I.  A STUDY OF THE CHEMISTRY LEADING TO PROBABLE STRUCTURES

FOR CYAMELURIC ACID AND SOME RELATED COMPOUNDS.


II.  THE DILITURATES OF SOME PHYSIOLOGICALLY IMPORTANT BASES.



A Thesis by



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# Ionization Constants and Hydrolytic Degradations of Cyameluric and Hydromelonic Acids

## BY C. E. REDEMANN AND H. J. LUCAS

Recently the question of the structure of cyameluric and hydromelonic acids has been reopened by Pauling and Sturdivant [1] It is rather surprising that cyameluric acid and related compounds, for example melon, melam, melem, and hydromelonic acid, should have received so little attention at the hands of organic chemists. With the exception of a limited amount of work by E. C. Franklin[2] and students, the problems in this field have been neglected for many years. Since most of these compounds are insoluble both in organic solvents and in water, show neither melting nor boiling points, are inert chemically with the exception that they undergo hydrolytic cleavage, and do not yield derivatives which are readily identified, it is probable that the reasons for this neglect bear some relation to their physical and chemical properties.

Tripotassium melonate, the potassium salt of hydromelonic acid, first described by Gmelin[3] as an undesirable by-product when too high a temperature was used in the preparation of potassium thiocyanate by the fusion of sulfur, potassium ferrocyanide and potassium carbonate, was obtained also by Liebig, who dissolved melon in fused potassium thiocyanate. [4,5] Potassium melonate is formed also by heating antimony or bismuth trichloride with potassium thiocyanate. As the result of numerous careful analyses of potassium and silver melonate, Liebig[6] proposed the empirical formula $C_9H_3N_{13}$[7] for hydromelonic[8] acid. Attempts to prepare the

pure acid have not been entirely successful due to the great tendency of the acid to polymerize in concentrated aqueous solution.

Cyameluric acid is probably the most important of the compounds discussed in this paper since its nucleus appears to be common to most members of the series. Potassium cyamelurate is formed by the alkaline hydrolysis of melon, or of potassium melonate.[5] When the potassium salt is acidified with a strong acid, sparingly soluble cyameluric acid separates. Henneberg named the acid and assigned to it the formula $H_3C_6O_3N_7$ on the basis of analyses of the salts and of the acid. It seems probable that Liebig[6] was the first to prepare this acid, but he was unable to obtain constant analyses for his product, probably because he recrystallized the acid from a hot hydrochloric acid solution, a procedure now known to cause rapid hydrolysis.

**Structures of Hydromelonic Acid.**—Only four structures have been proposed

$(C_3N_3)_3(NH)_3N$
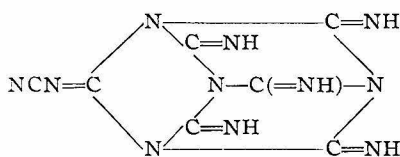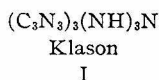
Klason

I
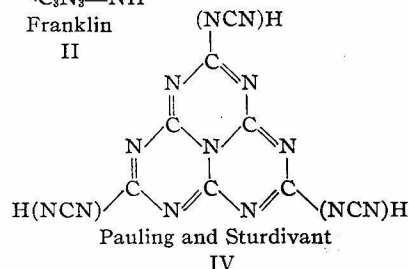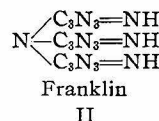


Structure I was proposed by Klason[8] in 1886, and II by Franklin[2a] in 1922. The latter appears to be nothing more than an interpretation of the former. His second structure,[9] III, proposed in 1935, is essentially the structure of hexamethylenetetramine in which three of the six pairs of hydrogen atoms are replaced by the cyanimino group, (=NCN), and the other three by the imino group, (=NH). Structure IV, proposed by Pauling and Sturdivant[1] in 1937, is based upon their belief that hydromelonic acid, $C_6N_7(NCNH)_3$, bears to cyameluric acid, $C_6N_7(OH)_3$, the same relation that

(1) Pauling and Sturdivant, *Proc. Natl. Acad. Sci.*, **23**, 615 (1937).

(2) (a) Franklin, THIS JOURNAL, **44**, 507 (1922); (b) Burdick, *ibid.*, **47**, 1485 (1925).

(3) Gmelin. *Ann.*, **15**, 252 (1835). This salt is also called potassium hydromelonate in the older literature.

(4) (a) Liebig, *Ann.*, **50**, 337 (1844); (b) **61**, 262 (1847).

(5) Henneberg. *ibid.*, **73**, 228 (1855).

(6) Liebig. *Ann.*, **95**, 257 (1855).

(7) Actually $C_{18}H_6N_{13}$ on the basis of the atomic weights of that time.

(8) The name was assigned by Gmelin on the basis that the polymer was converted to melon by loss of water when heated, hence the acid was thought to be a hydrate of melon. Klason, *J. prakt. Chem.*, [2] **33**, 289 (1886), called this compound cyamelon, under which name some of the literature appears.

(9) E. C. Franklin, "The Nitrogen System of Compounds," The Reinhold Publishing Corp., New York, 1935, p. 107.

cyanuric tricyanamide, $C_3N_3(NCNH)_3$, bears to cyanuric acid, $C_3N_3(OH)_3$. The planar cyameluric nucleus is shown to have, according to quantum mechanical calculations, a high degree of stability. The stabilization due to resonance is approximately 150 kcal. per mole.

**Structures of Cyameluric Acid.**—Only three structures have been proposed for cyameluric acid
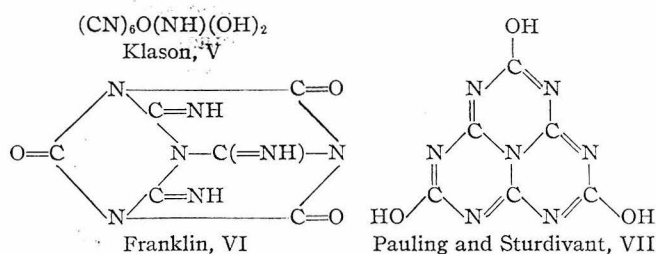


Structure V, proposed by Klason,[8] was thought by him to represent the anhydride of an acid having the formula $(HO)_2(CN)_3NH(CN)_3(OH)_2$ (VIII). In structure VI, proposed by Franklin, the central group of atoms has the hexamethylene arrangement as in the hydromelonic acid structure proposed by him, III, and in structure VII, proposed by Pauling and Sturdivant, this group has the planar cyameluric arrangement, as in their structure for hydromelonic acid, IV.

## Hydrolytic Degradations

If hydromelonic acid is correctly represented by Structure I or II, then on hydrolysis to cyameluric acid of structure V (the anhydride of VIII), one mole of I or II should yield approximately one mole of cyanuric acid, one mole of cyameluric acid, three moles of ammonia and no carbon dioxide on the assumption that the $C_3N_3$ groups represent cyanuric acid nuclei and that the cyanuric and cyameluric acids undergo no further hydrolysis. Cyameluric acid of structure V on further hydrolysis should be capable of yielding two moles of cyanuric acid, since in the acid VIII, of which V is the anhydride, there are two $C_3N_3$ nuclei.

On the other hand, if hydromelonic acid is either III or IV, on hydrolysis to cyameluric acid of structure VI or VII, respectively, one mole should yield not more than one mole of cyameluric acid and at the same time, six equivalents each of ammonia and carbon dioxide. Further hydrolysis of cyameluric acid should yield not more than one mole of cyanuric acid and, at the same time, four equivalents of ammonia and

six equivalents of carbon dioxide if converted to cyanuric acid. Actually Liebig[6] isolated from the alkaline hydrolysis of cyameluric acid ammeline, ammelide, and cyanuric acid by progressively increasing the duration of hydrolysis.

**Hydromelonic Acid.**—When potassium melonate was hydrolyzed in 6 $N$ nitric acid, 0.72 mole of cyanuric acid per mole of potassium melonate in the form of the insoluble cupric ammonium salt was obtained. Some hydrolysis of cyanuric acid took place at the same time. When hydrolyzed under alkaline conditions, the ratio of equivalents of carbon dioxide to those of ammonia varied from 1.25 to 1.11 (Table I). Even when hydrolysis was only a fraction of that possible, the $CO_2/2NH_3$ ratio was greater than unity. If hydromelonic acid had structure I or II, this ratio presumably would be below unity at the beginning of the hydrolysis, because carbon dioxide could come only from the breakdown of a $C_3N_3$ nucleus which is quite stable to further hydrolysis. Since

TABLE I

ALKALINE HYDROLYSIS OF POTASSIUM MELONATE

| Sample, g. | KOH, $N$ | Time, hrs. | $NH_3$ equiv. | $CO_2$ equiv. | Ratio $CO_2/2NH_3$ | Extent of hydrolysis,[a] % |
|---|---|---|---|---|---|---|
| 0.6531 | 5.45 | 1 | 0.00151 | 0.00188 | 1.25 | 15.7 |
| 1.6319 | 6.0 | 2 | .01796 | .02091 | 1.17 | 74.7 |
| 2.0526 | 3.5 | 2 | .01464 | .01628 | 1.11 | 59.3 |
| 2.5338 | 3.7 | 4 | .0328 | .0376 | 1.14 | 107 |

[a] Expressed as percentage of theoretical amount of ammonia, on the basis of structure III or IV, if the hydrolysis stopped at cyameluric acid.

potassium cyamelurate, under these conditions, was found to yield carbon dioxide and ammonia in the ratio of 2.24 (equivalents), the deviation from unity in the case of potassium melonate can be ascribed to the partial hydrolysis of the cyamelurate formed. The deviation from the ratio $^6/_4$ in the case of the latter compound probably is due to the formation of ammeline and ammelide, giving theoretical ratios of 3 and 2, respectively. Thus, the data from both acid and alkaline hydrolysis of hydromelonic acid favor structures III and IV over I and II. The hydrolysis is probably best represented by the equation

$$K_3C_9N_{13} + 6KOH + 6H_2O \longrightarrow$$
$$K_3C_6O_3N_7 + 6NH_3 + 3K_2CO_3$$
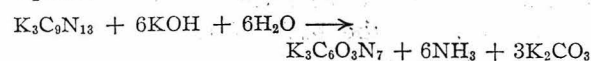
Henneberg[5] attempted to write an equation expressing this hydrolysis involving ammelide as one of the products and omitting carbonate.

**Cyameluric Acid.**—Hydrolysis at 100° in concentrated nitric acid, conditions under which cyanuric acid is attacked but slowly, yielded 0.935 mole of cyanuric acid per mole of cyameluric acid. These results show that cyameluric acid may be represented by either structure VI or structure VII, for only one mole of cyanuric acid would result, but not by structure V, for two moles of cyanuric acid should result if the acid has the last structure.

## Ionization Constants of the Acids

On the basis of the Franklin structures III and VI, the two respective acids, hydromelonic and cyameluric, should resemble each other closely as regards their acid strengths, because the atomic groupings responsible for acidity are identical in the two cases, and the groups responsible for the difference in structure, i. e., $C=NCN$ and $C=O$, respectively, are somewhat remote from the acid groups. Since the inductive effect of each of these two groups, before it can have an influence upon the acidic imino group, must pass through a tertiary nitrogen atom and a double bond, each of which alone has a pronounced damping effect upon induction, the acid strengths of III and VI would be expected to be similar. On the other hand, on the basis of the Pauling and Sturdivant structures, hydromelonic acid IV would be expected to be a much stronger acid than cyameluric acid VII. The hydromelonate ion, $C_9N_{13}^{\equiv}$, should have a much higher stability with respect to hydromelonic acid, $H_3C_9N_{13}$, than cyamelurate ion, $C_6O_3N_7^{\equiv}$, has with respect to cyameluric acid, $H_3C_6O_3N_7$. This is due to the fact that in the former case there are additional structures among which resonance can take place, for in the group of atoms IX, $(CNCN)^-$, the negative charge may be on either of the two nitrogen atoms as shown by $X \left( C-\overset{..}{\underset{..}{N}}-C\equiv N: \right)$ and $XI \left( C-\overset{..}{N}=C=\overset{..}{\underset{..}{N}}: \right)$. Since there are three such groups in the hydromelonate ion, the multiplicity of forms is markedly enhanced in comparison to the forms of the free acid, in which this additional type of resonance is not so important. Thus, from structural considerations, one would expect hydromelonic acid to be much stronger than cyameluric acid on the basis of the Pauling and Sturdivant structures, and to be little if any stronger on the basis of the Franklin structures.

Moreover, as Pauling and Sturdivant have pointed out, hydromelonic acid (IV) would bear the same relationship to cyameluric acid, VII, that tricyanomelamine bears to cyanuric acid. Tricyanomelamine is such a strong acid that the constant cannot be determined by conductimetric methods,[10] thus approaching the strong mineral acids in strength, whereas cyanuric acid is a weak acid.

The apparent ionization constants of hydromelonic, cyameluric and cyanuric acids were determined by titration of the potassium salts with standard hydrochloric acid, using a glass electrode to measure the $pH$. The solubility of the acids is too low to permit of their use for making titration curves and, in addition, hydromelonic acid polymerizes irreversibly. The cyanuric acid curve was made for the purpose of comparison. From the titration curves, apparent ionization constants were estimated for the acids by taking the $pH$ at the "half-neutralization" points. These approximate values for the apparent ionization constants were then adjusted until the calculated titration curves fitted the observed curves very accurately. In this way a value of $1.66 \times 10^{-7}$ was found for the first ionization constant of cyanuric acid, a value which is in fairly good agreement with that of $1.8 \times 10^{-7}$ found by Hantzsch[11] but in poor agreement with that of $3.8 \times 10^{-7}$, found by Bader.[12]

The curves for the titrations are shown in Fig. 1 and the values for the ionization constants of hydromelonic and cyameluric acids are listed in Table II. Those for the second ionization constant of hydromelonic and the first ionization constant of cyameluric acid are approximations only, because of the separation of a solid phase in the titration shortly before the respective "half-neutralization" points were reached. On this account the assumed values of these two constants, which have been adjusted so as to fit the remainder of the respective curves, are subject to some error.

### TABLE II
#### IONIZATION CONSTANTS

|       | Hydromelonic acid | Cyameluric acid | Cyanuric acid |
|-------|-------------------|-----------------|---------------|
| $K_1$ | Large | $Ca.\ 1.0 \times 10^{-3}$ | $1.66 \times 10^{-7}$ |
| $K_2$ | $Ca.\ 3.16 \times 10^{-3}$ | $6.30 \times 10^{-7}$ | |
| $K_3$ | $1.26 \times 10^{-5}$ | $1.12 \times 10^{-9}$ | |

Hydromelonic acid is a much stronger acid than cyameluric, as the curves and table show. These results favor structures IV and VII of Pauling and

(10) Madelung and Kern, Ann., **427**, 26 (1922).
(11) Hantzsch, Ber., **39**, 139 (1906).
(12) Bader, Z. physik. Chem., **6**, 289 (1890).

Sturdivant for these acids. That the cyameluric nucleus is strongly electronegative is shown by the comparison of ionization constants in Table III.

TABLE III

COMPARISON OF IONIZATION CONSTANTS

|  | $K_A$ |  | $K_A$ |
|---|---|---|---|
| Hydromelonic acid | Large | Cyameluric acid | $1 \times 10^{-3}$ |
| Benzoylcyanamide[12] | $1.86 \times 10^{-2}$ | Benzoic acid | $6 \times 10^{-5}$ |
| Acetylcyanamide[12] | $1.54 \times 10^{-4}$ | Acetic acid | $1.6 \times 10^{-5}$ |

In the first column, the common radical is the substituted cyanamino group, H(NCN)[13] and in the second, the OH group.

In a subsequent communication the results of attempts to prepare derivatives of cyameluric acid will be presented. The authors gratefully acknowledge the inspiration of Professor Linus Pauling, who suggested the investigation of cyameluric and hydromelonic acids.

### Experimental

**Melon.**—The following procedure based upon that of Henneberg[5] was most satisfactory. Chlorine gas was passed into a vigorously stirred solution of 1 kg. (12.3 moles) of pure[14] sodium thiocyanate in 2.5 liters of water. The temperature was maintained below 70-80° by external cooling. When the mixture became so thick that stirring was no longer effective, it was cooled to room temperature, the sludge of "pseudothiocyanogen"[15] was filtered off and the filtrate was treated again with additional chlorine. This process was repeated until no further pseudothiocyanogen was formed. The combined precipitate of pseudothiocyanogen was well washed with boiling water to remove all soluble salts, then dried at 120°, giving 512 g. of product.

The 512 g. of pseudothiocyanogen, divided into two batches, was converted into melon by heating in 25-cm. porcelain evaporating dishes with a large brush flame from a Meker type burner until all volatile products were expelled. The light yellow residue of crude melon weighed 240 g.

Other methods of preparing melon were less satisfactory on a laboratory scale. The slow heating of ammonium thiocyanate is reported to give good yields[16] but requires special equipment and much time.

**Potassium Melonate.**—The following modification of Liebig's[4b] method was most satisfactory. Eighty grams

(13) Madelung and Kern[10] believe that the group present in tricyanomelamine is —NH—C≡N, and not —N=C=NH. However, resonance between these two structures would be expected, and Dr. E. W. Hughes has verified this for the group in the molecule of dicyandiamide (private communication).

(14) A crude grade of sodium thiocyanate prepared by dissolving sulfur in fused sodium cyanide gave only slightly smaller yields.

(15) The name "pseudothiocyanogen" is here applied to the crude mixture composed of isoperthiocyanic acid, kanarin, and various polymers of isoperthiocyanic acid obtained by this procedure instead of to the part insoluble in alkali.

(16) Gludd, Keller and Klempt, Z. angew. Chem., **39**, 1071 (1926).
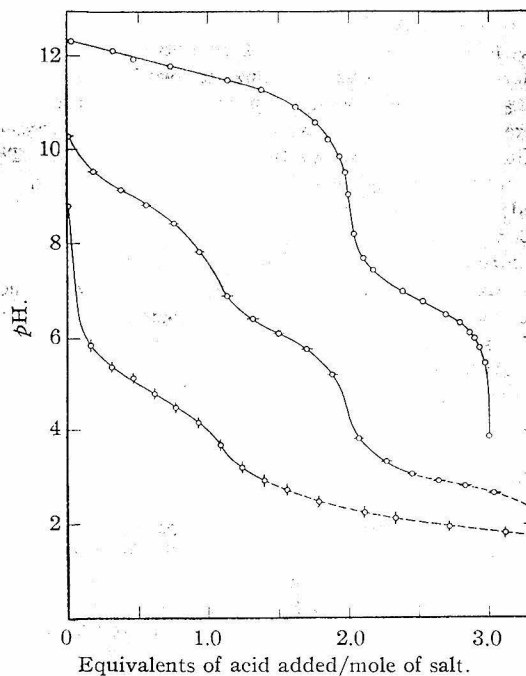


Fig. 1.—○, Cyanuric acid; -○-, cyameluric acid; ○, hydromelonic acid; - - -, solid separating out.

of pure potassium thiocyanate was slowly melted in a 10-cm. porcelain casserole and held at a moderate temperature until all moisture was expelled and a quiet melt was obtained. The temperature was then increased to a dull red heat and 40 g. of melon was added in portions of 5 to 10 g., each portion being allowed to dissolve before another was added. The carbon disulfide which is evolved was allowed to burn. When all the melon had dissolved the mixture was heated more strongly until only very little more carbon disulfide was produced. At this point a few drops of the melt were removed on the end of a Pyrex rod and its solubility[17] in hot water tested. Heating was continued until a 0.1 to 0.2 g. portion of the salt was completely soluble in 5 ml. of hot water. The entire operation required approximately one-half hour. After cooling, the salt was ground into coarse particles, dissolved in hot water, decolorized with carbon, filtered and allowed to cool. The fine felted needles, when air dried, weighed 38.8 g. Repeated crystallization gave a snow-white product.

Liebig's method using potassium thiocyanate and antimony trichloride gave a product which was hard to free from antimony salts.

**Sodium Melonate.**—Burdick[2b] prepared this salt by heating sodium thiocyanate with antimony trichloride. By dissolving 26 g. of melon in 50 g. of fused sodium thiocyanate, 11 g. of pure white fine needle crystals of sodium melonate was obtained. The sodium salt is very similar in appearance to and less soluble than the potassium salt.

**Potassium Cyamelurate.**—Two methods, both suggested by Henneberg,[5] were used.

(17) The test for solubility is very essential, for if heating has been for too short a time or at too low a temperature an insoluble product is formed.

**A.**—A solution of 20 g. (0.04 mole) of hydrated potassium melonate in 80 ml. of 4 $N$ potassium hydroxide solution was boiled under reflux for two hours. A crop of slightly colored crystals of potassium cyamelurate was filtered off after cooling, and a second crop after concentrating the filtrate to one-third its initial volume. The two crops of crystals were washed with alcohol and air-dried; weight 11 g. or 70%. Crystallization from a hot moderately dilute solution with generous use of decolorizing carbon yielded pure white stout needles.

**B.**—A suspension of 30 g. of crude melon was boiled with 300 ml. of 3 $N$ potassium hydroxide for forty-five minutes and the undissolved solid was filtered out. The crystals which separated from the filtrate were filtered off, washed with alcohol and air-dried. Boiling the original undissolved solid with the last filtrate and proceeding as above gave an additional amount. The total weight of potassium cyamelurate was 23 g.

**Sodium Cyamelurate.**—This salt, which was mentioned casually by Henneberg, is easily prepared in the same manner as the potassium salt by substituting 4 $N$ sodium hydroxide for the potassium hydroxide in method (A) above. The yield is 50 to 60% of the theoretical assuming structure (IV) for hydromelonic acid and (VII) for cyameluric acid.

*Anal.* Calcd. for $Na_3O_3C_6N_7 \cdot 5^1/_2H_2O$: Na, 17.8; $H_2O$, 25.6. Found: Na, 17.7, 17.8; $H_2O$, 25.3, 25.4.

**Cyameluric Acid.**—Acidification of a moderately dilute aqueous solution of the sodium or potassium salt with 6 $N$ hydrochloric acid added very slowly from a buret with effective stirring, followed by chilling in an ice-bath, gave a white crystalline powder. This was filtered off, washed well with cold water and air-dried.

*Anal.* Calcd. for $C_6H_3O_3N_7 \cdot 3H_2O$: C, 26.17; H, 3.27. Found: C, 25.88; H, 3.24.

Precipitation from a hot solution yields an impure product due to the rapid hydrolysis of cyameluric acid to ammelide and ammeline in acid solution. Crystallization from boiling water causes considerable decomposition due to the low $p$H of the solution of this comparatively strong acid.

The acid does not reduce alkaline permanganate either in the cold or upon prolonged boiling; it gives no enol reaction with ferric chloride. Most of its metallic salts are very sparingly soluble.

**Acid Hydrolysis of Hydromelonic Acid.**—A solution of 2.231 g. of potassium melonate in an excess of 6 $N$ nitric acid was gently boiled for one and one-half hours. The solution was made alkaline with a slight excess of 15 $N$ ammonium hydroxide, then sufficient cupric ammonium sulfate solution was added to color the solution a dark blue. The amethyst-red precipitate which gradually separated was filtered off, dried and weighed; weight 0.454 g. (72.5% of theoretical, assuming one mole of cyanuric acid per mole of hydromelonic acid).

**The Alkaline Hydrolysis of Potassium Melonate.**—A series of quantitative determinations of the amount of ammonia and carbon dioxide produced in the hydrolysis of potassium melonate to potassium cyamelurate was made as follows. The ammonia was carried over into standard hydrochloric acid by a current of purified air. The excess acid was then titrated with a standard sodium hydroxide solution using the mixed indicator, $p$-nitrophenol—methyl red. The amount of carbonate formed was determined by the method of Winkler as follows. The alkaline solution in the boiler was diluted to 250 ml., then an aliquot portion was taken. An excess of barium chloride solution was added to the aliquot, then the sodium hydroxide was carefully titrated with a standard hydrochloric acid solution using phenolphthalein as indicator. The data thus obtained are given in Table I.

As a check on the method, potassium melonate was replaced by urea. In this case the ratio of equiv. $CO_2$/equiv. $NH_3$ was 1.03. The difference between 1.03 and 1.00 represents about the accuracy to be expected from this method of analysis.

When potassium cyamelurate replaced potassium melonate, 2.24 was the ratio of equiv. $CO_2$/equiv. $NH_3$. This would indicate that the cause of a ratio greater than unity in the case of the hydrolysis of potassium melonate is a further hydrolysis of the potassium cyamelurate.

**Acid Hydrolysis of Cyameluric Acid.**—Two grams of cyameluric acid, purified through the copper ammonium salt, was digested with 10 ml. of concd. nitric acid on a steam-bath for four hours. The solution was diluted to 20 ml., cooled to 0°, saturated with the oxides of nitrogen obtained from the action of concd. nitric acid on metallic copper in order to destroy ammonium ions and make sure that all —NH₂ groups were converted into —OH groups, and evaporated to dryness on a water-bath. The residue was washed onto a weighed Gooch crucible, using 18 ml. of water, dried and weighed; weight 0.975 g. This represents 93.5% of that theoretically obtainable assuming one mole of cyanuric acid per mole of cyameluric acid. The residue gave the characteristic insoluble amethyst-colored copper ammonium salt of cyanuric acid.[18]

**Electrometric Titrations of Hydromelonic and Cyameluric Acids.**—Potassium melonate, 0.3707 g. (7.45 × $10^{-4}$ mole) crystallized four times from water, was dissolved in 50 ml. of water. Potassium cyamelurate, 0.2576 g. (6.62 × $10^{-4}$ mole) thrice crystallized from water, was dissolved in 50 ml. of water. In each solution was placed a glass electrode, a standard calomel electrode, and a mechanical stirrer. The former was titrated with 0.2899 $N$, the latter with 0.2493 $N$ hydrochloric acid. The e. m. f. measurements were made with a student type potentiometer and a high sensitivity galvanometer in the former case, and with a Beckman $p$H meter in the latter case. Conversion to $p$H values in the former case was made by comparison with standard buffer solutions. The results are shown as the curves in Fig. 1.

## Summary

Improved methods have been described for the preparation of melon, potassium and sodium melonate, potassium and sodium cyamelurate, and cyameluric acid. Titration of potassium melonate and cyamelurate, using the glass electrode, shows that hydromelonic acid is much stronger than cyameluric acid.

The titration data and results of hydrolysis

(18) S. P. Mulliken, "Identification of Pure Organic Compounds," Vol. II, John Wiley and Sons, Inc., New York, 1916, p. 84.

indicate that the molecules of these two acids contain the planar cyameluric nucleus of Pauling and Sturdivant.

# SOME DERIVATIVES OF CYAMELURIC ACID
## AND PROBABLE STRUCTURES OF MELAM, MELEM AND MELON

Since it has been shown recently that the structure proposed by Pauling and Sturdivant for the cyameluric acid nucleus[1], I, accounts more satisfactorily for the acidic strength and for the products of hydrolysis[2] than any other proposed structure, and because of the prediction made by these authors[1] that there should be a group of cyameluric compounds analogous to the cyanuric compounds, attempts have been made to prepare some of these analogues.

Cyameluric compounds analogous to cyanuric derivatives which have been prepared are a cupric ammonium salt, a mercuric salt, the tri-chloride, a tribenzyl nitrogen ester, two monomethyl esters which were not separated, and a diamide. The mixture of monomethyl esters was shown to be largely the nitrogen ester with a smaller amount of the oxygen ester.

The most characteristic of the several cupric ammonium cyanurates[3] is that of the composition $CuNH_4(C_3N_3O_3).NH_3$[4]. It is of sufficiently constant composition over a moderate range of temperature and concentrations that Mulliken[5] recommends it for the identification of cyanuric acid. Cyameluric acid forms

1   Pauling and Sturdivant, _Proc. Natl. Acad. Sci._, _23_, 615 (1937)

2   Redemann and Lucas, _J. Am. Chem. Soc._, _61_, 3420 (1939)

3   Benrath and Meckenstock, _Zeit. anorgan. allgem. Chem._, _151_, 35 (1926)

4   Claus and Putensen, _J. prakt. Chem._ [2], _38_, 216 (1888)

5   Mulliken, Identification of Pure Organic Compounds, Vol.II, p. 84, John Wiley and Sons, New York, _1916_.

a similar blue-lavender salt, $CuNH_4(C_6N_7O_3) \cdot NH_3$. The analogy between the two salts is pronounced, for they differ only in respect to the central nucleus, $C_3N_3O_3$ and $C_6N_7O_3$. The insoluble cupric ammonium cyamelurate is useful in purifying cyameluric acid, for the acid is regenerated readily from the salt by suspending it in water and adding hydrochloric acid.

The parallelism in the case of the mercuric salts is not so satisfactory. Hantzsch[6] reported two different mercuric cyanurates with the formula $Hg_3(C_3N_3O_3)_2$. One of these, precipitated from the reagents in ice-cold solutions, he called the oxygen salt since it gave an immediate precipitate of yellow mercuric oxide on the addition of sodium hydroxide; the other, precipitated from boiling solutions of the reagents, he called the nitrogen salt since it did not precipitate mercuric oxide upon the addition of sodium hydroxide. The specimens of mercuric cyamelurate, $Hg_3(C_6N_7O_3)_2$, obtained under these two conditions showed no difference in behavior with sodium hydroxide, both giving an immediate precipitate of yellow mercuric oxide with sodium hydroxide. From the Hantzsch point of view one would be inclined to say that cyameluric acid forms only the oxygen salt. So although in this case the analogy with cyanuric acid is not complete, nevertheless the behavior of the mercuric salt favors the Pauling and Sturdivant structure, I, rather than the Franklin structure, II, for in the latter case only a nitrogen salt is

6   Hantzsch, (a) Ber., 35, 2717 (1902); (b) ibid., 39, 139 (1906); (c) Zeit. anorgan. allgem. Chem., 209, 219 (1932)
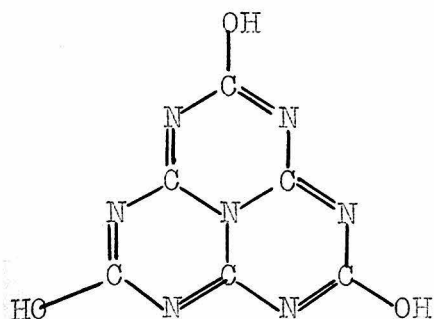
Pauling and Sturdivant

I
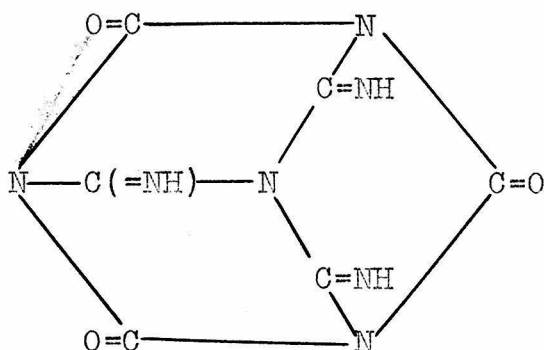
Franklin II

possible. However, this argument is open to criticism, for if the N-Hg bond has sufficient ionic character the salt would be expected to react with sodium hydroxide.

Cyanuryl trichloride, $C_3N_3Cl_3$, and cyameluryl trichloride, $C_6N_7Cl_3$, are entirely analogous. The former, although usually obtained by polymerizing cyanogen chloride, may be prepared by heating the anhydrous acid with phosphorus pentachloride[7]; the latter, although not quite analytically pure, is prepared from either the anhydrous acid or the anhydrous potassium salt by heating with the same reagent at 156° for several hours. Hydrolysis of the two chlorides is similar, except that cyameluryl chloride hydrolyzes more rapidly, as might be expected from its being a stronger acid[2]. The most striking similarities are the reactions of both acid chlorides with acetic acid and with alcohols. When heated with acetic acid each yields the respective acid and acetyl chloride. On alcoholysis each yields the respective acid and an alkyl chloride.

Esters of cyameluric acid are more difficult to prepare than those of cyanuric acid. There are two series of esters

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7  Beilstein, _Ann._, 116, 357 (1860)

for the latter: the oxygen esters obtained from sodium alkoxides and cyanuryl chloride, or from the alkali cyanurates and alkyl halides at low temperatures; and the nitrogen esters obtained from the alkali cyanurates and alkyl halides at elevated temperatures, or in the case of the methyl ester from diazomethane and cyanuric acid[8]. Potassium cyamelurate does not react readily with alkyl halides at room temperature. After standing with methyl iodide for nineteen months only a small amount of iodide ion was formed and no ester could be isolated. Likewise, cyameluryl trichloride with sodium methoxide ( or benzoxide) failed to give the ester. Potassium cyamelurate and allyl bromide gave an allyl derivative at 100° which was not obtained pure.

The tribenzyl ester was obtained from benzyl chloride and potassium cyamelurate at 156°. This ester is a nitrogen ester since it gave benzyl amine and no benzyl alcohol upon hydrolysis. The formation of the nitrogen ester at elevated temperatures is also observed for cyanuric acid[9]. From cyameluric acid and diazomethane was obtained a mixture of monomethyl esters with the nitrogen ester predominant, and also a trimethyl ester which was entirely a nitrogen ester.

Cyanuryl chloride and cyameluryl chloride both react with ammonia, the former to produce a monochlordiamide and a triamide, melamine, and the latter to produce a diamide and apparently some triamide, although not pure.

The resemblance of the derivatives of cyameluric acid to the corresponding derivatives of cyanuric acid, especially the

8  Palazzo and Scelsi, Gazz. chim ital., 38, 664 (1908)

9  Hantzsch and Bauer, Ber., 38, 1009 (1905)

trichloride, indicate that cyameluric acid contains hydroxyl groups. Therefore, cyameluric acid is better formulated as a planar $C_6N_7$ nucleus with three hydroxyl groups attached, structure I.

On the basis that cyameluric acid is represented by I, satisfactory structures can be assigned to melam, melem and melon. Melam, with empirical formula $C_6H_9N_{11}$ established by Liebig[10], is probably tetraaminodicyanurimide, as shown in structure III, which is essentially the one proposed by Klason[11] and amplified by Franklin[12]. This structure is supported by Rathke's[13] observation that when melam is heated to 150° with 30 percent aqueous ammonia the main product is melamine accompanied by considerable ammeline. Ammonolysis of melam, if structure III is correct, should yield melamine while hydrolysis should yield both melamine and ammeline. Structure III satisfactorily accounts both for the fact that melam, like melamine, is a feeble base, and for Liebig's[10] observation that cyanuric acid and ammonium nitrate are formed when melam is boiled with concentrated nitric acid.

Melem, for which Liebig[10] reported the formula $C_6H_6N_{10}$, may be cyameluryl triamide, IV. Melam and melem resemble each other so closely in physical and chemical properties that it was doubted for many years that Liebig had isolated two

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10  Liebig, Ann., 10, 10 (1834)

11  Klason, J. prakt. Chem., [2], 33, 287 (1886)

12  Franklin, J. Am. Chem.Soc., 44, 507 (1922)

13  Rathke, Ber., 23, 1675 (1890)

H₂N ... N—C—N—C ... NH₂

Melam

III

Melem

IV

C₃N₃=NH

HN

C₃N₃=NH
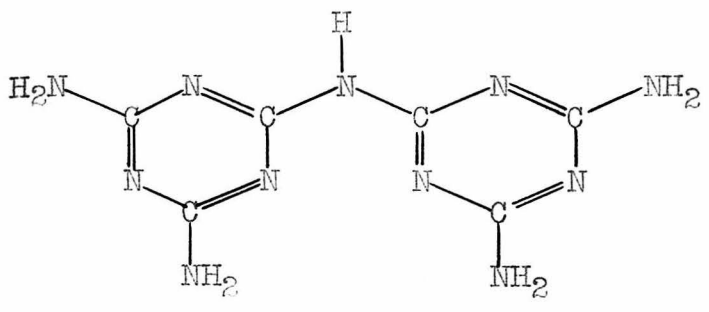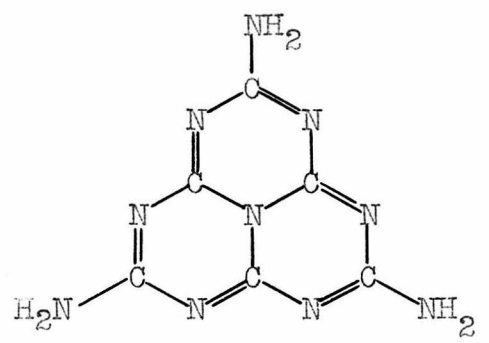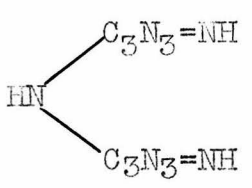
Melon
Franklin

V
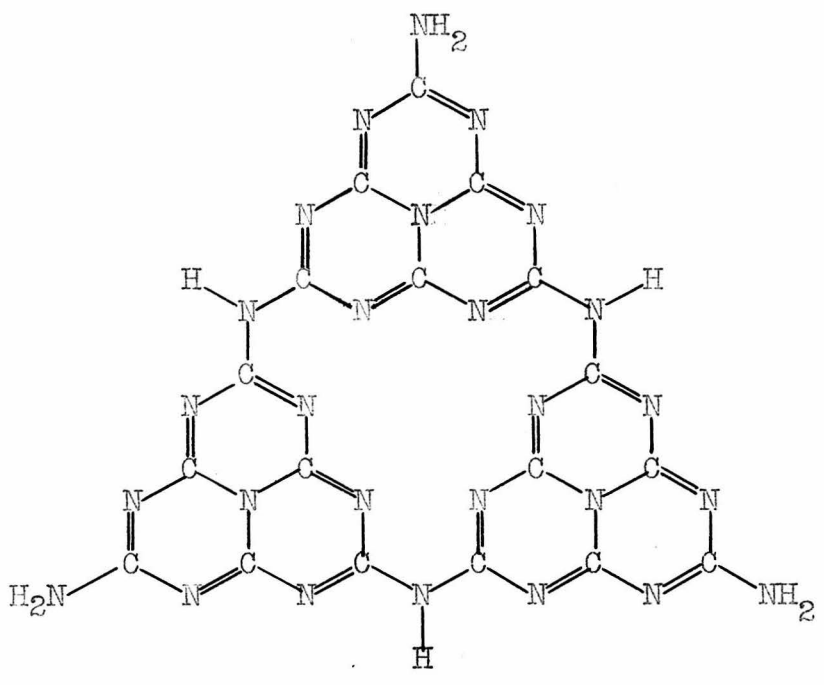
VI

different compounds; however, Klason[11] confirmed their existence. Compounds with structures as similar as III and IV would be expected to resemble each other closely. Structure IV satisfactorily accounts for the formation of large quantities of ammelide upon hydrolysis, and for the fact that melem is more resistant to hydrolysis than melam. Structures III and IV account satisfactorily for the observation that melem is a weaker base than melam, for the former is derived from much the stronger acid.

Melon, with empirical formula $C_6H_3N_9$ established by Laurent and Gerhardt[14] and less conclusively by Volckel[15], was assigned structure V by Franklin[12]. But since melon gives good yields of cyameluric acid upon alkaline hydrolysis[16] a satisfactory structure for melon must involve the planar nucleus characteristic of cyameluric acid, I. Such a structure results from cyameluric triamide, $C_6N_7(NH_2)_3$, IV, by the loss of ammonia from two or more molecules. One possibility is that shown by structure VI, where three molecules of ammonia have been split out from three molecules of cyameluric triamide. This compound, the molecule of which has three cyameluric nuclei, has the formula $C_{18}H_9N_{27}$, three times $C_6H_3N_9$, the accepted formula for melon. Here the side chains are $-NH_2$ groups, the $=NH$ group forming part of a new ring. Larger molecules of the compact type, where the maximum number of ring closures had taken place would have a higher carbon, lower hydrogen and lower nitrogen content. In such a molecule

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14 Laurent and Gerhardt, Ann. chim., [3], 19, 85 (1847)

15 Volckel, Pogg. Ann., 58, 151 (1834)

16 Volhard, J. prakt. Chim., [2], 9, 30 (1874)

hydrogen is found only along the periphery. The symmetrical triangular molecule with six cyameluric nuclei is $C_{36}H_{12}N_{52}$ or more simply $C_6H_2N_{8\frac{2}{3}}$. As condensations extend indefinitely the empirical formula approaches asymptotically the limit $C_3N_4$, Franklin's carbonic nitride. Another type of condensation product, in which the cyameluric nuclei, except for the two terminal ones, are joined to two other nuclei, would approach $C_6H_3N_9$ if extended indefinitely. This is essentially a zig-zag molecule.

On the basis of cyameluric nuclei joined by nitrogen atoms it is possible to account for the lack of constancy of composition of melon observed by Liebig, Franklin , and others. The hydrogen content of Franklin's preparations varied from 1.1 to 2.0%, while for the accepted formula, $C_6H_3N_9$, the hydrogen content is 1.5%. By taking extreme precautions to dry mercuric thiocyanate at 150° in the vacuum of a mercury vapor pump before decomposing it to melon, Franklin was able to obtain a product with a hydrogen content of only 0.6%. This corresponds to a compact condensation product, triangular in form, with twenty-one nuclei, and molecular formula, $C_{126}H_{21}N_{175}$ or more simply $C_6HN_{8\frac{1}{3}}$, with a hydrogen content of 0.5%. Franklin's material was probably composed of both larger and smaller units giving an average value corresponding to the above figures. It is probably incorrect to assign any one structure to melon, for it is more than likely a mixture of different sizes and shapes of molecules giving rise to its amorphous character.

It is seen that there is a formal resemblance between

melon and graphite, in that the molecules are infinitely large and planar. The formal resemblance becomes even more pronounced if in the molecule of melon the void between the three cyameluric nuclei is filled by writing in three atoms of carbon and one of nitrogen. Taking the density of graphite as 2.25 and neglecting the hydrogen we can predict a density for melon of less than 1.7. An observed value is 1.40 at 25°, which value may differ considerably with different preparations. Anhydrous cyameluric acid, which is not predicted to have large void spaces in its structure corresponding to those in melon, is found to have a density of 1.75 at 25°. The high stability of melon, like that of graphite, may be explained in terms of the enormous number of resonating forms contributing to the structure of the compound.

## Experimental

Cupric Ammonium Cyamelurate.- To a solution of 2 g. of cyameluric acid trihydrate in 200 ml. of hot 0.5 $\underline{N}$ ammonium hydroxide there was added an excess of cupric ammonium sulfate solution. After cooling, the resulting lavender precipitate was filtered off, washed and air dried. The color changed to a very blue shade of lavender upon drying, probably due to the loss of either ammonia to form a less amminated compound, or to the loss of water of crystallization.

Anal. Calcd. for $CuNH_4(C_6N_7O_3).NH_3$  Cu 20.08

Found: Cu (iodometrically) 19.84, 20.13

This salt is much less soluble than the one obtained from cyanuric acid under the same conditions.

Mercuric Cyamelurate.- Two samples of mercuric cyamelurate were prepared under conditions which Hantzsch found to yield two different types of salts in the case of cyanuric acid. (A) To a solution of 2 g. of pure potassium cyamelurate in 50 ml. of boiling water was added a slight excess of a boiling solution of mercuric chloride. The white flocculent precipitate of the mercury salt which separated immediately was well washed with water and dried.

Anal. Calc. for $(C_6N_7O_3)_2Hg_3$   Hg 57.99

Found: Hg 58.31; 58.33

The high values for mercury probably are due to adsorption of mercury by the semi-gelatinous precipitate.

(B) The same procedure was followed except that mercuric chloride was replaced by mercuric acetate, and the solutions were ice-cold. Both salts looked alike and gave immediate

precipitates of yellow mercuric oxide when treated with a cold
1 N sodium hydroxide.  Upon standing over night nearly colorless
crystals of trisodium cyamelurate separated in each case.

Cyameluryl Trichloride.- (A)  From tripotassium cyamelurate.
Thirty grams of the salt, dried at 150° for forty eight hours
and 60 g. of phosphorus pentachloride were ground to a fine
mixture in a mortar.  This was sealed in a large bomb-tube and
heated in a boiling water bath for seven hours.  The tube was
opened to relieve the pressure, then after resealing heated
for an additional nine hours at 139° (m-xylene vapor bath).
After phosphorus oxychloride had been removed by letting stand
in a desiccator over flake sodium hydroxide in a thin layer,
the residue was crushed into a coarse powder and slowly sprin-
kled into and well stirred with an ice-water mixture to re-
move potassium chloride and any remaining phosphorus compounds.
The light yellow solid was filtered off and dried in a vacuum
desiccator over concentrated sulfuric acid.  The yield of
light yellow crystalline powder which under the microscope was
seen to consist of thin pale yellow platelets, was 23 g. (93%).

Cyameluryl trichloride is highly insoluble in all organic
solvents tested, which included such solvents as chloroform,
anisole, nitrobenzene, acetonitrile, o-dichlorobenzene and
glacial acetic acid (with which it reacted giving acetyl
chloride and cyameluric acid).  The compound was shown to be
essentially free from inorganic salts by ignition upon plat-
inum foil, where no ash remained.  No melting was observed,
but the compound gradually disappeared by a combination of
oxidation and perhaps sublimation.  Attempts to secure purification

by sublimation at atmospheric pressure and under high vacuum
were unsuccessful. Analyses were finally run on the dry mater-
ial without further purification.

Anal. Calcd. for $C_6N_7Cl_3$   N 35.44; Cl 38.49

Found: N (Kjeldahl) 35.76, 35.32; Cl (Carius) 38.23,
37.4, 37.4

Results of analysis indicate that the compound was slightly
impure cyameluric trichloride. When completely decomposed
by digesting with nitric acid, the solution gave but a faint
test for phosphorus with ammonium molybdate.

(B) From cyameluric acid. Two grams of the acid which
had been dried for several days at 150° and six grams of
phosphorus pentachloride were ground and intimately mixed.
The mixture was sealed in a heavy walled bomb-tube and heated
to 218° (naphthalene vapor bath) for thirty-six hours. The
tube was opened periodically to relieve the pressure. The
contents of the tube were worked up, as in (A). Yield was
2.3 g. (92%) of product closely resembling that prepared from
tripotassium cyamelurate.

N-Tribenzyl Cyamelurate.- A mixture of 5 g. of anhydrous
trisodium cyamelurate and 17 ml. of freshly distilled benzyl
chloride in a sealed bomb-tube was heated for twenty-three
hours in a boiling water bath. As little reaction appeared to
take place at this temperature, heating was continued for an
additional twelve hours in a vapor bath at 156° (boiling
bromobenzene). The contents were transferred to a Soxhlet
extractor and extracted for four hours with boiling benzene.
Following removal of volatile compounds by distillation under
18 mm. pressure, the residue was crystallized from boiling

benzene. Weight was 4.2 g. (36%). After two additional re-
crystallizations from ethyl alcohol very small white needles
melting at 283-284° (corr.) were obtained.

Anal. Calcd. for $C_{27}H_{21}N_7O_3$  Mol. wt. 491; N 19.96;
C 65.96; H 4.31

Found: Mol. wt. (Rast Camphor) 497; N (Kjeldahl)
19.54, 19.57; C 65.46; H 4.46

Saponification of 0.2 g. of tribenzyl cyamelurate by re-
fluxing for one hour with 10 ml. of aqueous 6 N potassium
hydroxide, followed by distillation of the reaction mixture
gave a faintly cloudy distillate with an odor suggestive of
ammonia. Extraction of this with ethyl ether following acid-
ification with hydrochloric acid gave no trace of benzyl
alcohol. However, extraction of the aqueous solution
with ether after the addition of an excess of sodium hydrox-
ide gave a few drops of a viscous residue which reacted
readily with benzoyl chloride. The resulting solid after
crystallization from aqueous ethyl alcohol melted at 105.5-
106.0°, and melted at the same temperature when mixed with
an authentic sample of N-benzylbenzamide, m.p. 105°. This
shows that benzyl amine but no benzyl alcohol is formed when
tribenzyl cyamelurate is saponified and that the tribenzyl
compound is a nitrogen, not an oxygen ester.

Action of Cyameluryl Trichloride on Benzyl Alcohol.- A
mixture of 1.0 g. of cyameluryl trichloride and 1.5 g. of dry
benzyl alcohol reacted spontaneously. The mixture became very
hot and the yellow color of the cyameluryl trichloride changed

to a pure white. The mixture was then boiled for one minute,
cooled and 2 ml. of benzene added. The solid was removed by
filtration and the filtrate was fractionally distilled. The
fraction boiling between 170-190° (uncorr.),had an unmistakable
odor of benzyl chloride. This was confirmed by converting it
into the p-bromobenzenesulfon-p'-anisidide, m.p. 169.5-170.0°
(uncorr.), after recrystallizing from ethanol. The melting
point was 170.0-170.5° when mixed with a known sample, m.p.
170-171°[17].

The white residue was shown to be cyameluric acid by
its solubility in sodium bicarbonate solution from which the
trisodium salt was precipitated in characteristic colorless
needles upon adding an excess of strong sodium hydroxide
solution.

Methyl Cyamelurate from Cyameluric Acid and Diazomethane.-
An excess of an ethereal solution of diazomethane was added to
1.7 g. of very finely powdered cyameluric acid. The evolution
of gas, vigorous at first, soon became rather slow. A strong
yellow color from excess diazomethane was still present after
standing for three days in the refrigerator, although the
evolution of gas had become quite slow. The solid was filtered
off and dried over concentrated sulfuric acid. The dry pale
yellow solid thus obtained weighed 1.8 g. No melting was
observed in a capillary tube; no solvent was found from which
the material could be purified without some decomposition.

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[17] Gillespie, J. Am. Chem. Soc., 56, 2740 (1934), gives 167.5°
which is too low.

Anal. Calcd. for $C_6H_2N_7O_3(CH_3)$   C 35.7;  H 2.12;  $CH_3$ 6.38

Found:   C 35.4, 35.1;  H 3.22, 3.05

$CH_3$ (methoxyl) 0.58, 0.62;   $CH_3$ (methylimide) 6.95, 6.48

Analysis indicates slightly more than one methyl group per nucleus and some methylation of the hydroxyl groups.

The partially methylated product from the above experiment after fine pulverization was treated again with an excess of diazomethane at room temperature for four days.  Since all apparent reaction had ceased, the solid was filtered off, dried over concentrated sulfuric acid, and analysed.

Anal. Calcd. for $C_6N_7O_3(CH_3)_3 \cdot 1\frac{1}{2}H_2O$   C 36.72;  H 4.12;

$H_2O$ 9.18;  $CH_3$ 15.3

Found:   C 36.22;  H 4.14;  $H_2O$ 9.13;  $CH_3$ (methoxyl)

0.060, 0.062.

When heated on platinum foil the anhydrous compound melted but in a capillary tube no melting was observed up to 290°, but instead extensive charring.

Attempts to Prepare Cyameluric Triamide.- (1)  On adding 25 ml. of 15 $\underline{N}$ ammonium hydroxide to 1.19 g. of cyameluryl chloride, a very vigorous reaction took place immediately. The light yellow color of the cyameluryl chloride disappeared and a white flocculent precipitate took its place.  After standing for 1 hour this was filtered off, washed well with cold water and dried in the oven at 75°.  Weight 0.88 g.  As no solvent was found from which this material could be recrystallized, the sample was analyzed without further purification.

Anal.  Calcd. for $C_6N_7(NH_2)_3$   N 64.2;  for $C_6N_7(NH_2)_2Cl$

N 53.1; Cl 14.93;  for $C_6N_7(NH_2)_2OH$   N 57.6

Found:   N (Kjeldahl) 54.28; 54.17;  Cl (Carius) 3.32, 3.50

The analytical data indicate an impure mixture largely composed
of one or both diamides, cyameluryl monochlorodiamide, and
cyameluryl diamide.

(2) Two grams of cyameluryl chloride was suspended in
100 ml. of anhydrous ethyl ether into which was passed gaseous
ammonia until the solution was saturated. It was then allowed
to stand for two hours and again saturated with ammonia gas
and allowed to stand over night. Twenty-five ml. of water was
then added and the mixture was vigorously shaken. The pre-
cipitate was separated by filtration, washed with concentrated
ammonium hydroxide, and air dried. It was then crushed and
digested with 100 ml. of warm 1 $\underline{N}$ ammonium hydroxide for thirty
minutes, filtered, and dried at 100° for one hour.

Anal. Found; N, 59.88, 60.01

Since this analytical result agreed most nearly with a possible
monohydrate of the triamide or the ammonium salt of the acid
diamide the compound was dried for twenty-six hours at 150°.
A loss in weight of 4.52% took place, with but little change
in the analysis, but the material still appeared to be impure.

Anal. Found: N 60.20, 61,96

(3) Two grams of cyameluryl chloride was sealed in a
bomb-tube with anhydrous liquid ammonia and left for twenty
hours at room temperature. The tube was opened and the
ammonia allowed to evaporate. The residue was extracted with
cold water to remove the ammonium chloride. The flocculent
solid was collected upon a filter and dried at 100° for four
hours.

Anal. Found: N 60.34, 60.01

None of these preparations has a nitrogen content as high
as that for the triamide (64.2%), but the purification is

hampered because no satisfactory solvent has been found from which the compound can be crystallized.

## Summary

1. Cyameluric acid has been shown to form a group of compounds entirely analogous to those of cyanuric acid. The analogy is complete for the cupric ammonium salts, the trichlorides, and the nitrogen esters formed by the reaction of benzyl chloride with the respective alkali salts at elevated temperature. The analogy is less exact for the diamides, the mercuric salts, the oxygen esters and the behavior with diazomethane.

2. The existance of a trichloride and an oxygen ester indicate that hydroxyl groups are present in the molecule of cyameluric acid.

3. The analogy with cyanuric compounds and the presence of hydroxyl groups substantiate the planar ring structure of cyameluric acid proposed by Pauling and Sturdivant.

4. Melam is probably dicyanurylimide and melem, cyameluryl triamide.

5. It is proposed that melon is a condensation product of cyameluryl triamide, and that the resulting very large molecules are planar cyameluryl rings joined through nitrogen atoms.

# THE DILITURATES (5-NITROBARBITURATES) OF SOME
# PHYSIOLOGICALLY IMPORTANT BASES.

Both the qualitative and the quantitative isolation of
basic compounds from natural sources are, in general, most
satisfactorily accomplished when the base in question can
be obtained as the sparingly soluble salt of a suitable
acid[1]. As a group, organic nitro compounds have found the
greatest application of the acidic reagents employed in the
past. The functional group used in salt formation in re-
agents of this class is the contiguous nitro-phenolic (or
enolic) array*. Examples of compounds containing this
grouping which have been used for isolating bases are:
picric acid, styphnic acid[2] (sym-trinitroresorcinol),
picrolonic acid[2] (1-p-nitrophenyl-3-methyl-4-nitropyrazolone-5)
nitranilic acid[3] (2,5-dihydroxy-3,6-dinitro-p-benzoquinone),
3-nitrodiketohydrindene[4], 2,4-dinitronaphthol-1[5], 2,4,6-tri-
nitro-m-cresol (methylpicric acid), 3-chloro-2,4,6-trinitro-
phenol (chloropicric acid), 2,3,4,6-tetranitrophenol, and
nitrophloroglucinol.

During the past year it was found that dilituric acid
(5-nitrobarbituric acid) is superior to the hitherto em-
ployed nitro-enolic compounds as a reagent for isolating
many naturally occurring bases. It was the purpose of this
investigation to study the properties of the diliturates of
a large number of physiologically important bases.

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\* This is an essential but not necessarily sufficient
characteristic of these reagents.

Dilituric acid[6] is both conveniently and economically prepared by the direct nitration of barbituric acid giving without difficulty an analytically pure product. When crystallized from water dilituric acid contains two molecules of water of crystallization which it slowly looses at room temperature and more rapidly at elevated temperatures. The solubility of the pure acid at 25° in several common solvents was found to be as follows: in methanol 0.0992 moles per liter; in 96 percent ethanol, 0.0853; in water, 0.0631; in absolute ethanol, 0.0353; in acetone, 0.0246; in ethyl ether, 0.00092; and in benzene, 0.004. Solutions of dilituric acid in hydroxylic solvents have a strong yellow color, whereas those in non-hydroxylic solvents are colorless.

In aqueous solution dilituric acid behaves as if it were a strong monobasic acid (compare Fig. 1), and from the electrometric titration of a 0.00904 $\underline{N}$ solution it appears that dilituric acid is completely dissociated within the limit of error of the method. This is in agreement with the finding of Trubsbach[7] that dilituric acid is too strong an acid to give a constant by the conductimetric method. However, dilituric acid is not as strong an acid as hydrochloric acid, for when the ratio of diliturate ion to dilituric acid becomes large there is considerable depression of the pH over that calculated for complete ionization. In general, it appears that dilituric acid, in aqueous solution, is intermediate in strength between picric and hydrochloric acid.

The alkali and alkaline earth diliturates are probably the most interesting of the inorganic salts of this acid which have been prepared[6i,8]. Examination of Table I shows that

there is a ten-fold difference in the solubilities of the potassium and sodium salts in water at 25°. This difference is sufficiently great that Fredholm[61], Frediani[8], and Dermer[9] have proposed these salts for differentiating sodium and potassium in binary mixtures, or for distinguishing them when alone. The alkaline earth diliturates show increasing solubility in water at 25° in the order magnesium, barium, strontium and calcium.

While a quantitative separation of magnesium and barium is not possible, it may be shown by the solubility product principle that a solution containing 10 mg. of magnesium ion would have to contain about 50 mg. of barium ion before simultaneous precipitation would take place. The use of dilituric acid for the detection of magnesium in the presence of calcium, a common occurrence in many routine analyses, is much more favorable; a solution containing 10 mg. of magnesium ion theoretically requires 230 mg. of calcium ion before simeltaneous precipitation takes place. Since the crystal habit of magnesium barbiturate is very characteristic, this acid has been found to be an excellent reagent for magnesium. We have been able to demonstrate the presence of magnesium in the hydrolysate of the crude phospholipide obtained from bovine spinal cord by the use of dilituric acid.

It is felt that an investigation of the diliturates of the rare earth elements might result in a useful method for separating some of the members of this group of substances.

The properties of salts formed by the interaction of dilituric acid with seventy-one organic bases have been tabulated in Table II. Because of the limited number of salts

of the simple aliphatic amines studied, it is not possible to
give any positive statement regarding the effect of structure
upon their solubility in water. However, it is worthy of note
that ethylenediamine diliturate is the least soluble of all the
organic or inorganic diliturates that have been prepared. The
primary aliphatic amine diliturates show surprisingly small
solubilities in water at 25°, and within limits the solubility
increases with increase in chain length. In the one case
studied, the transition from a primary to a secondary amine
diliturate was accompanied by a decrease in solubility. On
the other hand, the salts of the tertiary amines are much more
soluble than the salts of the corresponding secondary amines.
We were, in fact, unable to isolate the diliturates of trimethyl-
and triethylamine because of their great solubility in water
and in aqueous ethyl alcohol. A series of qualitative exper-
iments were carried out with the more accessible aromatic
amines. These all gave beautifully crystalline salts of lim-
ited solubility in water. It appears that dilituric acid should
prove useful in isolating various primary and secondary aliphatic
amines, high molecular weight tertiary aliphatic amines, aro-
matic amines, and the diamines.

The heterocyclic bases quinoline, imidazole, and pyridine
formed sparingly soluble diliturates which could be recrystal-
lized from water without decomposition. From the properties of
these salts it is predicted that the diliturates of the nuclear
substituted quinolines, imidazoles, and pyridines will be crys-
talline salts of limited solubility in water. In contrast to

morpholine it was found that ethyl morpholine diliturate was extremely soluble in water. This is in agreement with the previous finding that the diliturates of the tertiary aliphatic amines are far more soluble in water than are those of the corresponding secondary amines.

The isolation of ethanolamine from the hydrolysates of phospholipids by the methods hitherto available has been a very laborious task, and still more serious, the methods were not capable of being developed to yield quantitative data[9]. The observation that ethanolamine diliturate posses but limited solubility in water has provided both a method for its qualitative isolation and a method which appears to be capable of yielding quantitative data by the so-called solubility product method[1, *]. An investigation of the diliturates of ethanolamine, isopropanolamine (1-amino-2-hydroxypropane), and a number of other alkanolamines has shown that without exception the diliturates were easily obtained in a crystalline state, a decided contrast to the picrates of these bases. Dilituric acid was also found to be a decidedly superior reagent for the isolation and determination of glucosamine.

The alkaloid salts of dilituric acid are well defined crystalline compounds of relatively low solubility in cold water. If a detailed micro-crystallographic study of the alkaloid diliturates were made it might provide a useful additional method for the toxicological investigation of alkaloids.

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* Unpublished observation taken from a study on the nature of the water soluble bases present in mammalian phospholipides.

An extensive study of the diliturates of the amino acids has been made. The properties of thirty-four salts are listed in Table II. The most insoluble amino acid diliturate invest-igated was that of l-diiodotyrosine. Since the basic amino acids arginine, histidine, and lysine can be removed from a protein hydrolysate by other means, and since there is a five-fold difference in the solubility of l-diiodotyrosine and l-tyrosine diliturates, it seems probable that the isolation of l-diiodotyrosine in the presence of l-tyrosine and all the remaining amino acids should present no great difficulty. While dilituric acid might be useful for the isolation of one of the basic amino acids in the absence of the others, it seems doubtful that a mixture of all three could be separated either by fractional precipitation or by fractional crystal-lization of their diliturates.

A comparative study of the solubilities of five l-, dl-pairs of amino acids failed to give consistent results. In three cases, i.e., l-, dl-lysine; l-, dl-aspartic acid, and l-, dl-leucine the diliturate of the dl- acid was the less soluble, whereas in the other two cases, i.e., l-, dl-alanine, and l-, dl-glutamic acid the opposite was true. The dilitur-ates of the monoamino monocarboxylic acids show interesting solubility behavior in that as the length of the side chain increases from zero to three carbon atoms the solubility of the diliturate increases in a regular manner; exactly the opposite is observed for the solubility of the amino acids themselves. In addition it is found that a branching of the side chain results in a decrease in solubility of the dilitur-ate. In general the diliturates of the amino acids are well

defined crystalline compounds which are suitable for isolating amino acids from aqueous solution. Examination of Table II leaves little doubt that there are many amino acid mixtures that can be separated with the aid of dilituric acid, but at present it can not be predicted whether one could successfully resolve such a complex mixture as a protein hydrolysate.

The diliturates of the proteinogenic amines tyramine, histamine, and phenylethylamine are only slightly soluble in water at 25°; hence dilituric acid should be useful for isolating these substances from aqueous solution under certain definite conditions.

As the temperature coefficient for the solubility of dilituric acid and the diliturates is large these compounds may be readily crystallized from hot solution. Further, since it is not anticipated that all these salts will have identical temperature coefficients it is possible that mixtures unresolvable at 25° may be satisfactorily separated at some other temperature.

Because dilituric acid is only moderately soluble in water at 25° there is a need for a more soluble form of this reagent. Fortunately the trimethylamine and ethylmorpholine diliturates are very soluble in water so that these salts may be used in lieu of the acid when the diliturate to be isolated is more soluble than the dilituric acid, when it is necessary to have an excess of diliturate ion present in solution, or when working with thermolabile substances.

One of the advantages of isolating bases in the form of their salts is that the base can be easily regenerated. It has been found that the regeneration of bases from their

diliturates can be achieved in the majority of cases by simply replacing the base in question by ethylenediamine, magnesium, or ammonia as the salts of these three substances are exceedingly insoluble in water and in fact, are in the order named the most insoluble of all the diliturates investigated. Thus in a typical case, the decomposition of glycine diliturate with ammonia gave an 89% yield of crystalline glycine.

The elementary analysis of dilituric acid and the diliturates deserves some comment since the ordinary Pregøl universal filling for the determination of carbon and hydrogen[10] must be modified before satisfactory results can be obtained. It was necessary to replace the original Pregøl copper oxide-lead chromate combustion zone filling by copper oxide, and to replace all of the silver plugs in front of the combustion zone by asbestos. In addition the sample was mixed with powdered cupric oxide prior to ignition. By observing these conditions satisfactory analyses were obtained.*

In conclusion it may be stated that dilituric acid possesses many of the characteristics of the ideal acidic precipitant for (a) it is readily available at low cost; (b) it behaves as a strong monobasic acid in aqueous solution thereby diminishing the possibility of forming mixed salts; (c) it is moderately soluble in water and the lower alcohols; (d) several very soluble salts are known which permits an excess of diliturate

-----------------------------------------------------------------

* The low carbon values obtained with the Pregøl filling are undoubtedly due to the fact that the combustion of dilituric acid is accompanied by the formation of hydrogen cyanide or cyanogen and that these substances react with silver and lead chromate to give the corresponding cyanides which are not completely decomposed at the usual operating temperature of 600°.

ion to be maintained in concentrated solutions; (e) all the dilliturates prepared were well defined crystalline substances; (f) the salts were characterized by a wide variation in solubility thus allowing mixtures to be fractionated; (g) the acid and its salts possess a high temperature coefficient of solubility which permits ready purification by recrystallization; and (h) in the majority of cases the base can be obtained easily from the salt by a simple double decomposition.

EXPERIMENTAL

Preparation of Dilituric Acid.-The acid may be prepared according to the directions given in Organic Syntheses[6h], or in better yield and with less trouble by the method of Fredholm[6i]. Since the latter reference is not in the Institute Library, directions for the preparation of dilituric acid by a modification of this method are given in detail here.

In a 400 ml. beaker are placed 25 g. of technical barbituric acid and 50 ml. of conc. nitric acid (d. 1.42). If the reaction does not start spontaneously the mixture is heated on the steam bath until a vigorous reaction takes place. After the preliminary vigorous reaction an additional 20 ml. of conc. nitric acid is added, and the mixture is heated for fifteen minutes on the steam bath. Thirty milliliters of water are added to the hot mixture after which it is cooled in an ice-water bath. The solid acid is separated by filtration and dried at 70° to constant weight. The yield is quantitative.

After a single crystallization from water the acid when dried to constant weight gives a correct analysis.

Anal. Calcd. for $C_4H_3O_3N_3$; C, 27.8; H, 1.8.

Found  C, 27.5; H, 2.0.

Titration Curve for Dilituric Acid.-A solution of 0.2317 g. of thrice crystallized anhydrous dilituric acid in 150 ml. of distilled water was titrated with 0.1042 $\underline{N}$ sodium hydroxide at 21° using a Beckman pH Meter (glass electrode) for determing the pH of the solution. The adjustment of the pH Meter was checked with standard buffer solutions at the time of use. The results so obtained are recorded in Table III and are shown graphically in Fig. I.

Table I

Inorganic Salts of Dilituric Acid

| Diliturate | Mol.Wt. | Analysis Calcd. | Found | Solubility[g] g./l. | Moles/l. | Appearance |
|---|---|---|---|---|---|---|
| Magnesium | 476.5[f] | Mg; 5.04 | 5.05 | 0.47 | 0.00099 | Thin rectangular plates |
| Barium | 517.5[c] | Ba; 26.55 | 26.43 | 0.66 | 0.00127 | Sandy powder |
| Strontium | 442.7[a] | Sr; 19.77 | 19.72 | 0.74 | 0.00171 | Platelets |
| Copper | 461.7[d] | Cu; 13.78 | 13.80 | 0.82 | 0.00176 | Pale green needles |
| Potassium | 211.1 | K; 18.52 | 18.40 | 0.82 | 0.00388 | Rhombic prisms |
| Calcium | 402.2[b] | Ca; 9.94 | 9.84 | 2.39 | 0.00570 | Needles |
| Silver | 352.0[e] | Ag; 30.60 | 30.60 | 4.40 | 0.01250 | Feathery platelets |
| Sodium | 195.0 | Na; 11.78 | 11.65 | 7.40 | 0.0379 | Needles or Prisms |

[a] Hemihydrate      [d] Trihydrate      [g] In water at 25°

[b] Monohydrate      [e] Tetrahydrate

[c] Dihydrate      [f] Hexahydrate

TABLE II

Organic Salts of Dilituric Acid

| Diliturate Base | Mol.Wt. | Analysis | | | | Solubility[h] | | Appearance |
| | | Calcd. | | Found | | g./l. | Moles/l. | |
| | | C | H | C | H | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Simple Amines** | | | | | | | | |
| Ethylene diamine[g] | 406.2 | 29.6 | 3.5 | 29.8 | 3.6 | 0.24 | 0.0006 | Crystalline Powder |
| Ammonia | 190.1 | 25.3 | 3.2 | 25.3 | 3.3 | 1.38 | 0.0075 | Fine flakes |
| Ethylamine | 218.1 | 33.0 | 4.6 | 33.1 | 4.2 | 2.84 | 0.0130 | Needles |
| Dimethylamine | 218.1 | 33.0 | 4.6 | 33.0 | 4.6 | 3.70 | 0.0145 | Crystalline powder |
| Phenylisopropylamine | 326.2[b] | 47.8 | 5.5 | 47.7 | 5.6 | 4.84 | 0.0147 | Yellow needles |
| n-Butylamine | 246.1 | 39.0 | 5.7 | 39.1 | 5.9 | 4.05 | 0.0165 | Scales |
| n-Amylamine | 260.2 | 41.6 | 6.2 | 41.8 | 5.8 | 6.19 | 0.0238 | Scales |
| Aniline | 266.1 | 45.1 | 3.8 | 45.2 | 4.1 | 6.93 | 0.0260 | Rectangular plates |
| Methylamine | 204.1 | 29.4 | 3.9 | 29.2 | 3.9 | 7.49 | 0.0367 | Crystalline powder |
| Tri-n-butylamine | 358.3 | 53.6 | 8.4 | 53.3 | 8.5 | 18.11 | 0.0506 | Rectangular prisms |
| **Simple Heterocyclic Bases** | | | | | | | | |
| Quinoline | 302.1 | 51.7 | 3.3 | 51.8 | 3.6 | 6.89 | 0.0228 | Yellow needles |
| Imidazole | 242.1 | 34.8 | 2.9 | 34.9 | 3.0 | 8.70 | 0.0359 | Long rectangular prisms |

TABLE II cont.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pyridine | 252.1 | 42.8 | 3.2 | 42.6 | 3.2 | 13.65 | 0.0542 | Stout prismatic needles |
| d(+)Glucobenzimidazole | 441.3 | 43.6 | 4.3 | 43.8 | 4.6 | 28.69 | 0.0652 | Colorless needles |
| Morpholine | 260.1 | 36.9 | 4.7 | 36.6 | 4.9 | 20.80 | 0.0800 | Platelets |

## Alkanolamines

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| dl-Ephedrine | 338.2 | 49.7 | 5.3 | 49.4 | 5.3 | 2.94 | 0.0087 | Pale yellow platelets |
| b-Hydroxyphenyl-ethylamine | 319.2[a] | 45.3 | 4.7 | 45.4 | 4.8 | 4.01 | 0.0126 | Flat spears |
| l-Ephedrine | 338.2 | 49.7 | 5.3 | 49.8 | 5.5 | 10.3 | 0.0303 | Pale yellow platelets |
| d-Pseudoephedrine | 365.2[c] | 46.1 | 5.8 | 45.9 | 5.8 | 11.7 | 0.0320 | Pale yellow leaves |
| l-Ephinephrine | 374.2[b] | 41.8 | 4.8 | 42.1 | 4.6 | 13.7 | 0.0365 | Buff flakes |
| Ethanolamine | 234.1 | 30.8 | 4.3 | 31.0 | 4.2 | 12.5 | 0.0534 | Rectangular plates |
| d-Glucosamine | 387.2[d] | 31.0 | 5.2 | 31.0 | 5.0 | 32.9 | 0.0849 | Fine white needles |
| Triethanolamine | 322.2 | 37.3 | 5.6 | 37.4 | 5.7 | 42.4 | 0.132 | Colorless prisms |
| 1-Amino-2-hydroxy-propane | 248.1 | 33.9 | 4.9 | 34.1 | 4.8 | 33.2 | 0.134 | Fine flakes |

## Alkaloids

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Quinine[g] | 697.3[c] | 48.2 | 4.4 | 48.2 | 4.4 | 1.28 | 0.0016 | Rectangular plates |
| Brucine[g] | 812.4[f] | 45.8 | 5.0 | 45.5 | 5.2 | 3.04 | 0.0037 | Rectangular plates |
| Strychnine[g] | 734.4[e] | 47.5 | 4.6 | 47.6 | 5.0 | 2.84 | 0.0039 | White needles |

TABLE II cont.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Cinchonine[g] | 658.3[b] | 49.2 | 4.6 | 49.4 | 4.7 | 6.19 | 0.0090 | Microscopic needles |
| Cinchonidine[g] | 658.3[b] | 49.2 | 4.6 | 49.1 | 4.7 | 6.71 | 0.0102 | Crystalline powder |
| Nicotine[g] | 508.2 | 42.5 | 4.0 | 42.2 | 4.3 | 6.23 | 0.0123 | Felted needles |
| Caffein | 385.2[b] | 37.5 | 3.9 | 37.8 | 4.0 | 26.2 | 0.068 | Pale yellow plates |

Amino Acids

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| l-Diiodotyrosine | 606.0 | 25.7 | 2.0 | 25.4 | 2.1 | 1.32 | 0.0022 | Cream colored powder |
| dl-Lysine[g] | 492.2 | 34.1 | 4.1 | 34.2 | 4.1 | 3.12 | 0.0064 | Pale yellow scales |
| l-Histidine[g] | 5ol.2 | 33.6 | 3.4 | 33.4 | 3.2 | 3.97 | 0.0079 | Fine needles |
| l-Lysine[g] | 492.2 | 34.1 | 4.1 | 34.1 | 4.3 | 4.40 | 0.0090 | Sandy crystals |
| l-Tyrosine | 372.2[b] | 41.9 | 4.3 | 42.1 | 4.4 | 3.73 | 0.0100 | Needles |
| l-Arginine | 347.2 | 34.6 | 4.9 | 34.5 | 4.8 | 3.54 | 0.0102 | Fine needles |
| l-Cystine | 586.3 | 28.7 | 3.1 | 28.4 | 3.1 | 8.56 | 0.0146 | Stout needles |
| dl-Phenylalanine | 356.2[b] | 43.8 | 4.5 | 43.5 | 4.6 | 5.70 | 0.0160 | White needles |
| dl-$\alpha$-Aminoiso-butyric acid | 276.1[b] | 32.6 | 4.8 | 32.6 | 4.8 | 5.41 | 0.0196 | Flat needles |
| l-Tryptophane | 337.2 | 47.7 | 4.0 | 47.4 | 4.2 | 7.54 | 0.0200 | Fine needles |
| dl-$\alpha$-Aminophenyl acetic acid | 324.1 | 44.4 | 3.7 | 44.3 | 3.4 | 8.94 | 0.0276 | Rhombic prisms |

TABLE II cont.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Sarcosine | 262.1 | 31.2 | 3.8 | 31.4 | 4.0 | 8.83 | 0.0337 | Long white needles |
| Betaine | 290.1 | 37.2 | 4.8 | 36.9 | 4.8 | 9.93 | 0.0342 | Fine needles |
| dl-$\alpha$-Amino-n-butyric acid | 294.2[b] | 32.6 | 4.8 | 32.6 | 4.9 | 11.6 | 0.0395 | Plates |
| l-Alanine | 281.1[b] | 30.0 | 4.3 | 30.0 | 4.3 | 13.3 | 0.0430 | Felted needles |
| Glycine | 248.1 | 29.0 | 3.3 | 28.8 | 3.5 | 12.1 | 0.0487 | Pale yellow plates |
| dl-Alanine | 281.1[b] | 30.0 | 4.3 | 30.1 | 4.3 | 14.0 | 0.0504 | Fine needles |
| dl-Aspartic acid | 306.1 | 31.3 | 3.3 | 31.5 | 3.6 | 18.6 | 0.0607 | Crystalline powder |
| l-Glutamic acid | 320.1 | 33.7 | 3.8 | 33.6 | 4.0 | 21.0 | 0.0666 | Crystalline powder |
| dl-$\beta$-Amino-n-butyric acid | 276.1 | 34.7 | 4.4 | 34.5 | 4.5 | 21.1 | 0.0765 | Scales |
| dl-Glutamic acid | 320.1 | 33.7 | 3.8 | 33.7 | 3.8 | 28.8 | 0.0898 | Cottony crystals |
| l-Cysteine | 303.2[a] | 27.3 | 3.6 | 27.6 | 3.5 | 28.0 | 0.0924 | Radiating needles |
| l-Aspartic acid | 306.1 | 31.4 | 3.3 | 31.5 | 3.7 | 28.6 | 0.0936 | Radiating needles |
| dl-Leucine | 304.2 | 39.4 | 5.3 | 38.9 | 5.1 | 28.6 | 0.0942 | White crystals |
| l-Proline | 288.1 | 37.5 | 4.2 | 37.3 | 4.3 | 28.9 | 0.100 | Pale yellow scales |
| l-Asparagine | 305.1 | 31.5 | 3.6 | 31.4 | 4.0 | 31.4 | 0.103 | White crystals |
| l-Leucine | 322.2[b] | 37.3 | 5.6 | 37.2 | 5.7 | 33.9 | 0.105 | Matted needles |

TABLE II cont.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| dl-Valine | 290.1 | 37.3 | 4.8 | 37.5 | 4.8 | 31.0 | 0.1067 | White crystals |
| dl-Isoleucine | 304.2 | 39.4 | 5.3 | 39.3 | 5.4 | 32.7 | 0.107 | Stout needles |
| dl-Norleucine | 304.2 | 39.4 | 5.3 | 39.7 | 5.4 | 35.0 | 0.109 | Minute plates |
| dl-Norvaline | 290.1 | 37.3 | 4.8 | 37.4 | 4.9 | 32.0 | 0.110 | Rosettes of needles |
| dl-Methionine | 331.2 | 25.7 | 2.0 | 25.4 | 2.1 | 37.2 | 0.112 | Yellow plates |
| dl-Serine | 278.1 | 30.2 | 3.6 | 29.9 | 3.6 | 31.2 | 0.112 | Thin Plates |
| l-Hydroxyproline | 304.1 | 35.6 | 4.0 | 35.9 | 4.2 | 42.8 | 0.141 | Yellow scales |

### Proteinogenic Amines

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Guanidine | 232.1 | 25.9 | 3.5 | 26.0 | 3.1 | 1.59 | 0.0069 | Needeles |
| Tyramine | 310.2 | 46.5 | 4.5 | 46.7 | 4.6 | 2.76 | 0.0087 | Hexagonal plates |
| Histamine | 284.1 | 38.1 | 4.2 | 38.3 | 4.4 | 4.87 | 0.0171 | Long Needles |
| Phenylethylamine | 303.2[a] | 47.6 | 5.0 | 47.9 | 4.8 | 5.77 | 0.0190 | Needles |
| Creatinine | 286.1 | 31.6 | 4.0 | 31.8 | 4.0 | 6.70 | 0.0230 | Crystalline powder |
| Urea | 233.1 | 25.7 | 3.0 | 25.5 | 3.1 | 8.46 | 0.0363 | White powder |

[a] Hemihydrate
[b] Monohydrate
[c] Sesquihydrate
[d] Dihydrate
[e] Trihydrate
[f] Tetrahydrate
[g] Diacid salt
[h] In water at 25

<u>Preparation of the Diliturates</u>.- A solution of 5 milli-
moles of dilituric acid and 5 millimoles of the base* (2.5
millimoles for a diacid base), or one of its soluble salts,
was prepared in the minimum amount of boiling water; the solution
was filtered and allowed to cool to room temperature.  The re-
sulting salts, which in general were distinctly crystalline,
were separated by filtration and dried in a vacuum desiccator
over concentrated sulfuric acid.  Thses salts were crystalliz-
ed one or more times before determining their composition and
solubility.  In common with many organic salts the diliturates
of many of the bases investigated do not have satisfactory
melting points.

<u>Determination of the Solubilities</u>.- It was necessary to
carry out the solubility measurements on a small scale in order
to prevent the cost of the investigation from becoming excessive,
since some of the bases cost in excess of four dollars per gram.
Preliminary tests made on glycine diliturate indicated that
reasonable accurracy could be obtained by use of a 10.00 ml.
portion of the saturated solution.  Furthermore, when equilib-
rium was approached from both the supersaturated and the un-
saturated side the results were in agreement within the limit
of error of the weighing operations.

The solubility vessel, shown in Fig. 2, was so designed
as to minimize errors resulting from lack of thermal and solute-
solution equilibrium.  At no time does the solution come in
contact with anything but Pyrex glass in this type of tube.

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* We wish to thank Dr. G. Alles for supplying a number of
the alkanol and proteinogenic amines.

## Table III

### Titration Data for Dilituric Acid

| Vol. in ml. of 0.1042 N NaOH added. | Base/Acid Ratio | pH of Solution |
|:---:|:---:|:---:|
| 0.00 | 0.00 | 2.03 |
| 1.00 | .077 | 2.07 |
| 1.99 | .155 | 2.10 |
| 3.00 | .233 | 2.18 |
| 5.00 | .388 | 2.29 |
| 7.00 | .544 | 2.44 |
| 8.00 | .622 | 2.53 |
| 10.01 | .778 | 2.79 |
| 11.00 | .855 | 3.01 |
| 12.00 | .933 | 3.40 |
| 13.00 | 1.01 | 7.86 |
| 14.00 | 1.09 | 9.27 |
| 15.00 | 1.17 | 9.58 |
| 16.00 | 1.24 | 9.75 |
| 18.00 | 1.40 | 10.04 |
| 20.00 | 1.55 | 10.27 |
| 22.00 | 1.71 | 10.46 |
| 24.00 | 1.86 | 10.67 |
| 26.00 | 2.02 | 11.15 |

Titration Curve for Dilituric (5-Nitrobarbituric) Acid
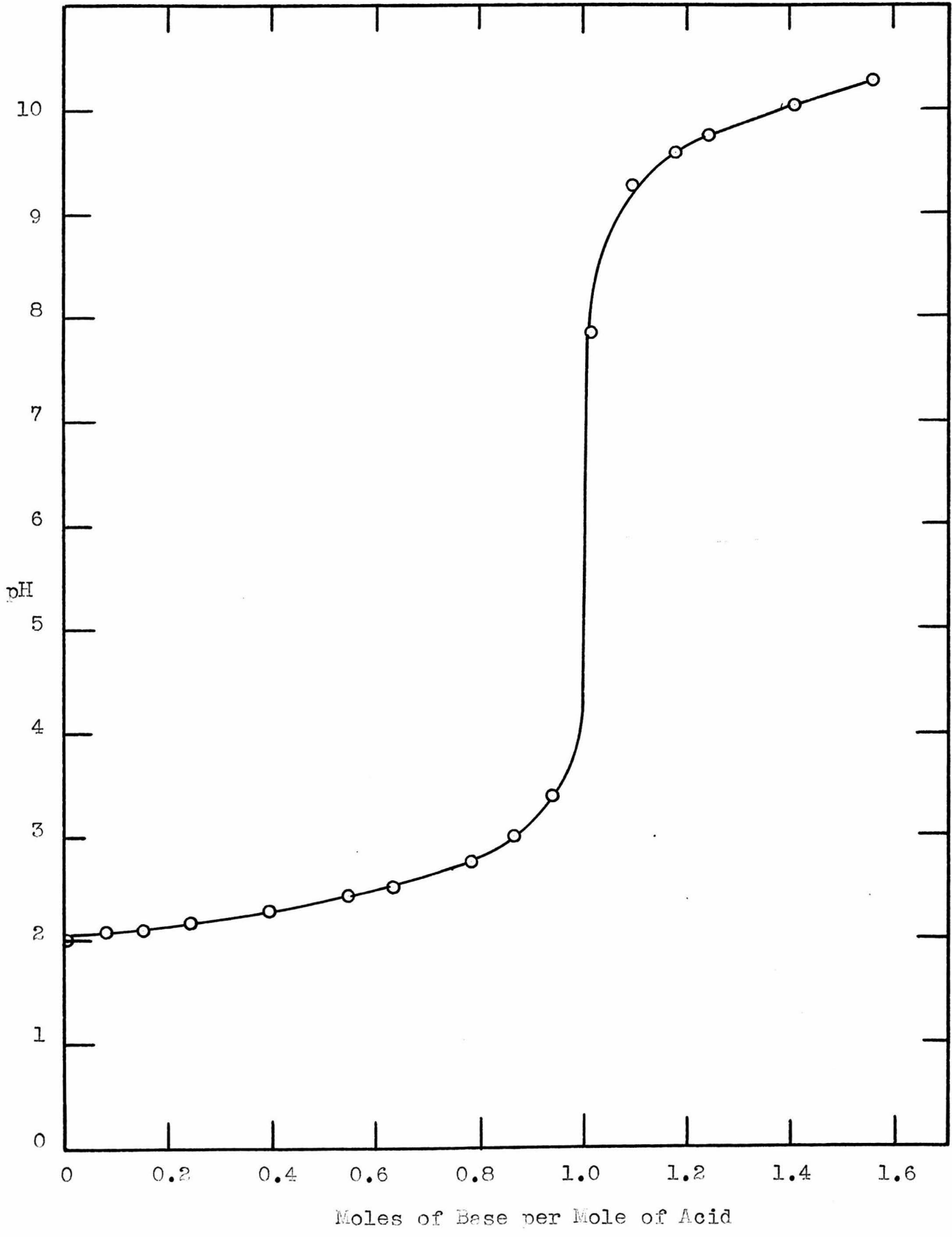


Moles of Base per Mole of Acid

Fig. 1

When in the thermostat the portion containing the solution
undergoing equilibration is 10 to 12 cm. below the surface of
the water in the thermostat, thus lessening errors from thermal
disturbances at the immediate surface of the thermostat bath.
The tube and its contents were periodically rocked through an
angle of 120° about an axis normal to the plane containing
the three arms of the vessel and passing through a point 5 cm.
to the right of the stopper. This motion brought about effect-
ive agitation of the solute in the solution.

In view of the previously mentioned considerations, and
since in this investigation a high degree of accurracy was not
necessary, only a single determination was made for each com-
pound reported. Saturated solutions were always approached from
the supersaturated side by placing samples saturated at 40-50°
and containing an excess of the solid phase in a thermostat
maintained at $25.0\pm 0.3°$. Forty-eitht or more hours were
allowed for the attainment of equilibrium in every case. A
10.00 ml. aliquot was withdrawn by sucking the solution thru
a suitable filter, Fig. 3, attached to a calibrated 10 ml.
pipette. Crystal clear solutions were secured in all cases.
The aliquot was evaporated to dryness at 80° and the residue
was weighed. The composition of the solid phase was determined
by drying the salts at 80° and analyzing for carbon and hydrogen.
The solubilites of the various diliturates, in water at 25°,
are given in Tables I and II, and those of dilituric acid,
in a number of different solvents at 25°, in the text.

The Analysis of Diliturates.- The determination of carbon
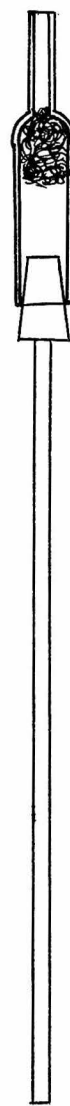and hydrogen was conducted on a semi-micro sacle with the

Solubility Tube

Pipette Filter
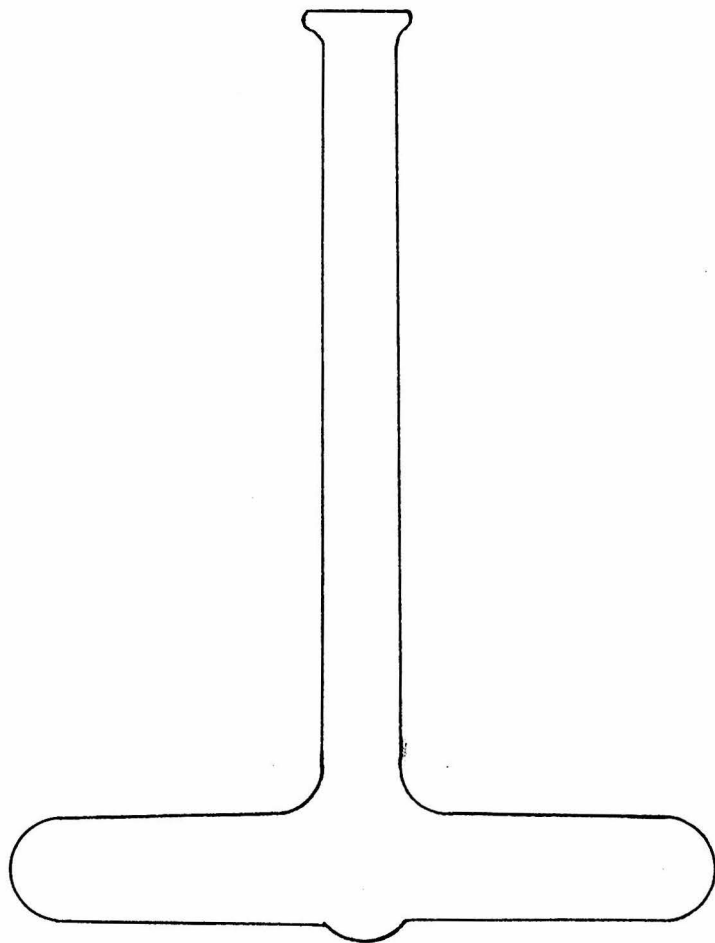


Actual Size

2/3 Actual Size

Fig. 2

Fig. 3

following combustion tube filling. A 12-13 mm. (O.D.) combustion tube constricted to a capillary at one end was charged, in the order named, with 1.5 cm. of silver wool, 0.5 cm. of asbestos, 3.0 cm. of lead peroxide, 0.5 cm. of asbestos, 2.0 cm. of silver wool, 1.0 cm. of asbestos, 3.0 cm. of 10% platnized asbestos (choking plug), 20.0 cm. of copper oxide wire and 4.0 cm. of 10% platnized asbestos. During an analysis the first 9.0 cm. of the tube, measured from the constricted end, was maintained at 200° and the remaining 25.0 cm. at 600°. The sample was mixed with 2-3 times its weight of copper oxide prior to ignition.

Recovery of Glycine from its Diliturate.- To 8.4 g. of glycine diliturate in 100 ml. of hot water were added 3 ml. of 15 N ammonium hydroxide. A precipitate of ammonium diliturate formed immediately. The solution was cooled to room temperature, the precipitate removed and the filtrate evaporated to 20 ml. Upon adding 100 ml. of ethanol to the concentrate glycine began to precipitate. After cooling to 5° the pure white product was recovered and dried in vacuo. The weight was 2.30 g. or 89% of the theoretical amount.

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# SUMMARY

Part I.      Improved methods have been described for the preparation of melon, potassium and sodium melonate, potassium and sodium cyamelurate, and cyameluric acid.  Cyameluric acid has been shown to form a group of compounds entirely analogous to those of cyanuric acid.

The existance of a trichloride and an oxygen ester indicate that hydroxyl groups are present in the molecule of cyameluric acid.

The analogy with cyanuric compounds and the presence of hydroxyl groups substantiate the planar ring structure of cyameluric acid proposed by Pauling and Sturdivant.

Melam is probably dicyanurylimide and melem, cyameluryl triamide.

It is proposed that melon is a condensation product of cyameluryl triamide, and that the resulting very large molecules are planar cyameluryl rings joined through nitrogen atoms.
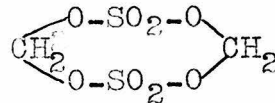
Part II.     A number of salts of dilituric acid (5-nitrobarbituric acid) have been prepared and a study of their properties has shown that dilituric acid is a satisfactory reagent for the isolation and determination of many organic and inorganic bases.

# PROPOSITIONS.

1. Runde, Scott and Johnson (J. Am. Chem. Soc., __52__, 1284 (1930)) likewise Reichstein and Zschokke (Helv. Chim. Acta, __15__, 1124 (1932)) observed that when the nitrile resulting from the treatment of alpha-furfuryl chloride with sodium cyanide is hydrolyzed the expected 2-furyl acetic acid was not obtained, but instead 5-methylfuroic acid was the main product. The anomaly is best explained as a type of allylic rearrangement. A similar rearrangement is predicted whenever the chlorine in alpha furfuryl chloride is replaced by a group R when the replacement process is essentially ionic.

2. The stable sulfur dithiocyanate, $S(SCN)_2$, of Bond and Weaver (J. Am. Chem. Soc., __60__, 2614 (1938) is predicted to be a derivative of thiocyanuric acid. The monomeric $S(SCN)_2$ has probably polymerized to polymers containing the cyanuric nucleus.

3. The substance extracted from the cotyledons of young Raphanus (var. French Breakfast) plants causing positive curvature in the Avena test is a true hormone.

4. The structure $CH_2 \langle {}^{O}_{O} \rangle SO_2$ for methylene sulfate explains the known chemical and physical properties of the compound more satisfactorily than does the structure $CH_2 \langle {}^{O-SO_2-O}_{O-SO_2-O} \rangle CH_2$ recently proposed by Baker (J. Chem. Soc., 86 (1932)).

5. The most effective method for teaching Organic Analyses would be to make it a year course with the portion dealing with quantitative determinations _preceding_ the portion dealing with qualitative determinations.

6. The substance from the Raphanus cotyledon which gives a positive curvature in the Avena test is probably an ester of one of the auxins.

7. The cyanuric bisulfide of Klason (J. prakt. Chem., (2), _33_, 120 (1886)) may have a cage-like structure of the type
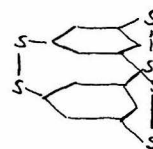
8. In opposition to the statement of Lassiter there is considerable evidence which may be interpreted as evidence for the existance of a weak hydrogen bond of the type S-H--X.

9. The 2- and 4-monohydroxypyridines cannot be adacuately represented by any single structure.

10. The relative amounts of isomers, ortho-para compared to meta, formed in a substituted benzene, $R\bigcirc$ , when a second group $R'$ is introduced should show a dependence upon the proton activity of the reaction mixture when $R$ is $COOH$, $CHO$, $CN$, $NH_2$, $OH$, and similar groups. The direction of shift in the ratio ortho-para/meta is predictable for each group.

11. The mechanism for the addition of silver iodobenzoate, $IAg(COOC_6H_5)_2$, to the ethylenic double bond forming a glycol dibenzoate involves (1) addition of $I^+$ and $Ag(COOC_6H_5)_2^-$ to

the double bond, (2) elimination of silver benzoate, and (3) replacement of iodine by benzoate with the formation of silver iodide.

12. A modification and extension of the mechanism for the formation of the butenes from 2,3-dibomobutane proposed by Winstein, Pressman and Young (J. Am. Chem. Soc., 61, 1645 (1939)) explains more facts than are explained by the unabridged theory. The modification involves the contribution from a quasi-ionic resonance form of the dibromide molecule.

Respectfully submitted

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August 4, 1939.