Jermstad, A., and Ostby, O. *Arch. Pharm. Chem.*, 41, 524.
(317) Krejci, L., and Svedberg, T. *J. Am. Chem. Soc.*, 56, 1706.
(318) Lavergne, V., Kissell, and Couillault. *Compt. rend. soc. biol.*, 116, 160. Through *C. A.*, 28, 5085.
(319) Madsen, C. J. T. *Dansk. Tids. Farm.*, 8, 62. Through *C. A.*, 28, 6520.
(320) Meyer, Erich. *Drug. and Cosmetic Ind.*, 34, 353.
(321) Olivier, S. C. J., and Weber, A. *Rec. trav. chim.*, 53, 869. Through *C. A.*, 28, 6121.
(322) Olivier, S. C. J. *Rec. trav. chim.*, 53, 891. Through *C. A.*, 28, 6122.
(323) Olivier, S. C. J., and Weber, A. P. *Rec. trav. chim.*, 53, 899. Through *C. A.*, 28, 6122.
(324) Osborn, T. W. B. *Biochem. J.*, 28, 423.
(325) Peters, A. F., and Osol, A. JOUR. A. PH. A., 23, 197.
(326) Quartaroli, A. *Gazz. chim. ital.*, 64, 243.
(327) Regnier, J., and David, R. *Bull. sci. pharmacol.*, 41, 321.
(328) Regnier, J., and David, R. *Compt. rend. soc. biol.*, 115, 1195. Through *C. A.*, 28, 4175.
(329) Stasiak, A. *Magyar Gyógyszerészstud. Társag. Értesitője*, 10, 384. Through *C. A.*, 28, 5177.
(330) Svedberg, T., and Quensel. *J. Am. Chem. Soc.*, 56, 1700.
(331) Svedberg, T. *Naturwissenschaften*, 22, 225.
(332) Walker, J. F. Can. 341,481. Through *C. A.*, 28, 3831.
(333) Zakharova, G. H. *Kolloid Z.*, 67, 222.

ASTRINGENT MOUTH WASH.

(Zinc Chloride Type.)

Zinc Chloride	2.0 Gm.
Menthol	0.6 Gm.
Oil of Cinnamon	1.4 cc.
Oil of Clove	0.3 cc.
Formaldehyde	0.4 cc.
Saccharin	0.4 Gm.
Alcohol	40.0 cc.
Water *q. s.* ad.	1000.0 cc.

A mouth wash preferred by some who desire the astringent effect of a zinc salt.

MOUTH RINSE NO. 1.

Saccharin, Soluble	0.10 Gm.
Fuchsin, basic	0.02 Gm.
Oil of Cinnamon	0.25 cc.
Oil of Peppermint	0.25 cc.
Oil of Clove	0.50 cc.
Alcohol	300.00 cc.
Talc	10.00 Gm.
Distilled Water, *q. s.*	1000.00 cc.

This makes a pleasant sweet spicy mouth rinse when diluted with 2–3 parts of water. No medication is intended in this formula. Especially suitable for the Spray Bottle.

MOUTH RINSE NO. 2.

Thymol	0.50 Gm.
Menthol	1.00 Gm.
Oil of Peppermint	3.00 cc.
Alcohol	300.00 cc.
Distilled Water, *q. s*,	1000.00 cc.
Color to suit.	

A pleasant mint-flavored mouth wash to be used diluted 2–3 times with water. Especially suitable for the Spray Bottle.