(37) G. B. Wood and F. Bache, U. S. Dispensatory, 19th Edition (1907), 687.

(38) R. Wright, "Occurrence and Distribution of Mydriatic Alkaloids in *Lactuca muralis*," *P. J.* (1905), 548; through PROC. A. PH. A., 53 (1905), 636.

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# THE GRAVIMETRIC AND VOLUMETRIC DETERMINATION OF ANTIPYRINE AS HYDROFERROCYANIDE IN THE PRESENCE OF AMIDOPYRINE.*,[1]

BY I. M. KOLTHOFF.

The simple iodometric determination[2] of antipyrine cannot be applied in the presence of amidopyrine, since the latter substance is oxidized by iodine. In the present work it has been found that antipyrine yields a crystalline precipitate with potassium ferrocyanide in acid medium whereas amidopyrine does not react under similar conditions. Use of this precipitation reaction has been made in the quantitative determination of antipyrine; the method can be applied in the presence of amidopyrine.

*Composition of the Hydroferrocyanide of Antipyrine.*—The crystalline precipitate formed in an acid medium of hydrochloric acid and containing an excess of potassium ferrocyanide was collected, washed with water, alcohol and ether, and air dried. On heating in vacuum at 70° no loss in weight was noticed. It should be mentioned that the air-dry precipitate obtained after washing with alcohol (no ether) contains 0.3 to 0.4% of water. The hydroferrocyanide content of the precipitate was determined by titrating 0.1000-Gm. samples with sodium hydroxide using phenolphthalein as an indicator. The hydroferrocyanic acid behaves as a quadrivalent acid; the antipyrine, being a very weak base, does not affect the titration. It was found that 0.1 Gm. required 12.78, 12.75, 12.72 cc., 0.0529*N* sodium hydroxide, respectively, corresponding to a molecular weight of the precipitate of 592.1. From the above it may be concluded that the crystals consist of a compound of 2 molecules antipyrine and 1 molecule hydroferrocyanic acid:

$$(C_{11}H_{12}N_2O)_2H_4Fe(CN)_6 . M = 592.1$$

The composition is different from that of the hydroferrocyanides of most alkaloids which ordinarily yield precipitates containing water of crystallization and one molecule of alkaloid per one molecule of hydroferrocyanic acid.

*Sensitivity of the Precipitation of Antipyrine.*—The sensitivity depends upon the concentration of ferrocyanide and the acidity of the mixture. In the following experiments the solution was acidified with hydrochloric acid. It appeared advantageous to have a large excess of potassium ferrocyanide. After some systematic experiments, the following procedure was adopted: 2 cc. 0.5 molar potassium ferrocyanide were added to 5 cc. antipyrine solution, the latter containing the concentration of hydrochloric acid as given in Table I.

The optimum acidity is 0.5 to 0.75*N* of hydrochloric acid. 2 mg. antipyrine can be detected if 2 cc. 0.5-molar potassium ferrocyanide and 0.5 cc. 6*N* hydro-

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[1] Contribution from the School of Chemistry of the University of Minnesota.

[2] Comp. I. M. Kolthoff, "Volumetric Analysis," Vol. 2, page 454, translated by N. H. Furman, John Wiley & Sons, New York, 1929.

chloric acid are added to 5 cc. of the solution. If no precipitate appears after ten minutes of standing, less than 2 mg. of antipyrine are present.

TABLE I.—SENSITIVITY OF PRECIPITATION OF ANTIPYRINE.

| Antipyrine Present in 5-cc. Solution Mg. | Concentration HCl in Mixture N | Result. |
|---|---|---|
| 2.5 | 0.1 | No precipitate after 3 hours. |
| 2.5 | 0.5 | Precipitate after 5–6 min. |
| 2.5 | 1.0 | Precipitate after 15 min. |
| 2.5 | 3.0 | No precipitate after 3 hours. |
| 1.25 | 0.5 | No precipitate after 2 hours. |

*Solubility of Antipyrine Hydroferrocyanide.*—In connection with the quantitative determinations it was of interest to know the losses in weight of the precipitate on washing with various solutions. Fifty cc. of the solvent were drawn through glass-filtering crucibles containing known weights of the precipitate at the rate of 10 cc. per minute. The crucibles were then dried at 110° and reweighed. The losses in weight are given in Table II.

The solubility in the various solvents with the exception of ether is appreciable and cannot be neglected in quantitative determinations.

TABLE II.—LOSS IN WEIGHT ON WASHING OF ANTIPYRINE HYDROFERROCYANIDE.

| Solvent. | Precipitate Dissolved in 50-cc. Solvent Mg. |
|---|---|
| Water | 71.8 |
| 95% Alcohol | 38.3 |
| Ether | 0.0 |
| 0.1*N* HCl | 22.7 |
| 1*N* HCl | 31.0 |
| 3*N* HCl | 107.5 |
| 0.1*N* $K_4Fe(CN)_6$ | 133[a] |
| 0.5*N* $K_4Fe(CN)_6$ | 343[a] |

[a] Determined by titrating the filtrate with standard sodium hydroxide.

*Gravimetric Determination of Antipyrine.*—Preliminary experiments carried out under various conditions yielded low results owing to the solubility of the antipyrine hydroferrocyanide in the precipitation mixture and the wash liquids. Therefore it was decided to use a saturated solution of antipyrine hydroferrocyanide in water as a wash liquid. The latter has to be freshly prepared every day by shaking some of the precipitate with water. After a day of standing, it turns bluish owing to decomposition of the hydroferrocyanic acid.

*Procedure.*—A weighed amount of the sample containing about 0.2 to 0.3 Gm. antipyrine is dissolved in about 30 cc. 0.8*N* hydrochloric acid. 20 cc. 0.5-molar potassium ferrocyanide are added slowly with stirring of the mixture. The precipitate is allowed to stand for thirty minutes and is then filtered on a Gooch crucible with paper disc or a glass-sintered crucible. The residual precipitate in the flask is transferred to the crucible by use of the filtrate, and when the transfer is complete it is finally washed four times with 2–3-cc. portions of the freshly prepared saturated solution of the precipitate in water. The crucible is then dried for thirty minutes at 105–110° and weighed after cooling. A correction for the loss by solubility is made by adding 5 mg. to the weight of the precipitate found. The latter contains 63.53% antipyrine.

*Volumetric Determination of the Precipitate.*—The gravimetric procedure is followed. It is recommended to use in this case the Gooch crucible with paper disc instead of the sintered glass crucible. After washing, the precipitate and filter paper are dislodged with the point of a spatula and transferred to an Erlenmeyer flask, any precipitate remaining in the crucible being carried over in the flask with distilled water in equilibrium with the atmosphere. A few drops of phenolphthalein are added to the mixture and standard (0.05 to 0.1*N*) sodium hydroxide run in with constant stirring. The precipitates dissolve rather slowly but finally disappear completely. The end-point is reached when the pink color is stable for 2 to 3 minutes. A titration is made with the same volume of water as used in the suspension of the precipitate and this blank subtracted from the volume of standard reagent required in the titration. This blank should not exceed 0.05 cc. 0.1*N* sodium hydroxide for 50 cc. A correction for the loss by solubility is made by adding 0.34 cc. 0.1*N* NaOH to the required volume of reagent.

TABLE III.

| Antipyrine Taken Gm. | Antipyrine Found (Corrected for Solubility). Grav. | Vol. | Error %. Grav. | Vol. |
|---|---|---|---|---|
| 0.2896 | 0.2908 | 0.2908 | +0.4 | +0.4 |
| 0.2896 | 0.2916 | 0.2910 | +0.7 | +0.5 |
| 0.2896[b] | 0.2912 | 0.2907 | +0.55 | +0.44 |
| 0.2896[a] | 0.2905 | 0.2898 | +0.3 | 0.0 |
| 0.2896[a] | 0.2926 | 0.2922 | +1.0 | +0.9 |
| 0.1159 | 0.1164 | 0.1154 | +0.4 | −0.4 |
| 0.1159 | 0.1168 | 0.1174 | +0.8 | +1.3 |
| 0.1159[b] | 0.1168 | 0.1174 | +0.8 | +1.3 |
| 0.1159[a] | 0.1129 | 0.1121 | −2.6 | −3.3 |
| 0.1159[a,b] | 0.1136 | 0.1130 | −2.0 | −2.5 |
| 0.1159[a,b] | 0.1136 | 0.1130 | −2.0 | −2.5 |

[a] 0.6 Gm. amidopyrine was added.
[b] 1 hour of standing before filtration.

One cc. 0.1*N* NaOH corresponds to 9.4 mg. antipyrine. Some results are given in Table III. It may be inferred that the method gives results accurate within 1% for quantities of antipyrine between 0.1 to 0.3 Gm. 0.6 Gm. of pyramidone with 0.3 Gm. antipyrine does not affect the results, the same amount of pyramidone with 0.1 Gm. antipyrine lowers the results about 2 to 3%. It is not recommended that the method be used for the determination of quantities of antipyrine much smaller than 100 mg.

Finally the author wishes to express his sincere appreciation to J. J. Lingane for his faithful help in carrying out the experiments.

## SUMMARY.

1. In acid medium antipyrine gives a crystalline precipitate with ferrocyanide having the composition $(C_{11}H_{12}N_2O)_2H_4Fe(CN)_6$.

2. A gravimetric and volumetric procedure has been described for the quanti-

tative estimation of antipyrine in the form of its hydroferrocyanide. The method can be applied in the presence of amidopyrine.

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May 1933.

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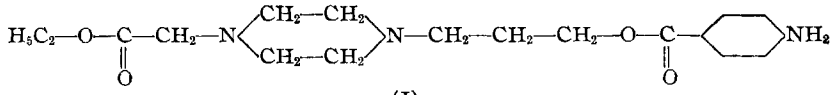
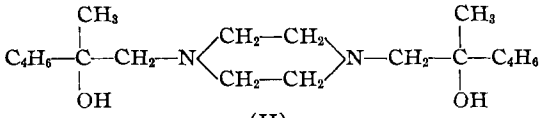
## PIPERAZINE DERIVATIVES AS LOCAL ANESTHETICS.*

BY W. BRAKER AND W. G. CHRISTIANSEN.

Several piperazine derivatives have been reported in the literature (1) to possess anesthetic activity. This investigation concerns the *p*-amino benzoate of 4-(carbethoxymethyl)-1-piperazine propanol (I) and the phenyl urethane of 1,4-bis-(β-hydroxy-β-methyl hexyl) piperazine (II).



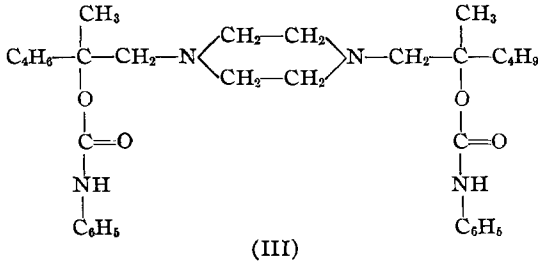
(I)



(II)

It is stated (2) that 1,4-*bis*(β-hydroxy-β-methyl hexyl)piperazine has a definite anesthetic action on the rabbit's tongue. An increase in the size of the alkyl groups was accompanied by increased activity so that the heptyl derivatives were considerably more effective than cocaine.

The method of preparation of 1,4-*bis*(β-hydroxy-β-methyl hexyl)piperazine is contained below. An effort to prepare a mono-phenyl urethane of this substance resulted in the isolation of only the diphenyl urethane derivative (III). No further attempt was made to prepare the mono-phenyl urethane.



(III)

The dihydrochloride of (III) was found to be soluble to the extent of only 1.1%. The $p_H$ of such a solution was found to be 2.2 and the solution would not permit of buffering. Consequently, it appeared impractical to further study such types of compounds.

The *p*-amino benzoate of 4-(β-hydroxyethyl)morpholine (IV) has been reported to be an active anesthetic (3). A study of the substitution of the oxygen atom in

* Scientific Section, A. PH. A., Madison meeting, 1933.