compound slowly precipitates out from the ether solution. This substance is readily freed from any traces of chloride or eugenol by treating with excess of ether, which readily dissolves either of the two substances. The red substance was carefully purified and analyzed. There was found: C, 55.78; H, 6.17; Cl, 14.42. Calculated for $C_{20}H_{24}O_4SCl_2$: C, 55.68; H, 5.57; Cl, 16.47; S, 7.42.

A determination of sulphur ran too high, giving results which at first led us to believe that the substance in hand was a dithio compound. Later experiments indicated, however, that the substance was not quite pure. The reaction is at the present time under further examination.

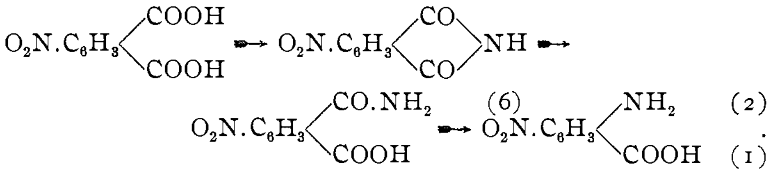
UNIVERSITY OF MINNESOTA.

[CONTRIBUTIONS FROM THE HAVEMEYER LABORATORIES, COLUMBIA UNIVERSITY, NO. 106.]

THE SYNTHESIS OF 5-NITRO-4-KETODIHYDROQUINAZOLINES FROM 6-NITRO-2-AMINOBENZOIC ACID, 6-NITRO-2-ACETYLAMINOBENZOIC ACID, AND FROM THE CORRESPONDING NITRO ACETYLANTHRANIL.[1]

BY MARSTON TAYLOR BOGERT AND VICTOR JOHN CHAMBERS.

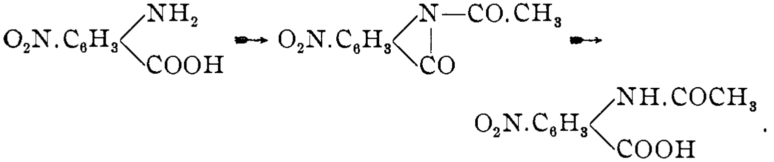
3-NITRO-*o*-PHTHALIC acid was converted into the imide, and the latter then changed to 3-nitrophthal-1-amic acid and to 6-nitro-2-aminobenzoic acid by the usual reactions with bromine and alkali:



$$O_2N.C_6H_3\left\langle\begin{matrix}COOH\\COOH\end{matrix}\right. \rightarrow O_2N.C_6H_3\left\langle\begin{matrix}CO\\CO\end{matrix}\right\rangle NH \rightarrow$$

$$O_2N.C_6H_3\left\langle\begin{matrix}CO.NH_2\\COOH\end{matrix}\right. \rightarrow \overset{(6)}{O_2N}.C_6H_3\left\langle\begin{matrix}NH_2\\COOH\end{matrix}\right. \begin{matrix}(2)\\(1)\end{matrix}.$$

By the action of excess of acetic anhydride upon this nitroanthranilic acid, the nitro acetylanthranil was obtained, which, by crystallization from boiling water, was hydrolyzed to the nitro acetylanthranilic acid:



$$O_2N.C_6H_3\left\langle\begin{matrix}NH_2\\COOH\end{matrix}\right. \rightarrow O_2N.C_6H_3\left\langle\begin{matrix}N-CO.CH_3\\ |\\ CO\end{matrix}\right. \rightarrow$$

$$O_2N.C_6H_3\left\langle\begin{matrix}NH.COCH_3\\COOH\end{matrix}\right..$$

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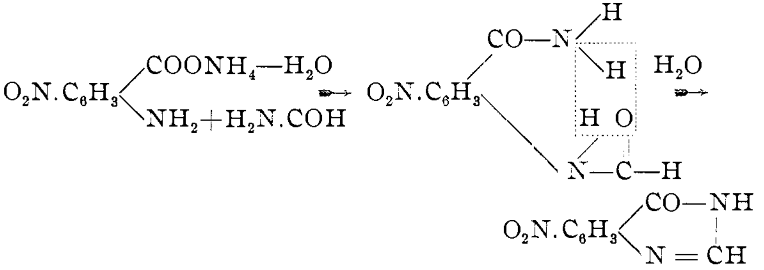
[1] Read at the meeting of the New York Section, April 7, 1905

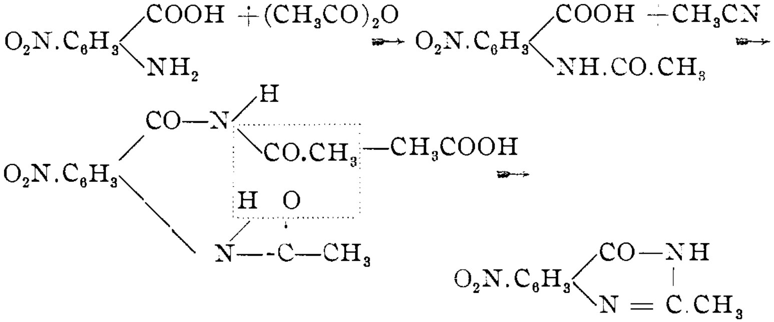
From the nitro anthranilic acid, its acetyl derivative, and the nitro acetylanthranil, quinazolines were readily obtained as follows:

I. By heating the ammonium salt of the nitro anthranilic acid with formamide[1]—



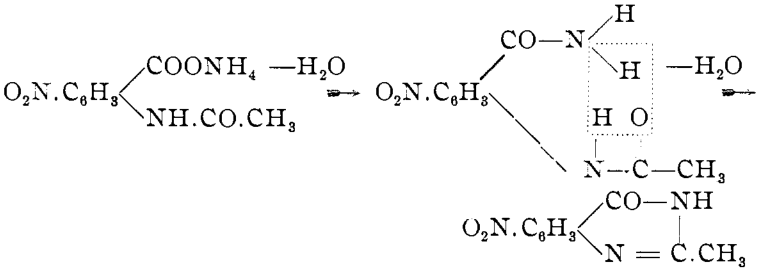
The higher amides do not work so well as formamide.

II. By heating the acid in sealed tubes with acetic anhydride and acetonitrile[2]—



The yield was very poor by this method.

III. By heating the ammonium salt of the acetylanthranilic acid[3]—



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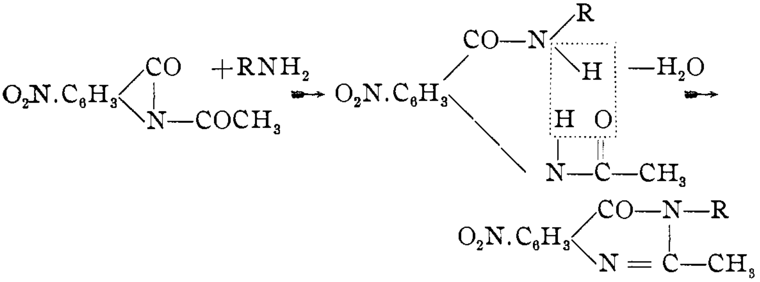
[1] Niementowski: *J. prakt. Chem.* (2), **51**, 564 (1895).

[2] Bogert and Gotthelf: This Journal, **22**, 129, 524 (1900); **23**, 611 (1901).

[3] Bischler and Burkart: *Ber. chem. Ges.*, **26**, 1349 (1893).

IV. By the action of primary amines upon the nitro acetylanthranil[1]—



The yields by this method are nearly quantitative, and the products are very pure.

Of the four possible Bz-nitro-2-methyl-4-ketodihydroquinazolines two have been known since 1891.

Of these, the 6-nitro compound was first obtained by Dehoff,[2] by the direct nitration of 2-methyl-4-ketodihydroquinazoline. The position of the nitro group in Dehoff's product was established by Thieme's synthesis of the same substance from the ethyl ester of 5-nitro-2-acetaminobenzoic acid and alcoholic ammonia at 170°.[3] By a similar process, using the ester of 3-nitro-2-acetaminobenzoic acid, Zacharias[4] prepared the 8-nitro isomer.

In the present paper, the 5-nitro-2-methyl-4-ketodihydroquinazoline is described, and we are engaged now in the preparation of the 7-nitro isomer, to complete the series.

These nitro quinazolines may be reduced to amino quinazolines, and the latter are also being studied in this laboratory. We would, therefore, like to reserve this field for further investigation.

EXPERIMENTAL.

6-*Nitro-2-aminobenzoic Acid.*—3-Nitro-*o*-phthalic acid was prepared by the direct nitration of phthalic anhyride.[5] Care should be taken that the first reaction does not become too violent, or the phthalic anhydride may be entirely destroyed. The yield of pure 3-nitro acid is usually about one-third the weight of phthalic anhydride used. More may be recovered from the mother-liquors by

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[1] Anschütz, Schmidt and Greiffenberg: *Ber. chem. Ges.*, **35**, 3480 (1902).

[2] Dehoff: *J. prakt. Chem.* (2), **42**, 347 (1890).

[3] Thieme: *Ibid.*, **43**, 473 (1891).

[4] Zacharias: *Ibid.*, **43**, 441 (1891).

[5] Miller: *Ann. Chem.* (Liebig), **208**, 223 (1881); Bogert and Boroschek: This Journal, **23**, 742 (1901).

concentration, but it is apt to be contaminated with the 4-nitro acid.

One molecule of the nitro acid is dissolved in a small amount of hot water, the solution neutralized with ammonia, any excess of ammonia boiled out, and a second molecule of the nitro acid then added. On cooling, the acid ammonium salt separates in quantitative yield. By the action of heat upon this acid ammonium salt, the imide is obtained in the calculated quantity.[1] It is best crystallized from a mixture of alcohol and acetone (1 : 2). The preparation of the imide from the anhydride, as recommended by Kahn,[2] works all right for small amounts, but we have found it much less satisfactory for the preparation of large amounts. In our experience, it takes much longer to get 500 grams of the pure imide from the anhydride than from the acid ammonium salt.

From the imide and caustic potash, the amic acid is readily prepared by Kahn's method.[3] If the solution of the potassium salt of the amic acid be well cooled before acidifying with hydrochloric acid, the amic acid separates immediately as a crystalline powder of pale brownish tint. By the addition of salt to the mother-liquor, more amic acid is separated, bringing the total yield up to 80-90 per cent. of the weight of imide used.

The amic acid is changed to the 6-nitro-2-aminobenzoic acid by the action of bromine and caustic potash, as described by Kahn.[4] It is, of course, essential to keep the solutions ice-cold until the necessary amount of alkali and bromine has been added. The cold solution should then be placed directly upon a boiling water-bath, and heated up as rapidly as possible, the close of the reaction (thirty to forty minutes) being indicated by the solution turning a rich red color, when it should be cooled down rapidly in an ice pack and carefully acidified with the calculated amount of hydrochloric acid. The amino acid then separates in beautiful yellow needles, which are practically pure. If the heating and cooling proceed slowly, the product will be darker in color and smaller in amount. When not perfectly pure, its tendency is to separate in a granular condition. In case the acid does not separate from the cold solution on shaking, it can generally be precipitated by the addition of a little salt. The yield is 80 to 85 per cent. of the weight of amic acid taken.

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[1] Bogert and Boroschek : *Loc. cit.*, p. 747.

[2] Kahn : *Ber. chem. Ges.*, **35**, 3866 (1902).

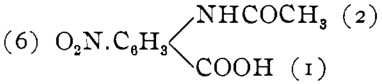
[3] Kahn: *Loc. cit.*, p. 3868.

[4] Kahn : *Loc. cit.*, p. 3863.

A further crop of less pure material may be recovered from the mother-liquors by adding more salt and stirring with a turbine for six to eight hours, or by extracting with ether or ethyl acetate, but the amount thus recovered does not pay for the time expended.

We have also tried the method of Seidel and Bittner,[1] by which the imide is converted directly into the amino acid by the action of caustic soda and bleaching-powder, without separation of the intermediate amic acid, and have found it much less satisfactory than the above.

6-Nitro-2-acetaminobenzoic Acid,



$$(6)\ O_2N.C_6H_3\left\langle\begin{matrix}NHCOCH_3\ (2)\\ COOH\ (1)\end{matrix}\right.$$

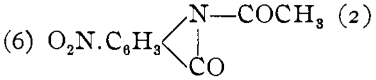
—Powdered nitro acetylanthranil is added to gently boiling water until no more is easily taken up. On cooling, nitro acetylanthranilic acid crystallizes out. It may be recrystallized from water in the same way, or from ethyl acetate.

It is obtained in large well-formed prismatic crystals, melting with decomposition at 212°-214°, according to the rapidity of the heating. A portion was kept at a temperature slightly above its melting-point for some time, but no nitro acetylanthranil could be detected in the resultant black tarry mass. The substance is soluble in water, and slowly hydrolyzed by it on long boiling. It is easily soluble in cold acetone, hot alcohol or hot ethyl acetate, slightly soluble in warm chloroform or benzene, insoluble in ether or petroleum ether.

Calculated for $C_9H_8O_5N_2$: N, 12.5. Found: N, 12.8.

Seidel and Bittner[2] attempted to prepare this compound by the direct action of acetic anhydride upon the nitro anthranilic acid, but failed to obtain a pure product.

6-Nitro Acetylanthranil,



$$(6)\ O_2N.C_6H_3\left\langle\begin{matrix}N—COCH_3\ (2)\\ |\\ CO\end{matrix}\right.$$

—This results when the nitroanthranilic acid is boiled for a few minutes with excess of acetic anhydride. On cooling, it separates in pale yellow prisms. If the nitro anthranilic acid used was perfectly pure, these crystals will be but faintly colored and prac-

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[1] Seidel and Bittner: *Monatsh. f. Chem.*, **23**, 421 (1902).

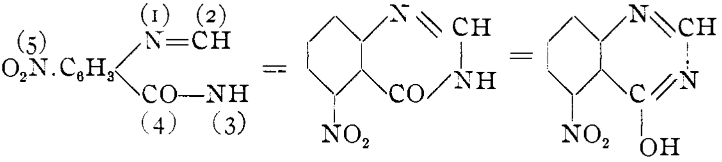
[2] Seidel and Bittner: *Ibid.*, p. 427.

tically pure. The substance may be re-crystallized from acetic anhydride or from ethyl acetate. If the crystallization from ethyl acetate causes any hydrolysis (which is quite likely to occur unless the acetate be perfectly dry), a further crystallization from acetic anhydride will remedy the difficulty. By evaporating the mother-liquor, at ordinary temperature, in a current of dry air, an additional amount may be obtained. The total yield is nearly theoretical.

When pure, the anthranil forms large colorless plates or prisms, m. p. 155°-156° (corr.), stable in dry air, slowly hydrolyzed in moist air, rapidly by boiling with water, to nitro acetylanthranilic acid. It is soluble in cold acetone or boiling chloroform, slightly soluble in hot carbon tetrachloride, ether, petroleum ether or benzene. It reacts very readily with primary amines, with formation of substituted anthranilamides, which easily condense to quinazolines.

Calculated for $C_9H_6O_4N_2$: C, 52.4; H, 2.9; N, 13.6. Found: C, 52.4; H, 3.1; N, 13.4, 13.4.

5-*Nitro-4-ketodihydroquinazoline*,



$$\overset{(5)}{O_2N.C_6H_3}\left\langle\begin{array}{l}\overset{(1)\quad(2)}{N{=}CH}\\ \underset{(4)\quad(3)}{CO{-}NH}\end{array}\right.$$

—The powdered ammonium salt of the nitroanthranilic acid is treated with slightly more than one molecule of formamide and heated for four or five hours at 150°-160° in a paraffin-bath, or until the liquid mixture becomes semi-solid. Ammonia is evolved during the reaction. When cold the mass is washed with a little cold water, dissolved in a large volume of boiling water, the solution bone-blacked and filtered hot. From the filtrate, on cooling, the quinazoline separates in a mass of needles. Recrystallized from hot water it forms beautiful colorless needles, melting at 255°-256° (corr.), with decomposition.

It is fairly soluble in boiling water, alcohol or acetone, sparingly soluble in the cold, practically insoluble in hot or cold ether, chloroform, petroleum ether or benzene. It dissolves readily in solutions of the caustic alkalies or of ammonia, and is reprecipitated from these solutions by carbon dioxide or by dilute acids.

Boiled with concentrated caustic potash no ammonia is split off.

Calculated for $C_8H_5N_3O_3$: C, 50.3; H, 2.6; N, 22. Found: C. 50.5; 50.3; H, 2.9, 2.8; N, 22.2.

Dimorphism of 5-Nitro-4-ketodihydroquinazoline.—When a hot aqueous solution of the quinazoline is allowed to cool quickly only fine needles separate at first, but small prisms soon appear on the walls of the vessel. On standing, the needles gradually disappear and the prisms on the side walls increase. This change is slow at room temperature, twenty-four to thirty-six hours being necessary usually for its completion. On the boiling water-bath the same change may be completed in three to four hours. The needles, when dry, crumble to a fine granular powder on the slightest touch. The prisms show the same melting-point and solubilities as the needles, and are easily reverted to them by solution in boiling water and rapid cooling. The prisms always show a pale green color, even when the needles from which they were obtained were perfectly colorless.

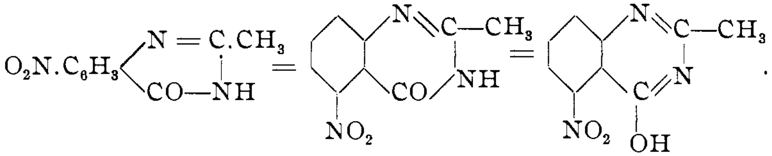
Chloride.—The addition of concentrated hydrochloric acid to the quinazoline changes it to a white amorphous salt which is soluble only in large excess of the hot concentrated acid. On cooling, it separates from such a solution as a white, microcrystalline powder, melting with decomposition at 240°–246°. When boiled with water, needles of the free quinazoline are obtained.

Chlorplatinate.—The quinazoline appears to dissolve more easily in hot concentrated hydrochloric acid when chlorplatinic acid is present. When such a solution cools the chlorplatinate separates in yellowish red crystals.

Calculated for $(C_8H_7O_4N_3.HCl)_2PtCl_4$: Pt, 24.5. Found: Pt, 24.4.

Nitrate.—The quinazoline dissolves rapidly in warm dilute nitric acid (1 : 4), and, on cooling, heavy, prismatic needles separate, which melt at about 218° with decomposition. When boiled with water the free quinazoline is regenerated.

5-*Nitro-2-methyl-4-ketodihydroquinazoline*,



$$O_2N.C_6H_3\left\langle\begin{array}{l}N = C.CH_3\\ \quad\quad\;\;|\\ CO—NH\end{array}\right. =$$

—This was prepared by the following methods:

(1) *From 6-Nitro-2-aminobenzoic Acid, Acetic Anhydride and Acetonitrile.*—Five grams of the nitro anthranilic acid, 3 cc. of acetic anhydride, and 3 cc. of acetonitrile were heated together in a sealed tube for six hours at 160°-170°. On opening the tube no pressure was evident. The tube contained a dark crystalline mass with a small amount of a reddish liquid. The mixture was repeatedly extracted with small amounts of warm ether. The residual reddish brown, granular mass was dissolved in potassium hydroxide solution, and precipitated with carbon dioxide. The precipitate obtained was dark-colored and flocculent. It was dissolved in warm alcohol and the solution bone-blacked. From the filtrate, on cooling, the quinazoline crystallized in fine white needles melting at 277°-279° (corr.), with decomposition. The yield was small. The ether extracts mentioned above contained nitro acetylanthranil and *m*-nitraniline, together with a small amount of a substance insoluble in alkali (possibly the quinazoline which would result from a combination of the anthranil and nitraniline).

(2) *From the Ammonium Salt of 6-Nitro-2-acetaminobenzoic Acid.*—The ammonium salt was prepared by dissolving the acid in dilute ammonia water and evaporating slowly on a water-bath. The dark-colored residue was then heated in a paraffin-bath until all effervescence had ceased. The mass thus obtained was nearly black. It was extracted with dilute caustic potash, the solution precipitated with carbon dioxide and the precipitate purified as above, giving fine needles, melting with decomposition at 277°-279° (corr.).

(3) *From Nitro-acetylanthranil and Ammonia.*—The anthranil was shaken with a moderate excess of dilute ammonia (1 : 2) until dissolved. On acidifying the solution with acetic acid the quinazoline separated, and without filtering out the precipitate the entire mixture was evaporated to dryness, and the residue recrystallized from a large amount of boiling water. Or, the following process was adopted. The first crop of quinazoline crystals was filtered out, and the filtrate concentrated for a second crop. The mother-liquor from the second crop was evaporated to dryness, heated to 220° as long as any water was given off, and the melt, combined with the second crop crystals, recrystallized from hot water. The object of the heating to 220° was the removal of any water which might have been taken up by the hy-

drolysis of some of the anthranil, *i. e.*, to change the ammonium salt of any nitro-acetylanthranilic acid to the quinazoline. The yield of pure quinazoline obtained from the anthranil was nearly quantitative.

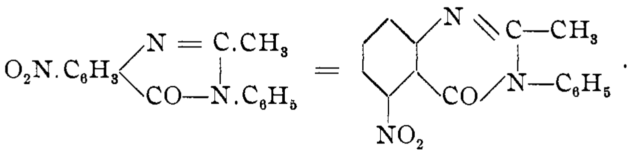
Properties of 5-*Nitro*-2-*methyl*-4-*ketodihydroquinazoline.*—The products obtained by the above three methods were identical in all respects. The pure quinazoline crystallizes from alcohol in fine colorless needles, melting with decomposition at 277°-279° (corr.). It is slightly soluble in hot water, more readily in warm acetone or alcohol, practically insoluble in cold water, hot or cold chloroform, ether, benzene, or petroleum ether. It dissolves readily in dilute alkalies, and is reprecipitated from such solutions by carbon dioxide. Boiling with concentrated caustic potash liberates no ammonia from it. We have not observed any dimorphism in the crystals.

Calculated for $C_9H_7O_3N_3$: C, 52.7; H, 3.4; N, 20.5. Found: C, 52.6, 52.6; H, 3.8, 3.6; N, 20.3.

Chloride.—On treating the quinazoline with concentrated hydrochloric acid the fine needles were changed to a white, amorphous powder, practically insoluble in the acid. All attempts to crystallize it from dilute acid gave only the characteristic crystals of the free quinazoline. The white, amorphous powder melted with decomposition at 276°-279°.

Nitrate.—The quinazoline dissolves with ease in warm dilute nitric acid (1 : 2), and, on cooling, warty masses of needle-like crystals separate. On recrystallization from water needles are obtained which begin to decompose at 205°, but do not melt completely below 260°.

5-*Nitro*-2-*methyl*-3-*phenyl*-4-*ketodihydroquinazoline*,



$$O_2N.C_6H_3\left\langle\begin{matrix}N = C.CH_3\\ \quad\ |\\ CO—N.C_6H_5\end{matrix}\right.$$

—Nitro-acetylanthranil was boiled with excess of aniline, the solution cooled, poured into water, acidified with acetic acid, and the mixture boiled for a few minutes. The quinazoline remained undissolved as a pale brown powder, which was filtered out, and crystallized from a large volume of boiling absolute alcohol.

It is thus obtained in compact cubes, m. p. 233°-234° (corr.), slightly soluble in cold acetone, warm benzene or amyl acetate, easily soluble in warm acetone or boiling nitro-benzene.

Calculated for $C_{15}H_{11}O_3N_3$: C, 64; H, 3.9; N, 14.9. Found: C, 64, 64.1; H, 3.9, 4; N, 14.7.

HAVEMEYER LABORATORIES, COLUMBIA UNIVERSITY,
March, 1905.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS.]

THE CHEMISTRY OF FLESH.

(SECOND PAPER.)[1]

IMPROVED METHODS FOR THE ANALYSIS OF ANIMAL SUBSTANCES.[2]

BY H. S. GRINDLEY AND A. D. EMMETT.

Received April 10, 1905.

THE proximate analysis of animal substances is as yet confined to the determination of only a few classes of chemical compounds. In continuing the study of the chemistry of the cooking of meats, upon which considerable work has been done in this laboratory in coöperation with the U. S. Department of Agriculture, Office of Experiment Stations,[3] it became apparent that the ordinary methods used in the analysis of food materials do not give a sufficient amount of information regarding the proximate constituents which uncooked and cooked meats and broths contain, to teach much regarding the nature of the changes resulting in the processes of cooking.

It is also true that the methods of analysis commonly used do not include the direct determination of several constituents of flesh which are of much importance in imparting to meats their characteristic flavors and which in addition possess real value as stimulants to digestion. These principles are the nitrogenous and non-nitrogenous extractives.

Further, there are also serious objections to the customary methods of analysis which require the preliminary preparation of air-dried samples, since this procedure brings about fundamental

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[1] First paper: This Journal **26**, 1086 (1904).

[2] This research was made possible through the valuable aid given by the Department of Animal Husbandry of the Agricultural Experiment Station of the University of Illinois.

[3] U. S. Department of Agriculture, Office of Experiment Stations, Bulls. 102 and 104.