fluorene and fluorene under the same conditions gave a 60% yield of 9-phenylfluorene-9-carboxylic acid. In both of these cases the crude acids appeared to be quite pure. They were identified by mixed melting point determinations and by determining the equivalent weight by titration with alkali. When phenylfluorene and phenylacetylene were used, however, the isolated acid was clearly a mixture. The equivalent weight (by titration) was found to be 181 (calcd. for phenylacetylene acid 146, for the fluorene derivative 286). The mixture was separated by fractional crystallization into the pure fluorene acid (identified by mixed melting points and equivalent weight determinations), and an impure phenylpropiolic acid. Similarly phenylfluorene and indene yielded a crude acid (first separating as an oil) melting at 90–100° with an equivalent weight of 217 (calcd. for the phenylfluoryl acid 286, for the indene acid, 160). Phenylacetylene and indene also yielded a mixture of acids as judged by the melting point 95–105°. The equivalent weight determination is here of little value; the calculated equivalent weights are 160 and 146; the value found was 161.

Summary

1. The interaction of twelve extremely weak acids and the corresponding sodium or potassium compounds has been studied in anhydrous ether. From the results of these metatheses, it is possible to arrange the acids in a scale of increasing strength. The use of this scale in estimating the strength of other very weak acids is illustrated by a consideration of aniline.

2. The rates of interaction of certain phenylated hydrocarbons and the corresponding sodium derivatives have been estimated at several different temperatures.

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ALIPHATIC AMMONO ALDEHYDES[1]

BY HAROLD H. STRAIN

The aromatic imines, hydramides and Schiff's bases undergo many reactions which support the view that these substances are aldehydes of an ammonia system of compounds.[2] It is to be expected, therefore, that similar aliphatic nitrogen compounds should exhibit reactions characteristic of aliphatic aldehydes.

A search of the literature revealed to our surprise that but few aliphatic imines and hydramides are known. Subsequent experiments demonstrated that conditions conducive to the formation of aromatic ammono aldehydes did not necessarily promote the formation of the corresponding aliphatic compounds. Our present knowledge of the occurrence of the common aliphatic ammono aldehydes is summarized in Table I.

TABLE I

ALIPHATIC AMMONO ALDEHYDES*

| Aldehyde	Imine	Hydramide	Schiff's bases
Formaldehyde[a]	Unknown	Unknown	Known
Acetaldehyde[b]	Known	?	Known
Chloral[c]	Known	Unknown	Known
Propionaldehyde[d]	Unknown	Unknown	Known
Butyraldehyde[e]	Unknown	Unknown	Known
Isobutyraldehyde[f]	?	Known	Known
Heptaldehyde[g]	Unknown	?	Known

* Compare Beilstein, "Handbuch der organischen Chemie," 4te. Aufl. Bd. I: [a] p. 583; [b] p. 607; [c] p. 624; [d] p. 630; [e] p. 663; [f] p. 674; [g] p. 697.

All the aliphatic ammono aldehydes, particularly the Schiff's bases, undergo characteristic aldehyde reactions such as hydrolysis to the corresponding aquo aldehydes and formation of addition compounds with bisulfites and hydrocyanic acid.[2] Aliphatic Schiff's bases also form condensation products[3] which we regard as ammono aldol-acetals, as shown by the following equation.[4]

$$2CH_3CH=NC_6H_5 \longrightarrow \begin{array}{c} CH_3CH-NHC_6H_5 \\ | \\ CH_2CH=NC_6H_5 \end{array}$$

Ammono aldehyde-acetal   Ammono aldol-acetal
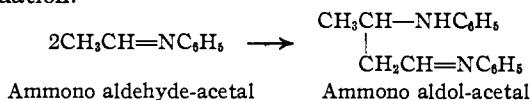
In addition to the known reactions of the aliphatic imines, hydramides and Schiff's bases we have found that such substances undergo ammonolysis, reduction, nitridation, polymerization, depolymerization and condensation reactions. These reactions support the view that such substances are aliphatic ammono aldehydes.

When aldehyde ammonia is heated[5] or when aldehydes and alcoholic ammonia are heated,[6] pyridine derivatives are formed, particularly the 2,3,5-trisubstituted pyridines. Thus aldehyde ammonia forms 2-methylpyridine; propionaldehyde, 2-ethyl-3,5-dimethylpyridine; and butyraldehyde, 2-propyl-3,5-diethylpyridine. The formation of these substances may be explained reasonably as follows, assuming a complex ammono aldol to be formed which subsequently loses ammonia and hydrogen.
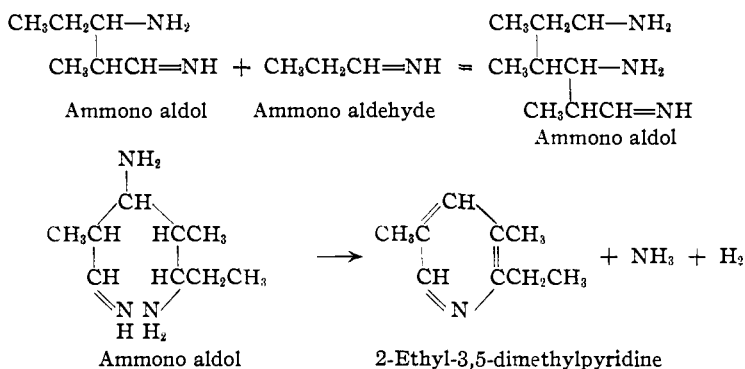
$$CH_3CH_2CH=NH + CH_3CH_2CH=NH = CH_3CH_2CH-NH_2$$

Ammono aldehyde   Ammono aldehyde $\begin{array}{c} | \\ CH_3CHCH=NH \end{array}$
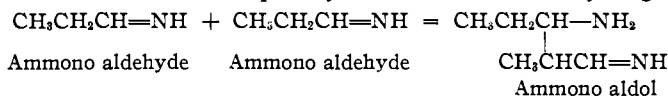
Ammono aldol

[3] (a) Schiff, Ann., Suppl., 3, 343 (1864); (b) Miller, Plöchl and Eckstein, Ber., 25, 2029 (1892); (c) Miller, ibid., 25, 3072 (1892); (d) Schiff, Ann., 140, 129 (1866); ibid., 210, 127 (1881).

[4] These substances are ammono aldol-acetals in the same sense that the analogous aromatic compounds are ammono benzoin-acetals.[2e]

[5] Dürkopf and Schlaugk, Ber., 21, 297 (1888).

[6] (a) Waage, Monatsh., 4, 724 (1883); (b) Dürkopf and Göttsch, Ber., 23, 685 (1890); (c) Tschitschibabin, Chem. Zentr., [I] 77, 1439 (1906); (d) Schiff, Ann., Suppl., 3, 343 (1864).

$$CH_3CH_2CH-NH_2 \qquad\qquad CH_3CH_2CH-NH_2$$

$$CH_3\overset{|}{C}HCH=NH + CH_3CH_2CH=NH \rightleftharpoons CH_3\overset{|}{C}HCH-NH_2$$

Ammono aldol   Ammono aldehyde $CH_3\overset{|}{C}HCH=NH$

                                              Ammono aldol

Ammono aldol   2-Ethyl-3,5-dimethylpyridine

Experimental evidence indicates that aquo ammono aldols containing one oxygen atom rather than ammono aldols are intermediates in this reaction. As will be shown in the experimental part the higher normal aliphatic aldehydes react with liquid ammonia to form aquo ammono aldols rather than imines or hydramides. It should be pointed out, however, that these aquo ammono aldols may contain nitrogen and oxygen in variable proportions and in different positions in the molecule, depending upon whether aquo or ammono aldehydes first enter the reaction. Further support of this reaction mechanism is afforded by the reaction of iso-butyraldehyde in liquid ammonia. As is well known, isobutyraldehyde resembles the aromatic aldehydes in that it undergoes intermolecular oxidation and reduction when treated with alkalies (Canizzaro reaction). Accordingly one should expect this substance to form an imine or an hydramide in liquid ammonia solution rather than an aldol and such has been found to be the case. Although the above mechanism indicates that hydrogen should be produced, we have been unable to detect it. Whether the aldols or dihydropyridines are dehydrogenated by complex organic compounds present in the mixture is problematical.

Experimental

Methylene Imine.—Reactions which should lead to the formation of methylene imine invariably produce hexamethylenetetramine.[7] According to Franklin [2a] this reaction probably takes the following course[8]

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[7] Butlerow, *Ann.*, **116**, 322 (1860); Höland, *Ann.*, **240**, 225 (1887).

[8] Many reactions, as well as the crystal analysis, support the structure given above for hexamethylenetetramine [Duden and Scharff, *Ann.*, **288**, 218 (1895); Dickinson and Raymond, This Journal, **45**, 22 (1923)] which is to be regarded as a polymerized ammonoformaldehyde. Nevertheless a few investigators [Harvey and Baekeland, *Ind. Eng. Chem.*, **13**, 134 (1921); Marotta and Alessandrini, *Gazz. chim. ital.*, **59**, 942 (1929)] believe certain reactions indicate the presence of double bonds in the molecule. Yet it should be noted that such reactions are always carried out in the presence of solvents or reagents which cause the depolymerization or solvolysis of the hexamethylenetetramine. If hexamethylenetetramine does contain double bonds,

$$3CH_2=NH \longrightarrow CH_2=N—CH_2—N=CH_2 + NH_3$$
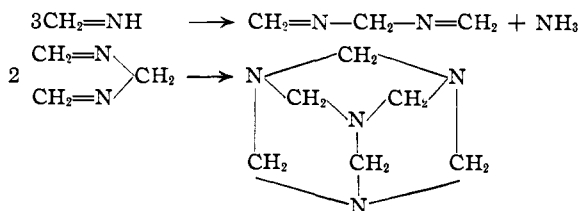
In view of the fact that benzylidene imine is stable in liquid ammonia solution,[2b] attempts to prepare methylene imine from methylene chloride in liquid ammonia solution were made with the surmise that the free imine might not lose ammonia to form hexamethylenetetramine. The methylene chloride, which was only slightly soluble in liquid ammonia at room temperature, showed no sign of reacting after standing for 24 hours. Upon heating the solution to 180° for two hours the methylene chloride dissolved, forming hexamethylenetetramine which separated from the solution in large colorless crystals. These crystals are only slightly soluble in liquid ammonia at room temperature.

Hexamethylenetetramine.—In trying to depolymerize hexamethylenetetramine we passed the vapors through an evacuated glass tube which was heated to redness without producing any change. Soda-lime placed in the tube caused no depolymerization or decomposition to take place. Dilution of the vapors with ammonia gas also proved to be without effect.

When hexamethylenetetramine is heated with liquid ammonia at 210° for eighteen hours no ammonation takes place, although the small crystals which are used originally are converted into large hexagonal crystals which decrepitate upon heating or upon dissolving in water and alcohol. The addition of aniline or potassium amide to the solution does not cause reaction to take place during the heating.

Hexamethylenetetramine is not nitridized by a solution of iodine in liquid ammonia at −33°, nor by hydrazoic acid in liquid ammonia at 260–270° for twelve hours. The marked stability of hexamethylenetetramine toward metallic nitrides has been reported by Schurman and Fernelius.[9]

Anhydroformaldehyde Aniline.—Anhydroformaldehyde aniline (ammono formaldehyde-acetal) is but slightly soluble in liquid ammonia at room temperature. It is nitridized very slowly by a solution of iodine in liquid ammonia at −33°.

When anhydroformaldehyde aniline is permitted to stand in contact with liquid ammonia at room temperature for thirty-five days no reaction takes place. The addition of ammonium chloride to the solution is also without effect. On the other hand, 3.0 g. of the ammono aldehyde-acetal, 1 g. of ammonium chloride and 15 cc. of liquid ammonia were found to react when heated to 150–180° for twelve hours, producing a clear solution. When cooled and agitated this solution deposited 0.3 g. of transparent hexagonal crystals which proved to be hexamethylenetetramine. The free aniline in the mother liquor was identified by the furfural test.

Ethylidene Imine.—Delépine[10] reports that acetaldehyde ammonia is converted into ethylidene imine when permitted to stand over sulfuric acid in a desiccator evacu-

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then it should be hydrogenated with colloidal platinum and hydrogen. As a matter of fact, the writer was unable to effect such a reduction in aqueous or absolute alcohol solution using Adams' catalyst and hydrogen pressure of four atmospheres [cf. Pummerer and Hofmann, Ber., **56**, 1255 (1923)].

[9] Schurman and Fernelius, THIS JOURNAL, **52**, 2425 (1930).

[10] Delépine, Ann. chim., [7] **16**, 103 (1899).

ated with a water pump. He also demonstrated that ethylidene imine thus prepared was a trimer which could be completely dissociated by heating to 260°. The formation of ethylidene imine may be regarded as the dehydration of aquo ammono ortho acetaldehyde to ammono acetaldehyde while the polymerization and depolymerization of ethylidene imine is analogous to the formation and dissociation of paraldehyde.

Although Delépine does not state the exact pressure at which he dehydrated aldehyde ammonia, we have found that dehydrations performed at different pressures yield quite different results.[11] When the pressure is very low (less than 1 mm.), all the aldehyde ammonia volatilizes and is absorbed by the sulfuric acid. At slightly higher pressures (1–10 mm.) large cube-shaped, transparent crystals of ethylidene imine are formed but the yields are small (5–25%). At a pressure of 3 cm. a nearly quantitative yield of ethylidene imine is obtained in two to three days, particularly if the depth of the layer to be dehydrated is not over 1–2 cm. The crystals obtained at this pressure are small and opaque. They are readily soluble in pyridine, forming a clear solution. The crystals dissolve in cold glacial acetic acid forming a light yellow solution which becomes quite dark in color upon standing or upon gentle warming.

Because of the ease with which aldehyde ammonia is dehydrated with sulfuric acid we concluded that ethylidene imine should be formed when aldehyde ammonia is treated with a dehydrating agent in liquid ammonia. Although potassium amide caused the formation of dark condensation products, calcium amide was found to serve as a suitable dehydrating agent. The ethylidene imine is obtained in large transparent crystals by evaporating the ammonia solution after it has been decanted from the slightly soluble calcium hydroxide and excess calcium amide.

Monomolecular ethylidene imine was obtained as a clear mobile liquid at room temperature by heating the trimolecular form to 260°, then suddenly cooling the vapors. This reaction was accomplished by placing the polymerized compound in a glass bulb which was in turn connected to another bulb by means of a glass tube about 28 cm. long so arranged that the connecting tube could be heated to 260–270° while the receiver was immersed in liquid ammonia. After evacuating and sealing the system, the ethylidene imine was heated until it volatilized, when it slowly distilled through the hot tube, condensing as a clear mobile liquid in the cold receiver. This liquid failed to crystallize when seeded with the original crystals. After standing for several hours (sometimes several days were necessary) the liquid slowly polymerized to the crystalline trimmer. By alternately heating and cooling the bulbs of the apparatus the depolymerization could be repeated as often as desired. During the heating process no ammonia was liberated, indicating that monomolecular ethylidene imine does not lose ammonia to form hydracetamide, a reaction which one would predict from the behavior of benzylidene imine.[2b]

A solution of ethylidene imine in liquid ammonia was treated with an excess of iodine and the temperature maintained at 0° until the iodine color had completely disappeared. The clear solution was then evaporated to dryness and the residue taken up in water. This aqueous solution deposited a yellow picrate melting at 244–245°, the melting point of acetamidine picrate, when treated with an aqueous solution of picric acid. Attempts to identify cyanethine as a nitridation product of ethylidene imine were fruitless.

Ethylidene imine reacts with malonic acid in hot pyridine with the evolution of carbon dioxide just as aquo aldehydes do. This ammono acetaldehyde also reacts with 2,4-dinitrophenylhydrazine in anhydrous pyridine or alcohol to form acetaldehyde 2,4-dinitrophenylhydrazone and ammonia.

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[11] A good grade of aldehyde ammonia is easily obtained by recrystallizing commercial aldehyde ammonia from propyl or isopropyl alcohol.

Hydracetamide.—Both Schiff[12] and Strecker[13] found that an amorphous substance was produced when aldehyde ammonia was permitted to stand for long periods. Although the writer made many attempts to prepare this substance, no evidence for the formation of a pure compound was obtained. Pure aldehyde ammonia was found to be stable over long periods especially when preserved in sealed vessels in the dark. The ability of ethylidene imine to withstand heating without losing ammonia to form hydracetamide has already been commented on.

Propionic Aldehyde.—By heating propionaldehyde with ammonia,[6a] ammonium chloride,[14] or propionaldehyde ammonia[6b] 2-ethyl-3,5-dimethylpyridine has been obtained. That this reaction is dependent upon the formation of an intermediate aquo ammono aldol is shown by the following experiments.

Freshly distilled propionaldehyde was dissolved in liquid ammonia at room temperature and treated with a large excess of calcium amide. After twenty to thirty minutes the clear solution was decanted from the calcium hydroxide and excess calcium amide. The solvent was evaporated and the residue dried at 35° and 1 mm. pressure. The product was a colorless transparent viscous liquid.

Anal. Found: C, 64.0, 62.6; H, 12.3, 11.7; N, 18.4.

A second preparation in which the calcium amide treatment was omitted resulted in the formation of a similar viscous liquid.

Anal. Found: C, 62.6, 62.9; H, 11.7, 11.9; N, 16.8, 16.5.

Calcd. for	C, %	H, %	N, %
$CH_3CH_2CH{=}NH$	63.2	12.3	24.5
$(C_3H_6)_3N_2$	70.1	11.7	18.2
$CH_3CH_2CH(OH)NH_2$	48.0	12.0	18.7
$C_9H_{20}ON_2$	62.8	11.6	16.3

Both of the above products failed to produce propionaldehyde when warmed with aqueous hydrochloric acid. Upon distillation they decomposed, forming water, ammonia, and a high boiling substance. The absence of hydrogen was proved by distilling the preparations in a current of carbon dioxide, which was absorbed in dilute alkali. After two distillations a small quantity of material boiling at 195–200° was obtained; yields about 12%. A portion from each preparation formed a mercuric chloride compound which melted at 116–120°. The mercuric chloride compound of 2-ethyl-3,5-dimethylpyridine melts at 117–119°.[6b] The remaining portions from each high boiling fraction were combined and oxidized with a slight excess of 2% potassium permanganate solution at 60° for three days. After separating the manganese dioxide the acids in the filtrate were precipitated with copper sulfate. The copper salts were decomposed with hydrogen sulfide and after boiling and neutralization with sodium carbonate the acids were converted into the slightly soluble silver salts. After decomposing the silver salts with hydrogen sulfide, the solution was evaporated to dryness and the residue dissolved in the least possible quantity of hot water. Upon cooling crystals were obtained which melted at 316–318°. The melting point of pyridine 2,3,5-tricarboxylic acid is given as 318°[6b] and 323° with dec.[6c]

Butyric Aldehyde.—Butyric aldehyde reacts with liquid ammonia to form a slightly soluble clear viscous liquid and water. Calcium amide added to the solution removes the water but is apparently without effect upon the slightly soluble product. The solvent was evaporated and the product dried for two hours at 35° under 1 mm. pressure.

[12] Schiff, *Ann., Suppl.*, **6**, 1 (1868).

[13] Strecker, *ibid.*, **6**, 255 (1868).

[14] Plöchl, *Ber.*, **20**, 722 (1887).

Anal. Calcd. for $C_{12}H_{26}ON_2$: C, 67.3; H, 12.1. Found: C, 66.8, 66.8; H, 12.4, 12.4.

The material was not hydrolyzed to butyraldehyde when heated to 60° with 6 N hydrochloric acid. When distilled it formed water and ammonia (no hydrogen was formed) as well as a high boiling liquid. The latter, after two distillations, boiled at 245–250° at 763 mm.; yield 30%. Its density was 0.914 at 20°. It was soluble in aqueous hydrochloric acid but was not decomposed. Oxidized with 2% potassium permanganate at 60° for three and one-half days as described for the analogous compound obtained from propionaldehyde, we obtained a crystalline acid which melted at 317°. It is to be concluded that an aquo ammono aldol was formed which upon distillation gave rise to 2-propyl-3,5-diethylpyridine. The latter compound was obtained by Tschitschibabin upon heating butyraldehyde and alcoholic ammonia to 150° for fifty hours.[6c]

Isobutyraldehyde.—Isobutyraldehyde reacts with liquid ammonia to form a moderately soluble clear liquid. This liquid is much more mobile than the corresponding compounds obtained from butyraldehyde and unlike the latter it is rapidly hydrolyzed to isobutyraldehyde by dilute hydrochloric acid. A preparation which had been dried at −35° at 1 mm. pressure indicated the presence of ammonia or isobutylidene imine.

Anal. Calcd. for $C_3H_7CH=NH$: C, 67.6; H, 12.7; N, 19.7. Calcd. for $(C_3H_7-CH=)_3N_2$: C, 73.4; H, 12.2; N, 14.3. Found: C, 70.0, 70.2; H, 12.4, 12.4; N, 17.0.

Dried at 45° and 0.5 mm., the analysis approximated that of hydroisobutyramide.

Anal. Found: C, 73.0, 73.1; H, 12.0, 11.8; N, 14.0.

When heated rapidly the compound distilled at 150–155° at 760 mm. As its analysis was unchanged, it was evidently the same hydroisobutyramide isolated by Lipp as the distillation product of a compound $C_{28}H_{62}ON_6$ obtained in turn by the action of concentrated aqueous ammonia upon isobutyraldehyde.[15]

Heptaldehyde.—Heptaldehyde reacts with liquid ammonia to form a slightly soluble, viscous compound which is not hydrolyzed to heptaldehyde by aqueous acids. The analyses of this oil, dried at 45° at 1 mm., indicate the formation of an aquo ammono aldol.

Anal. Calcd. for $C_{21}H_{44}ON_2$: C, 74.1; H, 12.9; N, 8.2. Found: C, 73.8, 73.5; H, 12.6, 12.7; N, 8.5.

A similar liquid was obtained when an ether solution of heptaldehyde was saturated with ammonia. Both preparations gave off water and ammonia when distilled. The organic portion of the distillate boiled at 355–365°. This material was but slightly soluble in aqueous hydrochloric acid and was not hydrolyzed by the latter, indicating that it was not an hydramide as postulated by Schiff.[3] It was stable in liquid ammonia over long periods. It also failed to dissolve in a solution of potassium amide in liquid ammonia with the evolution of hydrogen, a reaction characteristic of aromatic hydramides.[2d] If heptaldehyde is analogous to propionic and butyric aldehydes in its reactions, we should expect this high-boiling compound to be 2-hexyl-3,5-dipentylpyridine. The reactions described above as well as the analysis support this structure. For analysis a 15-g. portion was distilled five times, each time the first and last 1 g. portions being discarded.

Anal. Calcd. for $C_{21}H_{37}N$: C, 83.2; H, 12.2. Calcd. for $C_{21}H_{42}N_2$: C, 78.3; H, 13.0. Found: (H. H. S.) C, 83.6, 82.8; H, 13.0, 12.9; (Schiff), C, 78.17; H, 13.13.

Attempts to oxidize the high-boiling fraction from heptaldehyde to a pyridine tricarboxylic acid with potassium permanganate gave negative results. As this com-

[15] Lipp, *Ann.*, **205**, 4 (1880).

pound is extremely hard to oxidize, the pyridinecarboxylic acid may have been destroyed during the oxidation.

The writer is indebted to Dr. E. C. Franklin for many helpful suggestions.

Summary

Evidence is presented to support the postulation that aliphatic imines, hydramides and Schiff's bases are ammono aldehydes. Aside from the known reactions which support this view, it is shown that (1) reactions which should lead to the formation of methylene imine (ammono formaldehyde) yield only hexamethylenetetramine (polymerized ammono formaldehyde), (2) anhydroformaldehydeaniline (ammono formaldehyde-acetal) is ammonolyzed to hexamethylenetetramine and aniline, (3) ethylidene imine (ammono acetaldehyde) is nitridized to acetamidine (ammono acetic acid), (4) ethylidene imine reacts with malonic acid and hydrazine derivatives just as aquo aldehydes do. The formation of pyridine derivatives from aldehydes and ammonia has been shown to be dependent upon the formation of aquo ammono aldols.

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STUDIES ON OXIDATION–REDUCTION. XVII[1] NEUTRAL RED

BY W. MANSFIELD CLARK AND MARIE E. PERKINS

Neutral red,[2] named *Toluylenroth* by its discoverer, Witt,[3] has become the best known of those azine dyes called eurhodines. Early in its history it was recognized as a valuable histological and vital stain; and, as has often happened when a dye is constantly available for such purposes, its several properties have been adapted to other biochemical applications. As an acid–base indicator neutral red is used in a range of P_H important biologically. As a reducible dye it has been employed by the bacteriologist and in a manner which will have a particular interest when we shall have described the characteristics of the oxidation–reduction system.

For the moment we are concerned with neutral red exclusively as an

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[1] Previous papers of this series have been published in *Public Health Reports* and *Supplements to Public Health Reports*, 1921–1931. The first ten articles have been republished as *Hygienic Laboratory Bulletin*, No. 151, United States Public Health Service. (Manuscript first received July 17, 1931.)

[2] Neutral red is dye No. 825 in Rowe's "Colour Index."

[3] Witt, *Ber.*, **12**, 931 (1879).