From our study thus far of the barbituric acids certain negative data are presented for the purpose of narrowing down the scope of future investigation. The following tentative conclusions may be drawn, supplementary to those of Fischer and Mering.

1. To manifest hypnotic action without undesirable after-effects, the two alkyl groups in the 5-position of the pyrimidine ring should have a total number of carbon atoms not less than four or more than eight.

2. At least one of the alkyl groups must be in the form of an open chain.

3. The benzyl group is undesirable because of its tendency to cause convulsions.

4. The urea grouping —NH—CO—NH— may not be replaced by the amidine grouping —NH—CR=NH—.

5. Increase in the size of the molecule beyond, say, a molecular weight of 250 results in loss of hypnotic activity.

6. Not more than one of the two alkyl groups should be aromatic in character.

7. We believe that the hypnophore group in the veronal series is —CR_2—CO—NH—CO—.

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U. S. Patents on Dialkylbarbituric Acids.

Diethyl	782,739 (1905)	veronal	Phenylallyl	1,056,793 (1913)	
Phenylmethyl	1,025,526 (1912)		Isopropylethyl	1,255,951 (1918)	
Phenylethyl	1,025,872 (1912)	luminal	Dibutyl	1,331,712 (1920)	
Diallyl	1,042,265 (1912)	dial	Isopropylallyl	1,444,802 (1923)	allonal

DEPT. OF CHEMICAL RESEARCH,
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PAPER NO. 20.

THE HYDROGEN ION CONCENTRATION OF SOME U. S. P. PRODUCTS.

SHOULD LITMUS BE SUPPLEMENTED BY MORE SENSITIVE INDICATORS?

BY PETER MASUCCI AND MARGARET I. MOFFAT.

The hydrogen ion concentration of certain U. S. P. products was determined electrometrically by means of a hydrogen electrode. These measurements were made on routine samples which were submitted to the Analytical Laboratory to be tested for identity and purity. The solutions of each substance was made

according to the directions given by the U. S. P. under the respective product. In the majority of cases an aqueous solution 1 in 20 was used.

The purpose of this investigation was twofold, (1) to determine the uniformity of reaction of the different lots of the same substance, and (2) to compare the hydrogen ion concentration found, with the statements made in the U. S. P. with reference to the reaction of that substance to litmus. Incidentally, this enabled us to compare the sensitiveness of litmus with the Clark and Lubs phenolsulphonephthalein series of indicators.

The products tested were: (1) Codeine Sulphate, (2) Morphine Sulphate, (3) Quinine Dihydrochloride, (4) Quinine Hydrochloride, (5) Quinine Sulphate, (6) Strychnine Sulphate, (7) Atropine Sulphate, (8) Caffeine Alkaloid, (9) Sodium Glycerophosphate and (10) Sodium Cacodylate.

EXPERIMENTAL.

As previously stated the hydrogen ion concentration of each solution was determined electrometrically. The reaction of each solution was then tested by means of litmus paper or litmus solution, and also by the appropriate Clark and Lubs indicator.

The hydrogen ion concentration is expressed in terms of p_H. The reaction of the solutions to the various indicators is given in terms of the change of color. In order to facilitate the comparison the color change and p_H range of the indicators used are given.

Name.	Color change.	p_H range.
Thymol Blue	Red-yellow	1.2-2.8
Brom Phenol Blue	Yellow-blue	3.0-4.6
Methyl Red	Red-yellow	4.4-6.0
Brom Cresol Purple	Yellow-purple	5.2-6.8
Phenol Red	Yellow-red	6.8-8.4
Cresol Red	Yellow-red	7.2-8.8
Thymol Blue	Yellow-blue	8.0-9.6

The results obtained are given below in Tables I–X inclusive.

TABLE I—CODEINE SULPHATE AQUEOUS SOLUTION 1 IN 40.

Lot no.	Manuf.	Date rec.	p_H.	Litmus paper.	Litmus sol.	Brom Phenol Blue.	Methyl-Red.	Brom Cresol Purple.
4112	"A"	2/12/21	4.81	Neutral	Neutral	Blue	Red	Yellow
4256	"A"	8/8/21	5.15	Neutral	Neutral	Blue	Red	Yellow
5067	"A"	11/12/21	4.90	Neutral	Neutral	Blue	Red	Yellow
5710	"A"	2/23/22	4.61	Neutral	Neutral	Blue	Red	Yellow
6827	"A"	6/12/22	4.53	Neutral	Neutral	Blue	Red	Yellow
9366	"A"	11/11/22	4.56	Neutral	Neutral	Blue	Red	Yellow

TABLE II——MORPHINE SULPHATE AQUEOUS SOLUTION 1 IN 20.

Lot no.	Manuf.	Date rec.	p_H.	Litmus paper.	Litmus sol.	Brom Phenol Blue.	Methyl Red.
4183	"B"	7/5/21	3.67	Faintly red	Faintly red	Blue	Red
4242	"B"	8/5/21	3.80	Faintly red	Faintly red	Blue	Red
4298	"B"	8/11/21	3.80	Faintly red	Faintly red	Blue	Red
4626	"B"	9/23/21	3.76	Faintly red	Faintly red	Blue	Red
5560	"B"	2/2/22	4.28	Faintly red	Faintly red	Blue	Red
5905	"B"	3/5/22	3.94	Faintly red	Faintly red	Blue	Red

TABLE III—QUININE DIHYDROCHLORIDE AQUEOUS SOLUTION 1 IN 20.

Lot no.	Manuf.	Date rec.	p_H.	Litmus paper.	Litmus sol.	Thymol Blue.	Methyl Red.
4139	"B"	2/15/21	2.62	Red	Red	Yellow	Red
4274	"B"	8/10/21	2.79	Red	Red	Yellow	Red
4651	"B"	9/7/21	2.74	Red	Red	Yellow	Red
5934	"B"	3/17/22	2.70	Red	Red	Yellow	Red
7981	"C"	9/2/22	2.59	Red	Red	Yellow	Red
9924	"C"	12/7/22	2.45	Red	Red	Yellow	Red

TABLE IV—QUININE HYDROCHLORIDE AQUEOUS SOLUTION 1 IN 20.

Lot no.	Manuf.	Date rec.	p_H.	Litmus paper.	Litmus sol.	Methyl Red.	Brom Cresol Purple.
2960	"B"	5/27/21	5.92	Neutral	Neutral	Yellowish red	Purple
4146	"B"	7/18/21	5.70	Neutral	Neutral	Yellowish red	Purple
4881	"B"	10/25/21	5.93	Neutral	Neutral	Yellowish red	Purple
5418	"B"	1/3/21	5.83	Neutral	Neutral	Yellowish red	Purple
6742	"C"	6/5/22	5.60	Neutral	Neutral	Red	Greenish yellow

TABLE V—QUININE SULPHATE AQUEOUS SOLUTION SATURATED.

Lot uo.	Manuf.	Date rec.	p_H.	Litmus paper.	Litmus sol.	Methyl Red.	Brom Cresol Purple.
4912	"B"	10/27/21	5.79	Neutral	Neutral	Reddish yellow	Yellowish purple
10769	"C"	2/2/23	5.66	Neutral	Neutral	Reddish yellow	Yellowish purple
10988	"C"	2/16/23	6.34	Neutral	Neutral	Reddish yellow	Yellowish purple
11091	"D"	2/22/23	5.24	Neutral	Neutral	Red	Yellow
11179	"B"	2/27/23	5.12	Neutral	Neutral	Red	Yellow
11228	"C"	2/16/23	5.49	Neutral	Neutral	Red	Yellow

TABLE VI—STRYCHNINE SULPHATE AQUEOUS SOLUTION SATURATED.

Lot no.	Manuf.	Date rec.	p_H.	Methyl Red.	Brom Phenol Blue.	Brom Cresol Purple.	Litmus paper.
4872	"E"	10/22/21	4.48	Red	Blue	Yellow	Neutral
6041	"E"	3/27/22	5.07	Red	Blue	Yellow	Neutral
6267	"E"	4/20/22	4.98	Red	Blue	Yellow	Neutral
6825	"E"	6/12/22	4.48	Red	Blue	Yellow	Neutral
6946	"E"	6/20/22	4.48	Red	Blue	Yellow	Neutral
10441	"E"	1/12/23	4.73	Red	Blue	Yellow	Neutral

TABLE VII—ATROPINE SULPHATE AQUEOUS SOLUTION 1 IN 20.

Lot no.	Manuf.	Date rec.	p_H.	Brom Phenol Blue.	Methyl Red.	Brom Cresol Purple.
4345	"E"	8/19/21	4.39	Blue	Red	Yellow
4939	"E"	10/41/21	5.66	Blue	Red	Purple
5371	"F"	12/20/21	6.67	Blue	Reddish yellow	Purple
5583	"F"	2/6/22	6.20	Blue	Reddish yellow	Purple
5944	"F"	3/10/22	6.08	Blue	Red	Purple
6366	"E"	5/1/22	4.48	Blue	Red	Yellow

TABLE VIII—CAFFEINE ALKALOID AQUEOUS SOLUTION SATURATED.

Lot no.	Manuf.	Date rec.	p_H.	Brom Cresol Purple.	Phenol Red.	Brom Thymol Blue.
5184	"H"	11/23/21	5.91	Yellow	Yellow	Yellow
5433	"A"	1/5/22	4.98	Yellow	Yellow	Yellow
11008	"G"	2/16/23	7.35	Purple	Yellow	Blue

TABLE IX—SODIUM GLYCEROPHOSPHATE AQUEOUS SOLUTION 1 IN 20.

Lot. no.	Manuf.	Date rec.	p_H.	Phenol Red.	Thymol Blue.	Cresol Red.
4048	"H"	7/1/21	8.57	Red	Blue	Red
5703	Unknown	2/22/22	8.19	Red	Yellowish blue	Red
7180	"H"	7/6/22	8.11	Red	Yellowish blue	Red
7394	"H"	7/24/22	8.70	Red	Blue	Red
8266	"H"	9/18/22	8.74	Red	Blue	Red
9939	"H"	12/8/22	8.65	Red	Blue	Red

TABLE X—SODIUM CACODYLATE AQUEOUS SOLUTION 2 GM. IN 50 CC.

Lot no.	Manuf.	Date rec.	p_H.	Phenol Red.	Cresol Red.
4618	"I"	9/22/21	7.69	Red	Yellow
5092	"I"	11/16/21	7.69	Red	Yellow
8761	"A"	10/10/22	8.03	Red	Red
9540A	"I"	12/21/22	7.86	Red	Red

DISCUSSION OF RESULTS.

The results given in the tables are self-explanatory but in order to emphasize some of the points a couple of the substances tested will be discussed in detail.

(1) *Codeine Sulphate.*—The average p_H of six samples was 4.76. The p_H range was 4.53–5.15 or a difference of 0.62 p_H. The significant point to be noted is that all the samples were distinctly acid in reaction in reference to the true neutrality p_H 7.0. Yet they failed to change litmus paper or solution, that is, they were neutral to this indicator. This finding agrees with the statement in the Pharmacopœa—namely, that a solution of Codeine sulphate 1 : 40 is neutral or not more than faintly acid to litmus. When the solution is tested with more sensitive indicators, one finds that it is on the alkaline side of Brom Phenol Blue and on the acid side of Methyl Red and Brom Cresol Purple. These indicators, therefore, denote at once the true reaction of the solution.

(2) *Morphine Sulphate.*—The average p_H of six samples was 3.88. The p_H range was 3.67–4.28 or a difference of 0.61 p_H. This preparation was found to be slightly acid to litmus which again agrees with the statement made in the Pharmacopœa that a solution of Morphine sulphate 1:20 is neutral or slightly acid to litmus. It must be borne in mind, however, that a p_H of 3.88 is more acid than solution of $N/1000$ acetic acid and therefore the phrase "neutral or slightly acid to litmus" does not mean much. On the other hand the use of Brom Phenol Blue or Methyl Red would give the true reaction of the solution.

What has been said about Codeine Sulphate and Morphine Sulphate applies to the other substances tested. The use of litmus should be discontinued or at least supplemented by the more sensitive indicators. The litmus of commerce is of uncertain composition and is contaminated with impurities. Its degree of sensitiveness is not certain and is bound to vary. There is no doubt but that synthetic indicators are far superior. This class of indicators has for the most part displaced litmus especially in bacteriological work.

The writers are of the opinion that the Clark and Lubs series of indicators should be included in the next Pharmacopœa not only to determine the degree of acidity or alkalinity (hydrogen ion concentration) but also in certain titrations of alkaloids. Already Lizius and Evers[1] have studied the question of the use of indicators in the titration of acids and bases. They conclude that "the indis-

criminate use of phenolphthalein for all weak acids and of methyl orange for all weak bases cannot and does not give results of such accuracy as may easily be obtained if the right indicator is used."

McGill[2] determined the hydrogen ion concentration of certain alkaloidal salts by the potentiometer method. From the values obtained he chose the indicator which would give the most accurate results. He pointed out the greater accuracy of some of the phenolsulphonephthalein series of indicators.

The writers are also of the opinion that the new U. S. Pharmacopœa should include in Part II General Tests, the colorimetric method outlined by Clark[3] for the determination of hydrogen ion concentration. It should prove as useful for the pharmacists as it has for the biologists in the investigation of phenomena which is seriously influenced by the p_H of the solution.

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ON THE CALCIUM ION.

BY R. A. KUEVER.

It has long been known that calcium ion is of value in checking diarrhea. Taken in excessive quantities it produces constipation. Prepared chalk, which when taken into the stomach and converted into calcium chloride, is extensively used to control diarrhea and dysentery. Chalk is an effective antacid and valuable in the treatment of gastric hyperacidity. The objection to its continued use, however, in such cases, is the constipation that results. Magnesium carbonate, the antacid so commonly employed in gastiric hyperacidity, is distinctly laxative. And where this is objectionable, as it often is, the two carbonates may be administered mixed in equal proportion, thus producing neither a laxative nor constipating, but merely the antacid effect. No matter what calcium salt is employed, constipation follows—the more soluble salts being more efficacious than those which dissolve but sparingly. And while chalk, *per se*, is insoluble, it is converted to a very soluble form (calcium chloride) the moment it comes in contact with the hydrochloric acid of the gastric juice.

The value of calcium ion in the circulation, in order that blood may have a normal coagulating index, has also been known for some time. Thrombin causes blood to coagulate by converting dissolved fibrinogen into insoluble fibrin. Pope believes that the change takes place as follows: when the blood leaves the body, one of its constituents (probably the leucocytes) gives rise to a pro-enzyme, which is converted into the active enzyme under the influence of calcium ion. Gurber says that acid calcium phosphate is dissolved in the fluids of the body and that the calcium ion aids in the formation of fibrin ferment.