order, with — elongation. If the sirupy honey is removed from around these crystals by glacial acetic acid and the refractive indices are determined by the immersion method, the α of d-glucose is found to be about one unit in the second decimal place lower than that of melezitose, and the γ a like amount higher. Sucrose can also be readily distinguished from melezitose by its much greater double refraction, α being 1.45 and γ 1.57, and by breaking into irregular fragments with oblique extinction.

It is believed that this method of examination of the crystals which develop in honeys will be of much aid in the systematic search for the occurrence of melezitose.

WASHINGTON, D. C.

THE PREPARATION OF PARA-UREIDO-PHENYLACETYLUREA, AND RELATED COMPOUNDS.

BY MARY RISING.[1]

Received October 20, 1919.

A study of the preparation of ureido-phenylacetylurea was begun by the author, with the aid and advice of Professor Stieglitz, following the publication some time ago of the work upon the synthesis of phenylethyl-barbituric acid.[2] Phenylethyl-barbituric acid (luminal), widely used in the treatment of epilepsy, has hypnotic and sedative properties. Under certain conditions, the drug is known to have a toxic effect, and for this reason its use cannot be prescribed in all cases. With time of peace at hand, when there is leisure to work along lines of theory, rather along those laid down by the imperative demands of war needs, the building up of a new series of compounds, related chemically to phenylethyl-barbituric acid, was undertaken. The effort has been made to retain in these compounds the excellent hypnotic properties of phenylethyl-barbituric acid, avoiding meanwhile those properties which are harmful. The compounds prepared in this way are to be thoroughly tested physiologically, in the hope of discovering a hypnotic of even greater value than is phenylethyl-barbituric acid.

The fact that phenylethyl-barbituric acid possesses toxic properties which are not possessed by the closely related compound, diethyl-barbituric acid, suggested the toxicity of the phenyl group. For the modification of the phenyl group, we have first tried the introduction in the phenyl radical of a urea group, which might at the same time enhance the hyp-

[1] The material given in this report will be included in the dissertation of the author in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Chicago.

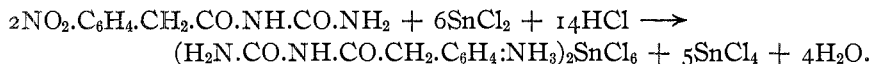[2] Rising and Stieglitz, THIS JOURNAL, **40**, 4, 725 (1918).

notic properties. Further, in place of the use of a dicarboxylic acid radical as in diethyl-barbituric acid (veronal), and in phenylethyl-barbituric acid, a monocarboxylic acid, phenylacetic acid, was first used, as in the case of the hypnotic diethylbromo-acetylurea (adalin), as giving products easier of approach. Finally, we are introducing into our compounds ethyl groups, and bromine, which have, as is well known, hypnotic properties. These considerations have led us to undertake the preparation of the following group of compounds: (1) p-Ureido-phenyl-acetylurea. (2) p-Ureido-phenylethyl-acetylurea. (3) p-Ureido-phenyldiethyl-acetylurea. (4) p-Ureido-phenylethyl-bromoacetylurea. The preparation of the first of these compounds is described in this paper.

p-Ureido-phenyl-acetylurea was made on the basis of the following series of reactions:

(1) p-Nitrophenyl-acetyl chloride is condensed with urea in boiling benzene, and p-nitrophenyl-acetylurea is formed.[1]

$$NO_2.C_6H_4.CH_2.COCl + NH_2.CO.NH_2 \longrightarrow$$
$$NO_2.C_6H_4.CH_2.CO.NH.CO.NH_2 + H_2O.$$
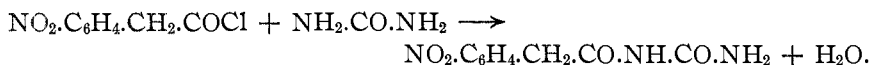
(2) p-Nitrophenyl-acetylurea is reduced quantitatively to p-aminophenyl-acetylurea by means of stannous chloride in glacial acetic acid in the cold.[2]

$$2NO_2.C_6H_4.CH_2.CO.NH.CO.NH_2 + 6SnCl_2 + 14HCl \longrightarrow$$
$$(H_2N.CO.NH.CO.CH_2.C_6H_4:NH_3)_2SnCl_6 + 5SnCl_4 + 4H_2O.$$

(3) The hydrochloride of p-aminophenyl-acetylurea is treated with potassium cyanate, whereupon rearrangement takes place, and p-ureido-phenyl-acetylurea is formed.

$$ClH_3N.C_6H_4.CH_2.CO.NH.CO.NH_2 + KCNO \longrightarrow$$
$$NH_2.CO.NH.C_6H_4CH_2.CO.NH.CO.NH_2 + KCl.$$
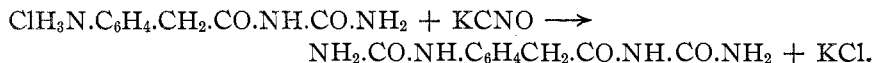
Some preliminary preparations of related urea derivatives are first to be described:

(1) The hydrochloride of p-aminobenzyl cyanide was treated with potassium cyanate, and p-ureidobenzyl cyanide was formed.

$$ClH_3N.C_6H_4.CH_2.CN + KCNO \longrightarrow NH_2.CO.NH.C_6H_4.CH_2.CN + KCl.$$
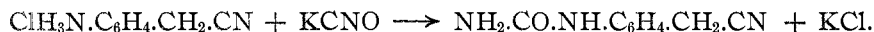
(2) The methyl ester of p-ureido-phenylacetic acid is prepared: (a) by the esterification of p-ureidobenzyl cyanide,

$$NH_2.CO.NH.C_6H_4.CH_2.CN + HOCH_3 + H_2O + HCl \longrightarrow$$
$$NH_2.CO.NH.C_6H_4.CH_2.COOCH_3 + NH_4Cl,$$

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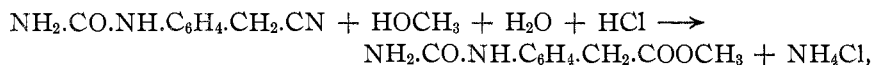
[1] Jacobs and Heidelberger, THIS JOURNAL, 39, 2418 (1917).

[2] Weyl, *Die Methoden der organischen Chemie*, 2, 211 (1909); cf. Thiele and Dimroth, *Ann.*, 305, 114 (1899). The first product isolated (see below), is the chlorostannate. Jacobs and Heidelberger (*Loc cit.*), effected this reduction with ferrous sulfate and ammonia.

and, (b) by the action of the hydrochloride of p-amino-phenylacetic methyl ester with potassium cyanate.

$$ClH_3N.C_6H_4.CH_2.CO.OCH_3 + KCNO \longrightarrow$$
$$NH_2.CO.NH.C_6H_4.CH_2.CO.OCH_3 + KCl.$$
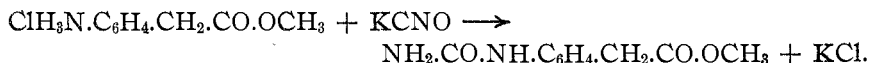
(3) By the hydrolysis of p-ureido-phenylacetic methyl ester, p-ureido-phenylacetic acid is obtained.

The ethylation of benzyl cyanide, preliminary to the preparation of p-ureido-phenylethyl-acetylurea and the other compounds listed above, will be discussed below in connection with the preparative details.

Experimental Part.

Benzyl cyanide was converted into p-nitrobenzyl cyanide according to the method of Pschorr, Wolfes, and Buckow.[1] The method of these authors, together with certain modifications suggested by Hanke,[2] was used for the reduction of nitrobenzyl cyanide. p-Aminobenzyl cyanide, prepared in this way, was used in the synthesis of the first of our ureids.

1. **p-Amino-phenylacetic Methyl Ester,** p-$NH_2.C_6H_4.CH_2.CO.OCH_3$.—The hydrochloride of the ester is prepared according to the method used by us for the preparation of phenylacetic methyl ester in the synthesis of phenylethyl-barbituric acid.[3] To a mixture of absolute methyl alcohol (112 g.), and water (6 g.) is added p-aminobenzyl cyanide (28 g.). When the saturation with hydrogen chloride is begun, the hydrochloride of p-aminobenzyl cyanide is precipitated. As the reaction progresses, the hydrochloride goes into solution gradually, and after some time a precipitate of ammonium chloride appears. When the process of esterification is complete, the alcoholic solution is cooled, decanted from the ammonium chloride, and almost all the alcohol evaporated in vacuo. On cooling, a heavy mass of the hydrochloride of p-amino-phenylacetic methyl ester settles out and is collected on a filter. The crude yield from 28 g. of cyanide was 32 g., containing some ammonium chloride. It was purified in the following way: A mixture of one part of absolute alcohol and 4 parts of dry ether was prepared, and 60 cc. of this solution shaken with 3 g. of the impure hydrochloride in a separatory funnel. All but a small sediment of ammonium chloride dissolved, and the supernatant solution of the hydrochloride was siphoned off. This solution was evaporated to 1/2 its volume in vacuo, the residue cooled, and a heavy mass of nearly white, silvery leaves obtained, which is the hydrochloride of p-amino-phenylacetic methyl ester. An analysis for chlorine showed the

[1] Ber., **33**, 17 (1900).

[2] Dr. Milton Hanke's paper including this preparation is shortly to appear in THIS JOURNAL.

[3] Loc. cit.

product to be pure. The analysis of the hydrochloride of this same ester as prepared by Salkowski[1] showed a very high chlorine content.

Subs., 0.1095: 0.1 N AgNO$_3$, factor 0.967, 5.59 cc.
Calc. for C$_9$H$_{12}$O$_2$NCl: Cl, 17.60. Found: 17.50.

The hydrochloride was dissolved in 25 cc. of water and the solution made just alkaline with sodium hydrogen carbonate, methyl orange being used as indicator. The solution was then titrated with silver nitrate in the usual way, potassium chromate being used as indicator.

The free base was prepared from the hydrochloride as follows: The hydrochloride (4 g.) was dissolved in 20 cc. of water and 50 cc. of ether was added. The calculated amount of sodium hydrogen carbonate (2.1 g., dissolved in 30 cc. of water) was added in small portions, and the whole shaken in a separatory funnel. The ether layer was separated, and the aqueous residue extracted twice with ether. The ether extractions were combined and dried over sodium sulfate, the ether evaporated, and the remaining oil fractionated. At 75°, and 20 mm. pressure, the oil commenced to boil. At 140–150° and 17 mm. pressure the main fraction, the ester itself, distilled. At 155° and 17 mm. pressure a last fraction was obtained. Salkowski gives no boiling point in his description of the amino ester.

2. **p-Ureidobenzyl Cyanide**, p-NH$_2$.CO.NH.C$_6$H$_4$.CH$_2$CN.—The hydrochloride of p-aminobenzyl cyanide is prepared by precipitation with dry hydrogen chloride from the solution of the free base in dry ether. The hydrochloride (13 g.), obtained in this way, is dissolved in 75 cc. of water, and to this solution is added potassium cyanate (7 g., the calculated amount and $1/3$ excess, dissolved in 24 cc. of water). There is slight effervescence, due to the formation of cyanic acid, and the solution thickens to a pasty mass as the ureido compound forms. This mixture is evaporated to dryness on the water bath, extracted with water to remove potassium chloride formed in the reaction, and any unchanged potassium cyanate, and the undissolved residue is collected on a filter. Recrystallization of this residue from 95% alcohol yielded a product melting sharply at 170.5°.

Subs., 0.0514: 10.92 cc. N (over 50% KOH) at 22° and 752.5 mm. (24°).
Calc. for C$_9$H$_9$N$_3$O: N, 24.00. Found: 23.91.

3. **p-Ureido-phenylacetic Methyl Ester,** p-NH$_2$.CO.NH.C$_6$H$_4$.CH$_2$.-CO.OCH$_3$.—This compound was prepared in two ways: (a) by the esterification of p-ureidobenzyl cyanide, and (b) from p-amino-phenylacetic methyl ester hydrochloride by treatment with potassium cyanate.

(a) *Esterification of p-Ureidobenzyl Cyanide.*—The ureidobenzyl cyanide (7 g.) is dissolved in a mixture of absolute methyl alcohol (42 g.) and water (2 g.). The process of esterification used in the preparation of

[1] *Ber.,* **28**, 1919 (1895).

p-amino-phenylacetic methyl ester is carried out. When the alcoholic solution is decanted from the ammonium chloride formed in the reaction, it is set aside for a few hours, and presently a precipitate of white crystals of the ureido ester separates. The crystals are collected on a filter and are found to melt at 110°. The yield of crude material was 4.5 g. Recrystallization from 95% alcohol gave a product melting at 132°.

(b) *Action of Potassium Cyanate on p-Amino-phenylacetic Methyl Ester Hydrochloride.*—The hydrochloride (6 g.) is dissolved in water (48 cc.) and potassium cyanate (4.2 g., the calculated amount and $^1/_3$ excess, dissolved in 10 cc. of water) is added. The reaction seemed to go to completion at once, and the pasty product of the reaction was not evaporated to dryness as in other similar preparations. When evaporation was carried out over the water bath, ammonia fumes were given off, showing decomposition. The mass was allowed to stand in the cold for about an hour, and was then collected on a filter and washed thoroughly with water. A yield of 5.6 g. of crude ester was obtained. It was recrystallized by solution in the smallest possible amount of warm 95% alcohol, and precipitation from this solution with a large volume of ether. White, shining needles were obtained in this way, of melting point 131–132°.

Subs., 0.1259: 18.22 cc. N (over 50% KOH), at 19° and 749.2 mm.
Calc. for $C_{10}H_{12}N_2O_3$: N, 13.46. Found: 13.46.

4. *p*-**Ureido-phenylacetic Acid,** $p\text{-}NH_2.CO.NH.C_6H_4.CH_2.COOH.$—This acid was first prepared by Traube.[1] Our preparation by the hydrolysis of *p*-ureido-phenylacetic methyl ester and recrystallization from alcohol gave a purer product. It melted with decomposition at 184–185°. (Traube, m. p. 174°.)

Subs., 0.1285: 17.00 cc. N (over 50% KOH) at 28° and 747.3 mm. (28°).
Calc. for $C_9H_{10}N_2O_3$: N, 14.43. Found: 14.32.[2]

The Preparation of *p*-Ureido-phenyl-acetylurea.

1. *p*-**Nitro-phenylacetic Acid,** $p\text{-}NO_2.C_6H_4.CH_2.COOH.$—The acid was prepared according to the method of Gabriel.[3] A quantitative yield was obtained, m. p. 151°. (Gabriel, m. p. 151.5–152°.)

2. *p*-**Nitro-phenylacetyl Chloride,** $p\text{-}NO_2.C.H_4.CH_2COCl.$—*p*-Nitrophenylacetic acid, prepared as indicated above, was converted into its chloride by the method described by Wedekind.[4] A quantitative yield of *p*-nitro-phenylacetyl chloride was obtained, m. p. 42–45°, which was considered sufficiently pure for use. (Wedekind, m. p. 47°.)

3. *p*-**Nitro-phenyl-acetylurea,** $p\text{-}NO_2.C_6H_4.CH_2.CO.NH.CO.NH_2.$—*p*-Nitro-phenylacetyl chloride was converted into *p*-nitro-phenyl-acetyl-

[1] *Ber.*, **15**, 2121 (1882).
[2] Traube found 14.04% N.
[3] *Ber.*, **15**, 834 (1882).
[4] *Ann.*, **378**, 289 (1911).

urea by treatment with urea in benzene solution.[1] When the reaction was complete the p-nitro-phenyl-acetylurea was collected on a filter. The crude material turned brown at 220° and melted with decomposition at 230°. Its purification was accomplished by recrystallization from warm, glacial acetic acid, or from amyl alcohol. The purified product turned slightly yellow at 230°, softened somewhat at 233°, and melted to a reddish brown liquid at 237–239°.[2] This liquid solidified on cooling, and when put in the bath again at 225°, melted.

Subs., 0.1027: 17.73 cc. N (over 50% KOH) at 26° and 746 mm. (23°).
Calc. for $C_9H_9O_4N_3$: N, 18.83. Found: 18.84.

4. p-Amino-phenyl-acetylurea, p-$NH_2.C_6H_4.CH_2.CO.NH.CO.NH_2$.— The reduction of p-nitro-phenyl-acetylurea was accomplished with stannous chloride in glacial acetic acid which was saturated with hydrogen chloride. The following method was found to be very successful, with each step in the process well defined: Its main advantage lies in the fact that the reduction takes place in the cold. The urea derivative had shown itself to be rather unstable when kept at a high temperature for any length of time. Dry hydrogen chloride was passed into 60 cc. of glacial acetic acid to saturation. To this acid was added 3 mols. of crystallized stannous chloride and 50% excess, in all, 11.6 g. of 85% stannous chloride being used. The acid was heated slightly to dissolve the stannous chloride. The mixture was then cooled and p-nitro-phenyl-acetylurea (2 g.) added, and a stream of dry hydrogen chloride led into the flask, while the contents of the flask were stirred gently with the aid of a motor. After about 10 minutes, the urea was dissolved completely. Within 15 minutes more a heavy, white precipitate settled out of the solution, which proved to be the complex tin salt of the amine. The flask meanwhile became somewhat warm from the heat of reaction. The stirring was continued till the mixture was quite cool (for about one hour). At the end of that time the tin salt was collected. When dry, the yield of this salt was 4.1 g., the mass probably containing some stannous chloride, and the crystals being somewhat solvated.

The free base was obtained as follows: The tin salt was dissolved in water and the solution made sufficiently acid with hydrochloric acid to give a blue-green tint with methyl violet.[3] Tin sulfide was then precipitated with hydrogen sulfide, about an hour and a half being used for a complete precipitation. The stannic sulfide was removed by filtration and the filtrate concentrated *in vacuo* at 45° to a small volume. It

[1] Later we found that Jacobs and Heidelberger (*Loc. cit.*) had prepared this compound by practically the same method.

[2] As decomposition occurs at this temperature, the melting point depends largely on the speed with which the bath is heated. Jacobs and Heidelberger give the melting point as 250–2°, with complete decomposition.

[3] Stieglitz, *Qualitative Analysis*, **1**, 214 (1913).

was then made slightly basic with ammonia when a heavy precipitate of slender, white needles settled out. The base thus formed may be recrystallized by solution in acid and reprecipitation with ammonia, or it may be recrystallized from boiling water, in which it is fairly soluble. It does not melt, but decomposes at 192-3°. The yield of the pure compound was 1.2 g., or 70% of the theoretical amount.[1]

> Subs., 0.0551: 10.75 cc. N (over 50% KOH) at 21.5° and 748.5 mm. (24°).
> Calc. for $C_9H_{11}O_2N_3$: N, 21.76. Found: 21.83.

5. **p-Ureido-phenyl-acetylurea,** p-$NH_2.CO.NH.C_6H_4.CH_2.CO.NH.$-$CO.NH_2$.—The hydrochloride of p-amino-phenyl-acetylurea was prepared by solution of the base (0.5 g.) in N hydrochloric acid (2.57 cc.). To this solution of the hydrochloride was added a solution of 0.28 g. of potassium cyanate (1 mol. and $1/8$ excess) in 10 cc. of water. After the addition of the cyanate, the mixture became at once thick and pasty, and was evaporated to dryness on the water bath. The residue was then taken up in a little water to remove the potassium chloride formed in the reaction and the solid collected on a filter. The ureido-ureid was found to be quite soluble in hot water and is recrystallized from it. The yield of purified product was 0.47 g., or 77.5% of the theoretical amount.

> Subs., 0.0816: 17.40 cc. N (over 50% KOH) at 21° and 745 mm. (22°).
> Calc. for $C_{10}H_{12}O_3N_4$: N, 23.72. Found: 23.79.

The Ethylation of Benzyl Cyanide.

α-Phenylbutyronitril, $CH_3.CH_2.CH(C_6H_5).CN$.—The substitution of an alkyl group for one of the aliphatic hydrogens in the benzyl cyanide molecule takes place in two stages, the formation of a sodium salt and the replacement of sodium by the ethyl group.[2]

The completeness of the reaction in which α-phenylbutyronitril is formed depends, first of all, clearly upon the formation of a maximum amount of the sodium salt of benzyl cyanide. In the first attempt to prepare this sodium salt, metallic sodium was used, but the method of Bodroux[2] for the preparation of α-phenylbutyronitril was otherwise followed. Bodroux used sodium amide in place of metallic sodium.

Fine sodium wire (2.4 g.) is placed in 40 cc. of sodium-dried ether, under a reflux condenser. Benzyl cyanide (12 g.) is then dropped slowly into the flask containing the sodium and ether, two or three drops of absolute alcohol are added, and the reaction begins promptly. The ether boils, and most but not all of the sodium dissolves in the course of an hour. At the end of that time the ether solution has turned red, and a mass of the sodium salt, mixed with small particles of sodium, is deposited on the bottom of the flask. The mixture is heated for half an hour over

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[1] Jacobs and Heidelberger effected the reduction with ferrous sulfate. Their crude yield was 73% of the theoretical amount.

[2] *Bull. soc. chim.*, **4**, Ser. 7, 666-667 (1910).

the water bath, and then cooled. Ethyl iodide (16 g.) is added slowly to the suspension of the sodium salt, whereupon the mixture becomes warm and boils, and a light colored precipitate (NaI) settles out. When the boiling has ceased, the contents of the flask are heated for half an hour over the water bath and are then treated with a little water to dissolve particles of sodium and the sodium iodide. The ether layer is separated and combined with ether extracts of the aqueous solution. The whole ether extract is dried with calcium chloride and the ether removed by evaporation. The residue from the ether solution is a dark red oil, which, when subjected to vacuum distillation, boils from 70–105°, at 10 mm. pressure, all but a few drops of the distillate passing over above 100°. The yield of distillate was 6.4 g.

When sodium amide[1] was used in the preparation of the sodium salt of benzyl cyanide, a better yield of the ethylated product was obtained. From 12 g. of benzyl cyanide, a yield of 10 g. of distillate boiling at 108–118°, at 12 mm., was obtained. This oils contains, as stated by Bodroux, α-phenylbutyronitril, and any unchanged benzyl cyanide. Since the boiling points of the two nitrils lie too close together to make a separation by fractionation possible, it was found necessary by us to saponify the nitrils, in order to effect a separation. Phenylacetic acid melts at 76°, and α-phenylbutyric acid at 42°. In order to determine the degree of completeness of the reaction just described, hydrolysis of the distillate of boiling point 108–118°, at 12 mm., was undertaken.

Our method of saponification was the following: The 10 g. of distillate was boiled for 8 hours with 15 g. of potassium hydroxide in 60 g. of 95% alcohol. At the end of this time the alcohol was distilled off *in vacuo* and the residue was extracted with ether to remove any unchanged nitrils. The alkaline solution was then made slightly acid with dil. hydrochloric acid and extracted with ether several times. The ether extracts were combined, dried over calcium chloride, and the ether evaporated. The residue, a thick oil, solidified slowly on standing *in vacuo*, and 10.3 g. of crystals were obtained melting at 37–40°. The crystals were mixed with some oily material, which was removed by purification. To this end, the oily crystals were dissolved in concentrated ammonia and the solution was cooled in a freezing mixture. To it was added slowly cold conc. hydrochloric acid and enough water to dissolve the ammonium chloride which formed. When an excess of acid had been added, the solution became turbid, and if it had been kept at a low temperature during the addition of the acid, the α-phenylbutyric acid precipitated out in fairly pure form. Crystals obtained in this way were slightly yellow and melted at 40–42°. From 12 g. of benzyl cyanide, a yield of 8.1 g. was obtained, or 48% of the theoretical amount.

[1] Bodroux, *Loc. cit.*

From a second preparation of α-phenylbutyronitril with sodium amide, in which 48 g. of benzyl cyanide was used, a yield of 49 g. of distillate boiling at 70–110°, at 10 mm., was obtained, all but a few drops of which distilled above 100°.

The distillate (6.4 g.) from the ethylation of 12 g. of benzyl cyanide with metallic sodium was hydrolyzed and a yield of about 4 g. of α-phenyl-butyric acid obtained, of melting point 41–42°.

An attempt to substitute calcium carbide for sodium amide and sodium in the action with benzyl cyanide was made, but proved unsuccessful, because the carbide was not attacked appreciably.

Summary.

The successful preparation of p-ureido-phenyl-acetylurea is described as the first of a series of ureidophenyl acyl derivatives of urea which are intended to form the basis for a study of their physiological activity, particularly as hypnotics. Intermediate products and their preparation are described. The preparation of other derivatives of the series, such as ureido-phenylethyl-acetylurea, and ureido-phenylethyl-barbituric acid, is well under way in this laboratory and will be reported on at a later date.

CHICAGO, ILLINOIS.

METHYL AND ETHYL AMMONIUM MERCURIC IODIDES: THEIR PREPARATION, CRYSTALLOGRAPHY, AND OPTICAL PROPERTIES.

BY GEORGE S. JAMIESON AND EDGAR T. WHERRY.

The compounds described in this paper were obtained by adding potassium mercuric iodide (Mayer's reagent) to aqueous solutions of the amines which had been acidified with hydrochloric acid. Woodward and Alsberg[1] discovered that minute quantities of tertiary methyl and ethyl amines could be precipitated and detected by means of Mayer's reagent in the presence of the primary amines as well as the secondary amines provided the latter were present in small amounts. However, when one cc. of solution contains more than 20 mg. of diethylamine or more than 4 mg. of dimethyl amine, these compounds are precipitated with Mayer's reagent. In addition to the trimethyl and triethyl ammonium mercuric iodides described by Woodward and Alsberg, Woodward prepared tetramethyl ammonium mercuric iodide, which was recently found

[1] A paper on "A New Reagent for Volatile Tertiary Amines," was presented September, 1916, at the New York meeting of the American Chemical Society, and will be published later.