acetate, aniline and nitrobenzene. Saponification yielded 23.1 per cent. formic acid. A pure monoformate should yield 24.2 per cent. Attempts made to introduce more formic acid radicles into the cellulose molecule by raising the temperature at which acylation was carried on gave only negative results. These experiments essentially go to confirm the results of Berl and Smith. Less agreement can be noted with the product described by Bemberg.[1] According to this patent it should be possible by essentially the same procedure as that outlined above to prepare a formate soluble in moderately concentrated aqueous acids. It is further stated that if cellulose be first soaked in formic acid and then pressed to a 100 per cent. gain in weight and placed in benzene containing from 3 per cent. to 10 per cent. of sulphuric acid a fibrous formate of cellulose may be obtained. It was not found possible to duplicate these results, but as the formation of a fibrous formate would have possessed considerable interest, experiments were made in which several other diluents were used instead of benzene. The latter seems particularly unsuitable for the purpose because it is not practicable to prepare a homogeneous mixture of the three liquids in the proportions suggested. Instead of benzene, experiments were made with ether, ethyl acetate, glacial acetic acid, acetone and a mixture of benzene and ether. All results were negative as far as the production of a fibrous formate was concerned. The following experiment was typical. Two grams of hydrated cellulose dried at 100° were treated with 20 grams formic acid (sp. g. 1.22), 2 grams sulphuric acid (sp. g. 1.836) and 5 grams ethyl acetate. The cellulose was unattacked and insoluble in formic acid after standing for three days. In a similar mixture which contained only 2 grams of ethyl acetate the cellulose partly dissolved but the fibrous portion was not soluble in formic acid. These experiments seem to show that the addition of even a small amount of a neutral solvent practically puts a stop to acylation, while, when the quantity of diluent is still further reduced, some acylation takes place but the product dissolves in the reacting mixture.

MASSACHUSETTS INSTITUTE OF TECHNOLOGY,
BOSTON, MASS.

[CONTRIBUTIONS FROM THE HAVEMEYER LABORATORIES OF COLUMBIA UNIVERSITY, NO. 169.]

RESEARCHES ON QUINAZOLINES (TWENTY-THIRD PAPER). ON 6-METHYL-7-AMINOQUINAZOLONES, 7-NITROQUINAZOLONE-6-CARBOXYLIC ACIDS, AND 1,3,7,9-NAPHTHOTETRAZINES.[2]

BY MARSTON TAYLOR BOGERT AND ALFRED H. KROPFF.

Received ———, 1909.

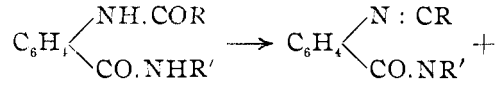
In a recent communication[3] the authors described the preparation and properties of certain amino and nitramino derivatives of benzoic, *m*-toluic and *m*-phthalic acids of anthranilic structure, *i. e.*, with an amino group adjacent to a carboxyl, and the present paper deals with some of the quinazoline condensations obtained from these anthranilic acids. In general, these condensations depend upon the intermediate formation

[1] *Loc. cit.*

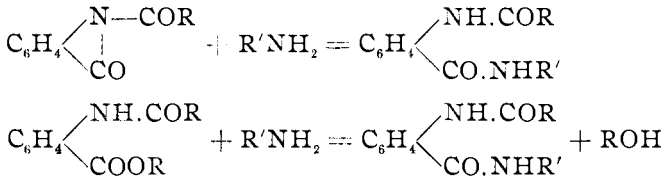
[2] Read at the meeting of the New York Section, May 14, 1909.

[3] THIS JOURNAL, 31, 841 (1909).

of an acylanthranilamide, which then forms the miazine cycle by loss of water,

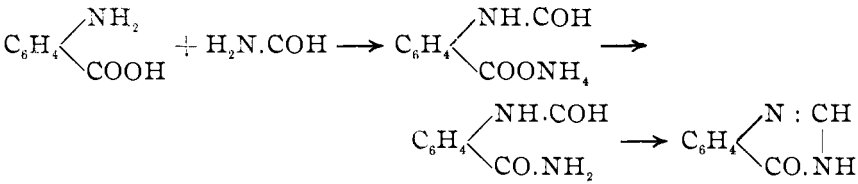


the acylanthranilamide being conveniently formed by the action of primary amines upon acylanthranils or acylanthranilic esters:

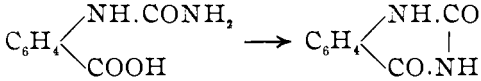


The intermediate amides were not separated, the reaction being carried through to the quinazoline.

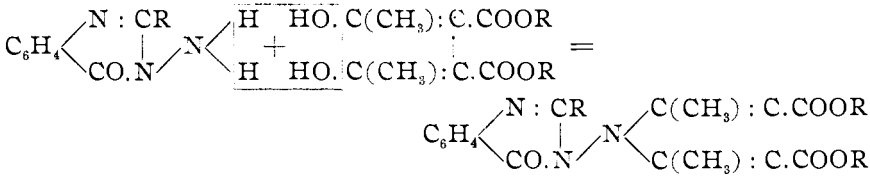
For the formyl condensation products, the reaction of Niementowski[1] is the most convenient:



For diketotetrahydro compounds, the uramino acids or their esters were used:



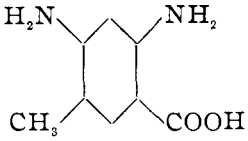
When the acylanthranils were condensed with hydrazine, N-aminoquinazolones resulted which, like other unsymmetrical secondary hydrazines, undergo the Bülow condensation[2] with diacetosuccinic ester, giving pyrrole derivatives:



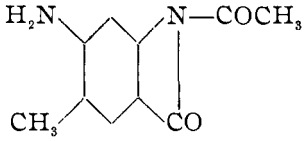
The acids used in the work, with their acetanthranils and quinazoline condensations, were as follows:

[1] *J. pr. Chem.* [2], **51**, 564 (1895).

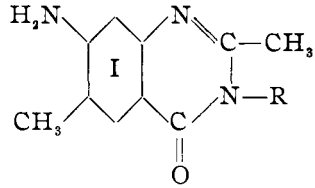
[2] *Ber.*, **35**, 4311 (1902); **37**, 2697 (1904); **39**, 3372 (1906).



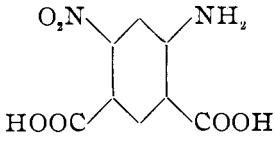
(4,6-Diamino-*m*-toluic acid.)



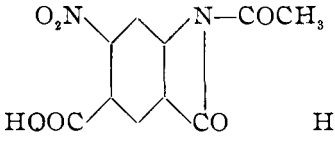
(Its acetanthranil.)



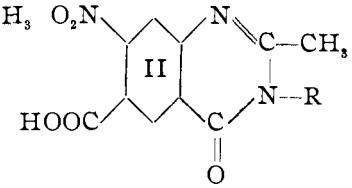
(2,6-Dimethyl-7-amino-3-R-4-quinazolone.)



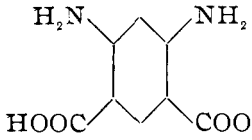
(4-Nitro-6-amino-*m*-phthalic acid.)



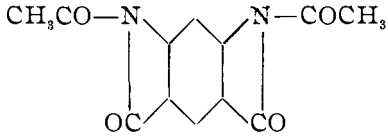
(Its acetanthranil.)



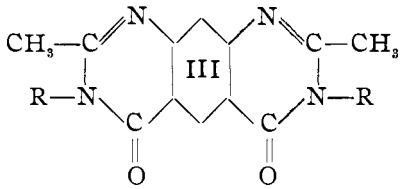
(2-Methyl-3-R-7-nitro-4-quinazolone-6-carboxylic acid.)



(4,6-Diamino-*m*-phthalic acid.)



(Its *bis*-acetanthranil.)



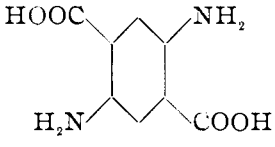
(2,8-Dimethyl-3,7-di-R-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine.)

These acetanthranils were described in the authors' recent paper.[1] The quinazolone condensations show the properties indicated by their constitutional formulas. Those having a free hydrogen in position 3 dissolve readily in dilute alkali, the —CO.NH— group presumably reacting in its enolic —C(OH):N— form. From such solutions they are precipitated by carbon dioxide or acetic acid. Those carrying a radical in position 3 do not dissolve in dilute alkali unless there happens to be an acid group somewhere else in the molecule (as in II above). The naphthotetrazines all melt very high. Some can be crystallized from alcohol, but most of them dissolve but slightly in the usual neutral organic solvents. The synthesis of 1,3,6,8-naphthotetrazines from succinylosuccinic ester and amidines has been reported by Pinner[2] and by Bogert

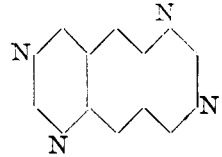
[1] *Loc. cit.*

[2] *Ber.*, **22**, 2609 (1889).

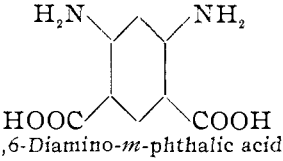
and Dox,[1] and Bogert and Nelson[2] obtained similar compounds from *p*-diaminoterephthalic acid, but, so far as we can find, the 1,3,7,9-naphthotetrazine nucleus has not been synthesized before. The relation between these naphthotetrazine nuclei and the diaminophthalic acids is evident from a glance at their formulas:



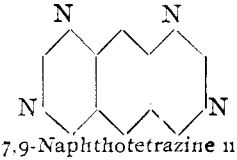
(*p*-Diaminoterephthalic acid.)



(1,3,6,8-Naphthotetrazine nucleus.)



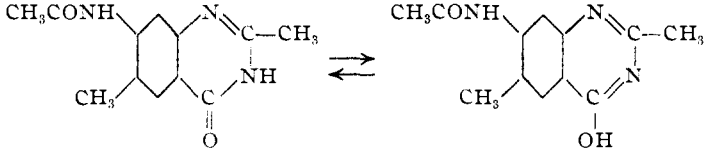
(4,6-Diamino-*m*-phthalic acid.)



(1,3,7,9-Naphthotetrazine nucleus.)

Experimental.

2,6-Dimethyl-7-acetamino-4-quinazolone (*2,6-Dimethyl-7-acetamino-4-hydroxyquinazoline*),



—1-Methyl-2-acetamino-4,5-acetanthranil was added to dilute ammonium hydroxide and the solution heated to boiling. The anthranil gradually dissolved and soon thereafter the quinazolone separated from the boiling solution. On boiling out the excess of ammonia and cooling, the quinazolone was obtained in colorless needles, m. p. about 330°.

Found: N, 18.4. Calculated for $C_{12}H_{13}O_2N_3$: N, 18.18.

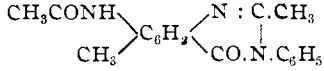
It is easily soluble in dilute caustic alkalies, and is reprecipitated from such solutions by acidification with acetic acid.

2,6-Dimethyl-7-amino-4-quinazolone (*2,6-Dimethyl-7-amino-4-hydroxyquinazoline*).—The above acetyl derivative was boiled for a few minutes with 10 per cent. potassium hydroxide solution, the solution filtered, and the filtrate saturated with carbon dioxide. The aminoquinazolone thus precipitated was purified by re-solution in potassium hydroxide solution and re-precipitation with carbon dioxide.

Found: N, 22.4. Calculated for $C_{10}H_{11}ON_3$: N, 22.22.

Colorless solid, melting above 300°; soluble in alcohol or in dilute hydrochloric acid.

2,6-Dimethyl-3-phenyl-7-acetamino-4-quinazolone,



[1] THIS JOURNAL, **27**, 1127 and 1302 (1905).

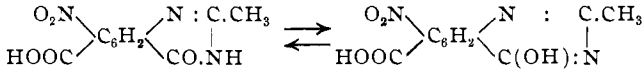
[2] *Ibid.*, **29**, 729 (1907).

was prepared by heating the acetanthranil with excess of aniline. On cooling, the quinazolone separated. It was freed from aniline by washing with dilute acetic acid, and was then crystallized from dilute alcohol.

Found: N, 13.75. Calculated for $C_{18}H_{17}O_2N_3$: N, 13.68.

Beautiful, glistening, diamond-shaped plates, m. p. 271° (uncorr.).

2-Methyl-7-nitro-4-quinazolone-6-carboxylic Acid (*2-Methyl-7-nitro-4-hydroxyquinazoline-6-carboxylic acid*),



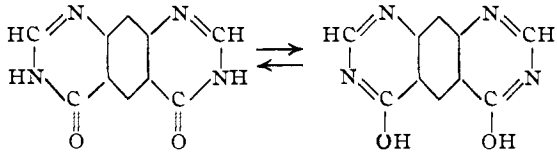
—4-Nitroacetanthranil-5-carboxylic acid was added to an excess of dilute ammonium hydroxide solution, the solution boiled for a few minutes, evaporated to dryness, the residue dissolved in dilute potassium hydroxide solution, filtered from impurities, and the quinazolone precipitated by careful neutralization with hydrochloric acid. Recrystallized from water, colorless needles were obtained, melting above 300°.

Found: N, 16.93. Calculated for $C_{10}H_7O_5N_3$: N, 16.8.

2-Methyl-3-phenyl-7-nitro-4-quinazolone-6-carboxylic Acid.—4-Nitroacetanthranil-5-carboxylic acid was boiled with a slight excess of aniline, the solution allowed to cool, dilute acetic acid added, and the precipitated quinazolone filtered out. Crystallized from alcohol, it forms beautiful, yellow prisms, m. p. 315° (uncorr.).

Found: N, 13.41. Calculated for $C_{15}H_{11}O_5N_3$: N, 13.4.

4,6-Diketotetrahydro-1,3,7,9 - naphthotetrazine (*4,6-Dihydroxy - 1,3,7,9 - naphthotetrazine*),

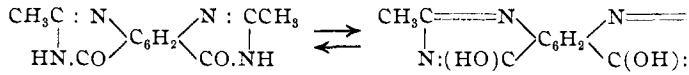


—Diethyl 4,6-diamino-*m*-phthalate was heated with excess of formamide for seven hours at 200–10° in a sealed tube. The crude crystalline product from the tube was dissolved in dilute potassium hydroxide solution, the solution boiled to expel all ammonia, filtered, the filtrate precipitated by carbon dioxide, the precipitate washed, redissolved in potassium hydroxide solution, and reprecipitated by carbon dioxide. Yield nearly theoretical.

Found: N, 26.11. Calculated for $C_{10}H_6O_2N_4$: N, 26.17.

Reddish yellow powder, melting above 310°, insoluble in water or the usual neutral organic solvents. In solutions of the caustic alkalies, it dissolves readily, and is reprecipitated by acetic acid or carbon dioxide.

2,8-Dimethyl-4,6-diketotetrahydro-1,3,7,9 - naphthotetrazine (*2,8-Dimethyl - 4,6 - dihydroxy-1,3,7,9-naphthotetrazine*),



—Ethyl 4,6-diacetamino-*m*-phthalate was heated with excess of alcoholic ammonia for five hours at 200° in a sealed tube. The solid material which separated in the tube was purified by solution in dilute potassium hydroxide solution, filtering, and reprecipitating with acetic acid. The precipitate was washed with hot water, redissolved in potassium hydroxide solution and precipitated with carbon dioxide. Dried to constant weight at 110° and analyzed, the result was as follows:

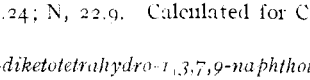
Found: N, 23.3. Calculated for $C_{12}H_{10}O_2N_4$: N, 23.1.

Pale yellow, amorphous powder, melting above 310°; insoluble in water, alcohol, ether, benzene or chloroform.

The yield by the above method was poor. The same substance was obtained, in nearly theoretical yield, by boiling the *bis*-acetanthranil (of the diaminophthalic acid) with dilute ammonium hydroxide solution. The anthranil dissolved at first, and the naphthotetrazine soon separated from the boiling solution. It was purified as above.

Found: C, 59.68; H, 4.24; N, 22.9. Calculated for $C_{10}H_{10}O_2N_4$: C, 59.5; H, 4.09; N, 23.1.

2,3,7,8-Tetramethyl-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine,



—The *bis*-acetanthranil was heated with excess of 33 per cent. aqueous methylamine solution. The anthranil gradually dissolved and after a few minutes' boiling the naphthotetrazine separated from the boiling solution in colorless crystals, which were washed with hot water and recrystallized from alcohol.

Found: N, 20.9. Calculated for $C_{14}H_{14}O_2N_4$: N, 20.74.

Long, colorless needles (from alcohol), melting above 350°; insoluble in water, benzene, ether or chloroform, moderately soluble in alcohol.

2,8-Dimethyl-3,7-di-n-propyl-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine.—The *bis*-acetanthranil was added to a cold dilute aqueous solution of propylamine and the temperature gradually raised to boiling. The anthranil dissolved and the naphthotetrazine soon separated from the boiling solution as a flocculent precipitate. It was purified by crystallization from dilute alcohol.

Found: N, 17.05. Calculated for $C_{18}H_{22}O_2N_4$: N, 17.1.

Small, glistening needles, softening somewhat at about 180°, and melting at 220° (uncorr.); insoluble in water, benzene, ether or chloroform, but quite readily soluble in alcohol.

2,8-Dimethyl-3,7-diphenyl-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine.—Aniline was without apparent action upon ethyl 4,6-diacetamino-*m*-phthalate when the two were heated together for two hours at 200° in a sealed tube. But when the *bis*-acetanthranil was boiled for 15 minutes with excess of aniline, colorless needles separated from the solution on cooling. They were washed with acetic acid, then with water, recrystallized from alcohol, and analyzed.

Found: N, 14.0. Calculated for $C_{24}H_{18}O_2N_4$: N, 14.21.

The compound crystallizes from alcohol in minute, colorless needles, m. p. 315°; insoluble in water, acetic acid, ether, ligroin or benzene.

2,8-Dimethyl-3,7-di-β-naphthyl-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine.—When the *bis*-acetanthranil and β-naphthylamine were heated together, the mixture liquefied and considerable frothing occurred (presumably from the water separated in the reaction). After the cessation of the frothing, the mass solidified. When cold it was pulverized, extracted repeatedly with hot, dilute hydrochloric acid (to remove unchanged naphthylamine), washed with water, and the grayish amorphous residue crystallized from alcohol. Grayish, fluorescent needles resulted, which were washed with alcohol, dried at 110°, and analyzed.

Found: N, 11.3. Calculated for $C_{32}H_{26}O_2N_4$: N, 11.24.

It melts at 304° (uncorr.), and is apparently insoluble in water, benzene, ether or chloroform. In alcohol, it dissolves sparingly, the solution being distinctly fluorescent.

2,8-Dimethyl-3,7-diamino-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine.—The *bis*-

acetanthranil was added to an aqueous solution of slightly more than two molecules of hydrazine hydrate and the mixture heated to boiling. The anthranil gradually dissolved, and the naphthotetrazine soon separated from the boiling solution in beautiful, yellow, nacreous scales, which were washed with water, dried at 110° and analyzed.

Found: N, 31.15. Calculated for $C_{12}H_{12}O_2N_6$: N, 30.9.

The substance appears to be insoluble in water or benzene, but dissolves sparingly in alcohol. It is soluble in hot concentrated hydrochloric acid and separates as the hydrochloride on cooling. With acetic anhydride, two acetyl groups are introduced. It undergoes the Bülow condensation[1] with diacetosuccinic ester. When its solution in dilute hydrochloric acid is treated with sodium nitrite, the amino groups are generaly replaced by hydrogens; but if, after the addition of the nitrite, the solution be pourled *immediately* into an alkaline solution of α- or β-naphthol, a deep red dye is formed.[2] If the hydrochloric acid solution of the diaminonaphthotetrazine is allowed to stand for many seconds after the addition of the nitrite, no dye is formed on adding it to the alkaline naphthol solution.

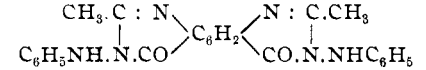
Hydrochloride.—Colorless prisms, melting with decomposition above 360°; readily soluble in cold water. Addition of sodium carbonate to the aqueous solution precipitates the free diaminonaphthotetrazine.

2,8-Dimethyl-3,7-diacetamino-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine was prepared from the above diamine and excess of acetic anhydride. The crystals which separated on concentrating the acetic anhydride solution were washed free from anhydride by carbon tetrachloride and recrystallized from alcohol.

Found: N, 23.9. Calculated for $C_{16}H_{16}O_4N_6$: N, 23.6.

Small, colorless needles (from alcohol), melting above 360°; practically insoluble in water, benzene, ether or chloroform, moderately soluble in alcohol. Boiling with acetic anhydride does not further acetylate the compound.

2,8-Dimethyl-3,7-dianilino-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine,

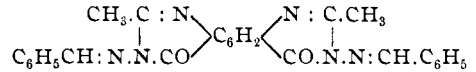


—Phenylhydrazine reacted readily with the *bis*-acetanthranil even in the cold. The reaction was completed by warming the mixture for a short time. On cooling, a granular solid separated. Alcohol was added, the temperature raised to boiling, and the hot mixture filtered. The insoluble material was thoroughly washed with boiling alcohol, leaving a colorless, granular solid, which gave the following figure on analysis:

Found: N, 20.05. Calculated for $C_{24}H_{20}O_2N_6$: N, 19.81.

The pure substance melts above 320° and is essentially insoluble in alcohol.

2,8-Dimethyl-3,7-dibenzalamino-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine,



—The diaminonaphthotetrazine was boiled for a few minutes with excess of benzaldehyde. Solution occurred, with evolution of steam, and on cooling a granular, yellow solid was obtained. This was washed repeatedly with boiling alcohol, to remove all benzaldehyde and benzoic acid, and then dried and analyzed.

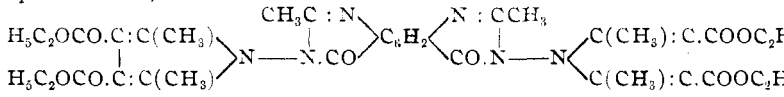
Found: N, 18.9. Calculated for $C_{26}H_{20}O_2N_6$: N, 18.7.

It melts above 350°, and is practically insoluble in the ordinary neutral organic solvents. It can be dissolved, however, in hot benzaldehyde, and crystallizes from this solution in granular form.

[1] *Loc. cit.*

[2] Compare Bogert and Gortner, THIS JOURNAL, **31**, 943 (1909).

2,8-Dimethyl-3,7-di(2,5-dimethyl-3,4-dicarbethoxypyrrole)-4,6-diketotetrahydro-1,3,7,-9-naphthotetrazine,

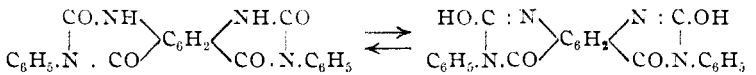


—The diaminonaphthotetrazine was boiled for an hour with a glacial acetic acid solution of the calculated amount of ethyl diacetosuccinate. On concentrating, some unchanged naphthotetrazine separated. This was removed and the mother liquor diluted with water. A white, amorphous precipitate appeared. On boiling the solution, the precipitate dissolved and, on cooling, minute, colorless prisms or needles crystallized out. A second crop of crystals was obtained by further dilution of the mother liquor. The crude product was recrystallized from alcohol, dried and analyzed.

Found: N, 12.1. Calculated for $C_{36}H_{40}O_{10}N_6$: N, 11.75.

The pure compound melts at 268.2° (corr.).

3,7-Diphenyl-2,4,6,8-tetraketo-octahydro-1,3,7,9-naphthotetrazine (*3,7-Diphenyl-2,8-dihydroxy-4,6-diketotetrahydro-1,3,7,9-naphthotetrazine*).



—When diethyl 4,6-diphenyluramino-*m*-phthalate was boiled with aniline, no change was evident. But when the two were heated together in a sealed tube for six hours at 225°, a reaction occurred accompanied by considerable decomposition. The crude product was boiled with glacial acetic acid, the solution filtered, and on cooling large, brownish-green crystals were obtained. These were washed with glacial acetic acid, then with water, dissolved in dilute potassium hydroxide solution and reprecipitated by carbon dioxide.

Found: N, 14.07. Calculated for $C_{22}H_{14}O_4N_4$: N, 14.07.

The pure compound is colorless and amorphous, melts above 300°, is apparently insoluble in water, alcohol or benzene, but dissolves in glacial acetic acid.

ORGANIC LABORATORY, June, 1909.

[FROM THE LABORATORY OF PHYSIOLOGICAL CHEMISTRY, DEPARTMENT OF ANIMAL HUSBANDRY, UNIVERSITY OF ILLINOIS.]

THE DETERMINATION OF UREA IN URINE.

NUTRITION INVESTIGATIONS, PUBLICATION NO. 26.

BY F. W. GILL, F. G. ALLISON, AND H. S. GRINDLEY.

Received July 6, 1909.

The method of Folin[1] for the determination of urea in urine has been very generally used since it was first described. It has been conclusively proven repeatedly that Folin's method gives quite uniform results when properly carried out with due regard to all details. On the other hand, the method requires very careful work, and it is long and tedious, requiring close attention continuously. The difficulties attending the accurate determination of urea in urines by the Folin method have been espe-

[1] *Z. physiol. Chem.*, **32**, 504 (1901); **36**, 333 (1902); **37**, 548 (1903); *Amer. Jour. Physiol.*, **13**, 45 (1905).